(54) Title: PASSIVATION, pH PROTECTIVE OR LUBRICITY COATING FOR PHARMACEUTICAL PACKAGE, COATING PROCESS AND APPARATUS

(57) Abstract: A method for providing a passivation layer or pH protective coating on a substrate surface by PECVD is provided, the method comprising generating a plasma from a gaseous reactant comprising polymerizing gases, for example an organosilicon precursor and optionally (¾. The lubricity, passivation, pH protective, hydrophobicity, and/or barrier properties of the passivation layer or pH protective coating are set by setting the ratio of the 0₂ to the organosilicon precursor in the precursor feed, and/or by setting the electric power used for generating the plasma. In particular, a lubricity and/or passivation layer or pH protective coating made by said method is provided.


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PASSIVATION, pH PROTECTIVE OR LUBRICITY COATING
FOR PHARMACEUTICAL PACKAGE,
COATING PROCESS AND APPARATUS

[01] Priority is claimed to U.S. Provisional Application Serial Nos. 61/558,885, filed November 11, 2011; 61/636,377, filed April 20, 2012; and U.S. Ser. No. 61/645,003, filed May 9, 2012.


[03] Also incorporated by reference in their entirety are the following European patent applications: EP10162755.2 filed May 12, 2010; EP10162760.2 filed May 12, 2010; EP10162756.0 filed May 12, 2010; EP10162758.6 filed May 12, 2010; EP10162761.0 filed May 12, 2010; and EP10162757.8 filed May 12, 2010.

FIELD OF THE INVENTION

[04] The present invention relates to the technical field of coated surfaces, for example interior surfaces of pharmaceutical packages or other vessels for storing or other contact with fluids. Examples of suitable fluids include foods or biologically active compounds or body fluids, for example blood. The present invention also relates to a pharmaceutical package or other vessel and to a method for coating an inner or interior surface of a pharmaceutical package or other vessel. The present invention also
relates more generally to medical devices, including devices other than packages or vessels, for example catheters.

[05] The present disclosure also relates to improved methods for processing pharmaceutical packages or other vessels, for example multiple identical pharmaceutical packages or other vessels used for pharmaceutical preparation storage and delivery, venipuncture and other medical sample collection, and other purposes. Such pharmaceutical packages or other vessels are used in large numbers for these purposes, and must be relatively economical to manufacture and yet highly reliable in storage and use.

BACKGROUND OF THE INVENTION

[06] One important consideration in manufacturing pharmaceutical packages or other vessels for storing or other contact with fluids, for example vials and pre-filled syringes, is that the contents of the pharmaceutical package or other vessel desirably will have a substantial shelf life. During this shelf life, it can be important to isolate the material filling the pharmaceutical package or other vessel from the vessel wall containing it, or from barrier coatings or layers or other functional layers applied to the pharmaceutical package or other vessel wall to avoid leaching material from the pharmaceutical package or other vessel wall, barrier coating or layer, or other functional layers into the prefilled contents or vice versa.

[07] Since many of these pharmaceutical packages or other vessels are inexpensive and used in large quantities, for certain applications it will be useful to reliably obtain the necessary shelf life without increasing the manufacturing cost to a prohibitive level.

[08] For decades, most parenteral therapeutics have been delivered to end users in Type I medical grade borosilicate glass vessels such as vials or pre-filled syringes. 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 biologies as well as such advanced delivery systems as auto injectors has exposed the physical and chemical shortcomings of glass pharmaceutical packages or
other vessels, 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.

In more detail, borosilicate pharmaceutical packages or other vessels 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% SiO₂, 10.5% B₂O₃, 5% Al₂O₃, 7% Na₂O 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. Glass forming processes used to create glass vessels expose some portions of the vessels to temperatures as great as 1200°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 biologies. Many proteins and other biologies must be lyophilized (freeze dried), because they are not sufficiently stable in solution in glass vials or syringes.

In glass syringes, silicone oil is typically used as a lubricant to allow the plunger tip, piston, stopper, or seal to slide in the barrel. Silicone oil has been implicated in the precipitation of protein solutions such as insulin and some other biologies. Additionally, the silicone oil coating or layer is often non-uniform, resulting in syringe failures in the market.

Glass pharmaceutical packages or other vessels are prone to breakage or degradation during manufacture, filling operations, shipping and use, which means that glass particulates may enter the drug. The presence of glass particles has led to many FDA Warning Letters and to product recalls.

Glass-forming processes do not yield the tight dimensional tolerances required for some of the newer auto-injectors and delivery systems.
As a result, some companies have turned to plastic pharmaceutical packages or other vessels, which provide tighter dimensional tolerances and less breakage than glass.

Although plastic is superior to glass with respect to breakage, dimensional tolerances and surface uniformity, its use for primary pharmaceutical packaging remains limited due to the following shortcomings:

1. Gas (oxygen) permeability: Plastic allows small molecule gases to permeate into (or out of) the device. The permeability of plastics to gases can be significantly greater than that of glass and, in many cases (as with oxygen-sensitive drugs such as epinephrine), plastics previously have been unacceptable for that reason.

2. Water vapor transmission: Plastics allow water vapor to pass through devices to a greater degree than glass. This can be detrimental to the shelf life of a solid (lyophilized) drug. Alternatively, a liquid product may lose water in an arid environment.

3. Leachables and extractables: Plastic pharmaceutical packages or other vessels contain organic compounds that can leach out or be extracted into the drug product. These compounds can contaminate the drug and/or negatively impact the drug's stability.

Clearly, while plastic and glass pharmaceutical packages or other vessels each offer certain advantages in pharmaceutical primary packaging, neither is optimal for all drugs, biologies or other therapeutics. Thus, there can be a desire for plastic pharmaceutical packages or other vessels, in particular plastic syringes, with gas and solute barrier properties which approach the properties of glass. Moreover, there can be a need for plastic syringes with sufficient lubricity and/or passivation or protective properties and a lubricity and/or passivation layer or pH protective coating which can be compatible with the syringe contents. There also can be a need for glass vessels with surfaces that do not tend to delaminate or dissolve or leach constituents when in contact with the vessel contents.

There are additional considerations to be taken into account when manufacturing a prefilled syringe. Prefilled syringes are commonly prepared and sold so
the syringe does not need to be filled before use, and can be disposed of after use. The syringe can be prefilled with saline solution, a dye for injection, or a pharmaceutically active preparation, for some examples.

[21] Commonly, the prefilled syringe can be capped at the distal end, as with a cap (or, if the hypodermic needle is preinstalled, a needle shield that can also be a cap), and can be closed at the proximal end by its drawn plunger tip, piston, stopper, or seal. The prefilled syringe can be wrapped in a sterile package before use. To use the prefilled syringe, the packaging and cap are removed, optionally a hypodermic needle or another delivery conduit can be attached to the distal end of the barrel, the delivery conduit or syringe can be moved to a use position (such as by inserting the hypodermic needle into a patient's blood vessel or into apparatus to be rinsed with the contents of the syringe), and the plunger tip, piston, stopper, or seal can be advanced in the barrel to inject the contents of the barrel.

[22] An important consideration regarding medical syringes can be to ensure that the plunger tip, piston, stopper, or seal can move at a constant speed and with a constant force when it is pressed into the barrel. A similar consideration applies to vessels such as pharmaceutical vials which have to be closed by a stopper, and to the stopper itself, and more generally to any surface which is to provide smooth operation of moving parts and/or be passivated or protectively coated.


**SUMMARY OF THE INVENTION**

[24] An aspect of the invention is a filled package comprising a vessel, a barrier coating or layer, and a passivation layer or pH protective coating on the vessel, and a fluid composition contained in the vessel. The calculated shelf life of the package can be more than six months at a storage temperature of 4°C.
The vessel can have a lumen defined at least in part by a wall. The wall can have an interior surface facing the lumen and an outer surface.

The barrier coating or layer comprises \( \text{SiO}_x \), wherein \( x \) is from 1.5 to 2.9, from 2 to 1000 nm thick. The barrier coating or layer of \( \text{SiO}_x \) can have an interior surface facing the lumen and another outer surface facing the wall interior surface.

The passivation layer or pH protective coating comprises \( \text{SiO}_x\text{C}_y \) or \( \text{SiN}_x\text{C}_y \) wherein \( x \) is from about 0.5 to about 2.4 and \( y \) is from about 0.6 to about 3. Optionally in one embodiment, \( x \) can be about 1.1 and \( y \) can be about 1.1. The passivation layer or pH protective coating can have an interior surface facing the lumen and an outer surface facing the interior surface of the barrier coating or layer. The passivation layer or pH protective coating can be effective to increase the calculated shelf life of the package (total Si / Si dissolution rate).

The fluid composition can be contained in the lumen and can have a pH between 4 and 10, alternatively between 5 and 9.

Another aspect of the invention can be a filled package comprising a vessel, a passivation layer or pH protective coating on the vessel, and a fluid composition contained in the vessel.

The vessel can have a lumen defined at least in part by a wall. The wall can have an interior surface comprising glass facing the lumen and an outer surface.

The passivation layer or pH protective coating comprises \( \text{SiO}_x\text{C}_y \) or \( \text{SiN}_x\text{C}_y \) wherein \( x \) is from about 0.5 to about 2.4 and \( y \) is from about 0.6 to about 3. The passivation layer or pH protective coating can have an interior surface facing the lumen and an outer surface facing the interior surface of the barrier coating or layer. The passivation layer or pH protective coating can be effective to decrease the Si dissolution rate of the glass interior surface.

The fluid composition can be contained in the lumen and can have a pH between 4 and 10, alternatively between 5 and 9.

Still another aspect of the invention can be an article comprising a wall, a barrier coating or layer, and a passivation layer or pH protective coating.

The wall can have an interior surface facing the lumen.
The barrier coating or layer comprises SiO$_x$, wherein $x$ is from 1.5 to 2.9, from 2 to 1000 nm thick. The barrier coating or layer of SiO$_x$ can have an interior surface facing the lumen and an outer surface facing the wall interior surface. The barrier coating or layer can be effective to reduce the ingress of atmospheric gas through the wall compared to an uncoated wall.

The passivation layer or pH protective coating can be on the barrier coating or layer, optionally with one or more intervening layers, and comprises SiO$_x$C$_y$ or SiN$_x$C$_y$ wherein $x$ is from about 0.5 to about 2.4 and $y$ is from about 0.6 to about 3. The passivation layer or pH protective coating can be formed by chemical vapor deposition of a precursor selected from a linear siloxane, a monocyclic siloxane, a polycyclic siloxane, a polysilsesquioxane, a linear silazane, a monocyclic silazane, a polycyclic silazane, a polysilsesquiazane, a silatrane, a silquasilatranne, a silproatranne, an azasilatranne, an azasilquasiatranne, an azasilproatranne, or a combination of any two or more of these precursors. The rate of erosion of the passivation layer or pH protective coating, if directly contacted by a fluid composition having a pH between 4 and 10, alternatively between 5 and 9, can be less than the rate of erosion of the barrier coating or layer, if directly contacted by the fluid composition.

Even another aspect of the invention can be a vessel comprising a wall, a fluid contained in the vessel, a barrier coating or layer, and a passivation layer or pH protective coating.

The wall can be a thermoplastic wall having an interior surface enclosing a lumen.

The fluid can be disposed in the lumen and can have a pH greater than 5.

The barrier coating or layer comprises SiO$_x$, in which $x$ is between 1.5 and 2.9. The barrier coating or layer can be applied by PECVD. The barrier coating or layer can be positioned between the interior surface of the thermoplastic wall and the fluid, and supported by the thermoplastic wall. The barrier coating or layer commonly can have the characteristic of being subject to being measurably diminished in barrier improvement factor in less than six months as a result of attack by the fluid, although this is not a required feature of the invention.
The passivation layer or pH protective coating comprises SiO$_x$C$_y$, in which $x$ is between 0.5 and 2.4 and $y$ is between 0.6 and 3. The passivation layer or pH protective coating can be applied by PECVD, and can be positioned between the barrier coating or layer and the fluid. The passivation layer or pH protective coating can be supported by the thermoplastic wall. The passivation layer or pH protective coating can be effective to keep the barrier coating or layer at least substantially undissolved as a result of attack by the fluid for a period of at least six months.

Yet another aspect of the invention can be a composite material comprising a substrate, a barrier coating or layer over the substrate, and a passivation layer or pH protective coating (which can have the same function as the passivation layer referred to in U.S. Patent No. 8,067,070) over the barrier coating or layer. The passivation layer or pH protective coating shows an FTIR absorbance ratio of greater than 0.75 between:

1. the maximum amplitude of the Si-O-Si symmetrical stretch peak of an FTIR spectrum between about 1000 and 1040 cm$^{-1}$, and
2. the maximum amplitude of the Si-O-Si asymmetric stretch peak of the FTIR spectrum between about 1060 and about 1100 cm$^{-1}$.

Optionally, the vessel further includes an opening communicating with the lumen and a closure. The method optionally further includes placing a fluid in the lumen via the opening and closing the opening with the closure. The fluid can be a pharmaceutical fluid such as a drug, for example.

Other aspects of the invention will become apparent to a person of ordinary skill in the art after reviewing the present disclosure and claims.

**BRIEF DESCRIPTION OF THE DRAWINGS**

FIG. 1 is an elevation view of a capped pre-assembly according to an embodiment of the disclosure.

FIG. 2 is a longitudinal section of the capped pre-assembly of FIG. 1.

FIG. 3 is an enlarged fragmentary view of the capped pre-assembly of FIGS. 1 and 2.
FIG. 4 is a schematic longitudinal section of the capped pre-assembly of FIGS. 1 and 2 seated on a chemical vapor deposition coating station.

FIG. 5 is a section taken along section lines A—A of FIG. 4.

FIG. 6 is a schematic view showing more details of the chemical vapor deposition coating station shown in FIGS. 4 and 5.

FIG. 7 is a view similar to FIG. 2 of the capped pre-assembly of FIGS. 1-6, filled with a pharmaceutical preparation and fitted with a plunger tip, piston, stopper, or seal to define a pre-filled syringe. In the option shown, a plunger tip, piston, stopper, or seal and plunger push rod are installed.

FIG. 8 is a longitudinal section of a vial fitted with a septum and crimp and having the same barrier coating or layer, passivation layer or pH protective coating, and other common features of FIG. 7.

FIG. 9 is a longitudinal section of a blister pack having the same barrier coating or layer, passivation layer or pH protective coating, and other common features of FIG. 7.

FIG. 10 shows a SEM image of Example P. The horizontal edge-to-edge scale is 5 µm.

FIG. 11 shows a SEM image of Example S. The horizontal edge-to-edge scale is 5 µm.

FIG. 12 shows a TEM image of a passivation layer or pH protective coating according to the invention coated on an SiOₓ barrier coating or layer, which in turn is coated on a COC substrate.

FIG. 13 shows a TEM image of an SiO₂ barrier coating or layer which is coated on a COC substrate.

FIG. 14 is a plot of silicon dissolution versus exposure time at pH 6 for a glass container versus a plastic container having an SiOₓ barrier coating or layer coated in the inside wall.

FIG. 15 is a plot of silicon dissolution versus exposure time at pH 7 for a glass container versus a plastic container having an SiOₓ barrier coating or layer coated in the inside wall.
Fig. 16 is a plot of silicon dissolution versus exposure time at pH 8 for a glass container versus a plastic container having an SiO$_x$ barrier coating or layer coated in the inside wall.

Fig. 17 is a plot of the SiO$_x$ coating thickness necessary initially to leave a 30 nm residual coating thickness when stored with solutions at different nominal pH values from 3 to 9.

Fig. 18 shows the silicon dissolution rates at pH 8 and 40°C of various PECVD coatings.

Fig. 19 is a plot of the ratio of Si-O-Si symmetric/asymmetric stretching mode versus energy input per unit mass (W/FM or KJ/kg) of a PECVD coating using as the reactive precursor gases OMCTS and oxygen.

Fig. 20 is a plot of silicon shelf life (days) versus energy input per unit mass (W/FM or KJ/kg) of a PECVD coating using as the reactive precursor gases OMCTS and oxygen.

Fig. 21 is a Fourier Transform Infrared Spectrophotometer (FTIR) absorbance spectrum of a PECVD coating.

Fig. 22 is a Fourier Transform Infrared Spectrophotometer (FTIR) absorbance spectrum of a PECVD coating.

Fig. 23 is a Fourier Transform Infrared Spectrophotometer (FTIR) absorbance spectrum of a PECVD coating.

Fig. 24 is a Fourier Transform Infrared Spectrophotometer (FTIR) absorbance spectrum of a PECVD coating.

Fig. 25 is a Fourier Transform Infrared Spectrophotometer (FTIR) absorbance spectrum of a PECVD coating, originally presented as FIG. 5 of U.S. Pat. No.8,067,070, annotated to show the calculation of the O-Parameter referred to in that patent.

The following reference characters are used in the drawing figures:
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<tr>
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<th>Capped pre-assembly</th>
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<tbody>
<tr>
<td>14</td>
<td>Barrel</td>
</tr>
<tr>
<td>16</td>
<td>Internal wall</td>
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<tr>
<td>18</td>
<td>Barrel lumen</td>
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<tr>
<td>20</td>
<td>Dispensing portion</td>
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<tr>
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<td>Proximal opening</td>
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<tr>
<td>24</td>
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<tr>
<td>26</td>
<td>Dispensing portion lumen</td>
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<tr>
<td>27</td>
<td>Shield</td>
</tr>
<tr>
<td>30</td>
<td>Barrier coating or layer</td>
</tr>
<tr>
<td>32</td>
<td>Opening</td>
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<tr>
<td>34</td>
<td>Passivation layer or pH protective coating</td>
</tr>
<tr>
<td>36</td>
<td>plunger tip, piston, stopper, or seal</td>
</tr>
<tr>
<td>38</td>
<td>Push rod</td>
</tr>
<tr>
<td>40</td>
<td>Fluid material</td>
</tr>
<tr>
<td>42</td>
<td>Rib</td>
</tr>
<tr>
<td>44</td>
<td>Cylindrical surface</td>
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<td>46</td>
<td>Barb</td>
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<tr>
<td>48</td>
<td>Catch</td>
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<td>Plot</td>
</tr>
<tr>
<td>60</td>
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<tr>
<td>82</td>
<td>Opening</td>
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<tr>
<td>84</td>
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<tr>
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<td>Gas inlet port</td>
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<td>Probe (counter electrode)</td>
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<td>Gas delivery port (of 108)</td>
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<tr>
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<td>Housing (of 50 or 112)</td>
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<tr>
<td>116</td>
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<td>118</td>
<td>Exterior surface (of 80)</td>
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<td>144</td>
<td>PECVD gas source</td>
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<tr>
<td>152</td>
<td>Pressure gauge</td>
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<tr>
<td>160</td>
<td>Electrode</td>
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<td>162</td>
<td>Power supply</td>
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<tr>
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<tr>
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<td>Exhaust</td>
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<td>574</td>
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<tr>
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<td>578</td>
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<td>582</td>
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<td>Main reactant feed line</td>
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<td>Organosilicon liquid reservoir</td>
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<td>Organosilicon feed line (capillary)</td>
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<td>Oxygen feed line</td>
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<td>Additional reservoir</td>
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<tr>
<td>604</td>
<td>Feed line</td>
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<tr>
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<td>Shut-off valve</td>
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<td>Headspace</td>
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<td>Pressure source</td>
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<tr>
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DEFINITION SECTION

[71] In the context of the present invention, the following definitions and abbreviations are used:

[72] RF is radio frequency.

[73] The term "at least" in the context of the present invention means "equal or more" than the integer following the term. The word "comprising" does not exclude other elements or steps, and the indefinite article "a" or "an" does not exclude a plurality unless indicated otherwise. Whenever a parameter range is indicated, it is intended to disclose the parameter values given as limits of the range and all values of the parameter falling within said range.

[74] "First" and "second" or similar references to, for example, processing stations or processing devices refer to the minimum number of processing stations or devices that are present, but do not necessarily represent the order or total number of processing stations and devices. These terms do not limit the number of processing stations or the particular processing carried out at the respective stations.

[75] For purposes of the present invention, an "organosilicon precursor" is a compound having at least one of the linkages:

\[ \begin{align*}
- & \text{O} - \text{Si} - \text{C} - \text{H} \\
\text{or} & \\
- & \text{NH} - \text{Si} - \text{C} - \text{H}
\end{align*} \]

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 PECVD apparatus, can be an optional organosilicon precursor. Optionally, the organosilicon precursor can be 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.

[76] The feed amounts of PECVD precursors, gaseous reactant or process gases, and carrier gas are sometimes expressed in "standard volumes" in the specification and claims. The standard volume of a charge or other fixed amount of gas is the volume the fixed amount of the gas would occupy at a standard temperature and pressure (without regard to the actual temperature and pressure of delivery). Standard volumes can be measured using different units of volume, and still be within the scope of the present disclosure and claims. For example, the same fixed amount of gas could be expressed as the number of standard cubic centimeters, the number of standard cubic meters, or the number of standard cubic feet. Standard volumes can also be defined using different standard temperatures and pressures, and still be within the scope of the present disclosure and claims. For example, the standard temperature might be 0°C and the standard pressure might be 760 Torr (as is conventional), or the standard temperature might be 20°C and the standard pressure might be 1 Torr. But whatever standard is used in a given case, when comparing relative amounts of two or more different gases without specifying particular parameters, the same units of volume, standard temperature, and standard pressure are to be used relative to each gas, unless otherwise indicated.

[77] The corresponding feed rates of PECVD precursors, gaseous reactant or process gases, and carrier gas are expressed in standard volumes per unit of time in the specification. For example, in the working examples the flow rates are expressed as standard cubic centimeters per minute, abbreviated as seem. As with the other parameters, other units of time can be used, such as seconds or hours, but consistent parameters are to be used when comparing the flow rates of two or more gases, unless otherwise indicated.
A "vessel" in the context of the present invention can be any type of article with at least one opening and a wall defining an inner or interior surface. The substrate can be the inside wall of a vessel having a lumen. Though the invention is not necessarily limited to pharmaceutical packages or other vessels of a particular volume, pharmaceutical packages or other vessels are contemplated in which the lumen can have a void volume of from 0.5 to 50 mL, optionally from 1 to 10 mL, optionally from 0.5 to 5 mL, optionally from 1 to 3 mL. The substrate surface can be part or all of the inner or interior surface or interior surface of a vessel having at least one opening and an inner or interior surface.

A vessel in the context of the present invention can have one or more openings. One or two openings, like the openings of a sample tube (one opening) or a syringe barrel (two openings) are preferred. If the vessel has two openings, they can be the same size or different sizes. If there is more than one opening, one opening can be used for the gas inlet for a PECVD coating method according to the present invention, while the other openings are either capped or open. A vessel according to the present invention can be a sample tube, for example for collecting or storing biological fluids like blood or urine, a syringe (or a part thereof, for example a syringe barrel) for storing or delivering a biologically active compound or composition, for example a medicament or pharmaceutical composition, a vial for storing biological materials or biologically active compounds or compositions, a pipe, for example a catheter for transporting biological materials or biologically active compounds or compositions, or a cuvette for holding fluids, for example for holding biological materials or biologically active compounds or compositions.

The vessel can be provided with a reagent or preservative for sample collection or analysis. For example, a vessel for blood collection can have an inner or interior surface defining a lumen and an exterior surface, the passivation layer or pH protective coating can be on the inner or interior surface, and the vessel can contain a compound or composition in its lumen, for example citrate or a citrate containing composition.
A vessel can be of any shape, a vessel having a substantially cylindrical wall adjacent to at least one of its open ends being preferred. Generally, the interior wall of the vessel can be cylindrically shaped, like, for example in a sample tube or a syringe barrel. Sample tubes and syringes or their parts (for example syringe barrels) are contemplated.

A "hydrophobic layer" in the context of the present invention means that the coating or layer lowers the wetting tension of a surface coated with the coating or layer, compared to the corresponding uncoated surface. Hydrophobicity can be thus a function of both the uncoated substrate and the coating or layer. The same applies with appropriate alterations for other contexts wherein the term "hydrophobic" is used. The term "hydrophilic" means the opposite, i.e. that the wetting tension is increased compared to reference sample. The present hydrophobic layers are primarily defined by their hydrophobicity and the process conditions providing hydrophobicity. Suitable hydrophobic coatings or layers and their application, properties, and use are described in U.S. Patent No. 7,985,188. Dual functional passivation layers or pH protective coatings that also have the properties of hydrophobic coatings or layers can be provided for any embodiment of the present invention.

The values of \( w, x, y, \) and \( z \) are applicable to the empirical composition \( \text{Si}_w\text{O}_x\text{C}_y\text{H}_z \) 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, octamethyldisiloxane, which has the molecular composition \( \text{Si}_4\text{O}_4\text{C}_8\text{H}_{24} \), 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: \( \text{Si}_1\text{O}_{1.67}\text{C}_2\text{H}_6 \). The values of \( w, x, y, \) and \( z \) are also not limited to integers. For example, (acyclic) octamethyltrisiloxane, molecular composition \( \text{Si}_3\text{O}_2\text{C}_8\text{H}_{24} \), is reducible to \( \text{Si}_1\text{O}_{0.67}\text{C}_2\text{H}_6 \). Also, although \( \text{SiO}_x\text{C}_y\text{H}_z \) can be described as equivalent to \( \text{SiO}_x\text{C}_y \), it is not necessary to show the presence of hydrogen in any proportion to show the presence of \( \text{SiO}_x\text{C}_y \).
"Wetting tension" is a specific measure for the hydrophobicity or hydrophilicity of a surface. An optional wetting tension measurement method in the context of the present invention is ASTM D 2578 or a modification of the method described in ASTM D 2578. This method uses standard wetting tension solutions (called dyne solutions) to determine the solution that comes nearest to wetting a plastic film surface for exactly two seconds. This is the film's wetting tension. The procedure utilized can be varied herein from ASTM D 2578 in that the substrates are not flat plastic films, but are tubes made according to the Protocol for Forming PET Tube and (except for controls) coated according to the Protocol for coating Tube Interior with Hydrophobic Coating or Layer (see Example 9 of EP2251 671 A2).

A "lubricity coating or layer" according to the present invention is a coating or layer which has a lower frictional resistance than the uncoated surface.

A "passivation layer or pH protective coating" according to the present invention passivates or protects an underlying surface or layer from a fluid composition contacting the layer (as more extensively defined elsewhere in this specification).

"Frictional resistance" can be static frictional resistance and/or kinetic frictional resistance.

One of the optional embodiments of the present invention can be a syringe part, for example a syringe barrel or plunger tip, piston, stopper, or seal, coated with a lubricity and/or passivation layer or pH protective coating. In this contemplated embodiment, the relevant static frictional resistance in the context of the present invention is the breakout force as defined herein, and the relevant kinetic frictional resistance in the context of the present invention is the plunger sliding force as defined herein. For example, the plunger sliding force as defined and determined herein is suitable to determine the presence or absence and the lubricity and/or passivating or protective characteristics of a lubricity and/or passivation layer or pH protective coating in the context of the present invention whenever the coating or layer is applied to any syringe or syringe part, for example to the inner wall of a syringe barrel. The breakout force can be of particular relevance for evaluation of the coating or layer effect on a prefilled syringe, i.e. a syringe which can be filled after coating and can be stored for
some time, for example several months or even years, before the plunger tip, piston, stopper, or seal is moved again (has to be "broken out").

[89] The "plunger sliding force" (synonym to "glide force," "maintenance force", or $F_m$, also used in this description) in the context of the present invention is the force required to maintain movement of a plunger tip, piston, stopper, or seal in a syringe barrel, for example during aspiration or dispense. It can advantageously be determined using the ISO 7886-1:1993 test described herein and known in the art. A synonym for "plunger sliding force" often used in the art is "plunger force" or "pushing force".

[90] The "plunger breakout force" (synonym to "breakout force", "break loose force", "initiation force", $F_b$, also used in this description) in the context of the present invention is the initial force required to move the plunger tip, piston, stopper, or seal in a syringe, for example in a prefilled syringe.

[91] Both "plunger sliding force" and "plunger breakout force" and methods for their measurement are described in more detail in subsequent parts of this description. These two forces can be expressed in N, lbs or kg and all three units are used herein. These units correlate as follows: $1\text{N} = 0.102 \text{kg} = 0.2248 \text{lbs (pounds)}$.

[92] Sliding force and breakout force are sometimes used herein to describe the forces required to advance a stopper or other closure into a pharmaceutical package or other vessel, such as a medical sample tube or a vial, to seal the stopper in a vessel to close the vessel. Its use can be analogous to use in the context of a syringe and its plunger tip, piston, stopper, or seal, and the measurement of these forces for a vessel and its closure are contemplated to be analogous to the measurement of these forces for a syringe, except that at least in most cases no liquid is ejected from a vessel when advancing the closure to a seated position.

[93] "Slidably" means that the plunger tip, piston, stopper, or seal or other removable part can be permitted to slide in a syringe barrel or other vessel.

[94] Coatings of SiO$_x$ are deposited by plasma enhanced chemical vapor deposition (PECVD) or other chemical vapor deposition processes on the vessel of a pharmaceutical package, in particular a thermoplastic package, to serve as a barrier coating or layer preventing oxygen, air, carbon dioxide, or other gases from entering the
vessel and/or to prevent leaching of the pharmaceutical material into or through the package wall. The barrier coating or layer can be effective to reduce the ingress of atmospheric gas, for example oxygen, into the lumen compared to a vessel without a passivation layer or pH protective coating.

[95] In any embodiment the vapor-deposited coating or layer optionally can also, or alternatively, be a solute barrier coating or layer. A concern of converting from glass to plastic syringes centers around the potential for leachable materials from plastics. With plasma coating technology, the coatings or layers derived from non-metal gaseous precursors, for example HMDSO or OMCTS or other organosilicon compounds, will contain no trace metals and function as a barrier coating or layer to inorganic, metals and organic solutes, preventing leaching of these species from the coated substrate into syringe fluids. In addition to leaching control of plastic syringes, the same plasma passivation layer or pH protective coating technology offers potential to provide a solute barrier to the plunger tip, piston, stopper, or seal, typically made of elastomeric plastic compositions containing even higher levels of leachable organic oligomers and catalysts.

[96] Moreover, certain syringes prefilled with synthetic and biological pharmaceutical formulations are very oxygen and moisture sensitive. A critical factor in the conversion from glass to plastic syringe barrels will be the improvement of plastic oxygen and moisture barrier performance. The plasma passivation layer or pH protective coating technology can be suitable to maintain the SiO_x barrier coating or layer or layer for protection against oxygen and moisture over an extended shelf life.

[97] Examples of solutes in drugs usefully excluded by a barrier layer in any embodiment include antibacterial preservatives, antioxidants, chelating agents, pH buffers, and combinations of any of these. In any embodiment the vapor-deposited coating or layer optionally can be a solvent barrier coating or layer for a solvent comprising a co-solvent used to increase drug solubilization.

[98] In any embodiment the vapor-deposited coating or layer optionally can be a barrier coating or layer for water, glycerin, propylene glycol, methanol, ethanol, n-
propanol, isopropanol, acetone, benzyl alcohol, polyethylene glycol, cotton seed oil, benzene, dioxane, or combinations of any two or more of these.

[99] In any embodiment the vapor-deposited coating or layer optionally can be a metal ion barrier coating or layer.

[100] In any embodiment the vapor-deposited coating or layer optionally can be a barrel wall material barrier coating or layer, to prevent or reduce the leaching of barrel material such as any of the base barrel resins mentioned previously and any other ingredients in their respective compositions.

[101] The inventors have found, however, that such barrier coatings or layers or coatings of SiOₓ are eroded or dissolved by some fluid compositions, 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 coating or layer in less time than the desired shelf life of a product package. This can be 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.

[102] The inventors have further found that without a protective coating borosilicate glass surfaces are eroded or dissolved by some fluid compositions, for example aqueous compositions having a pH above about 5. This can be 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 glass. Delamination of the glass can also result from such erosion or dissolution, as small particles of glass are undercut by the aqueous compositions having a pH above about 5.

[103] The inventors have further found that certain passivation layers or pH protective coatings of SiOₓCᵧ or SiNₓCᵧ formed from cyclic polysiloxane precursors, which passivation layers or pH protective coatings have a substantial organic
component, do not erode quickly when exposed to fluid compositions, and in fact erode or dissolve more slowly when the fluid compositions have higher pHs within the range of 5 to 9. For example, at pH 8, the dissolution rate of a passivation layer or pH protective coating made from the precursor octamethylcyclotetrasiloxane, or OMCTS, can be quite slow. These passivation layers or pH protective coatings of SiO\textsubscript{x}C\textsubscript{y} or SiN\textsubscript{x}C\textsubscript{y} can therefore be used to cover a barrier coating or layer of SiO\textsubscript{x}, retaining the benefits of the barrier coating or layer by passivating or protecting it from the fluid composition in the pharmaceutical package. These passivation layers or pH protective coatings of SiO\textsubscript{x}C\textsubscript{y} or SiN\textsubscript{x}C\textsubscript{y} also can be used to cover a glass surface, for example a borosilicate glass surface, preventing delamination, erosion and dissolution of the glass, by passivating or protecting it from the fluid composition in the pharmaceutical package.

[104] Although the present invention does not depend upon the accuracy of the following theory, it is believed that the material properties of an effective SiO\textsubscript{x}C\textsubscript{y} passivation layer or pH protective coating and those of an effective lubricity layer as described in U.S. Pat. No. 7,985,188 and in International Application PCT/US1 1/36097 are similar in some instances, such that a coating having the characteristics of a lubricity layer as described in certain working examples of this specification, U.S. Pat. No. 7,985,188, or International Application PCT/US1 1/36097 will also in certain cases serve as well as a passivation layer or pH protective coating to passivate or protect the barrier coating or layer of the package and vice versa.

[105] Although the present invention does not depend upon the accuracy of the following theory, it is further believed that the most effective lubricity and/or passivation layers or pH protective coatings are those made from cyclic siloxanes and silazanes as described in this disclosure. SiO\textsubscript{x}C\textsubscript{y} or SiN\textsubscript{x}C\textsubscript{y} coatings deposited from linear siloxane or linear silazane precursors, for example hexamethyldisiloxane (HMDSO), are believed to contain fragments of the original precursor to a large degree and low organic content. Such SiOxCy or SiN\textsubscript{x}C\textsubscript{y} coatings have a degree of water miscibility or swellability, allowing them to be attacked by aqueous solutions. SiO\textsubscript{x}C\textsubscript{y} or SiN\textsubscript{x}C\textsubscript{y} coatings deposited from cyclic siloxane or linear silazane precursors, for example octamethylcyclotetrasiloxane (OMCTS), however, are believed to include more intact
cyclic siloxane rings and longer series of repeating units of the precursor structure. These coatings are believed to be nanoporous but structured and hydrophobic, and these properties are believed to contribute to their success as passivation layers or pH protective coatings. This is shown, for example, in U.S. Pat. No. 7,901,783.

DETAILED DESCRIPTION

[106] The present invention will now be described more fully, with reference to the accompanying drawings, in which several embodiments are shown. This invention can, 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 or corresponding elements throughout. The following disclosure relates to all embodiments unless specifically limited to a certain embodiment.

PECVD TREATED PHARMACEUTICAL PACKAGES OR OTHER VESSELS

[107] A vessel with a passivation layer or pH protective coating as described herein and/or prepared according to a method described herein can be used for reception and/or storage and/or delivery of a compound or composition. The compound or composition can be sensitive, for example air-sensitive, oxygen-sensitive, sensitive to humidity and/or sensitive to mechanical influences. It can be a biologically active compound or composition, for example a pharmaceutical preparation or medicament like insulin or a composition comprising insulin. A prefilled syringe can be especially considered which contains injectable or other liquid drugs like insulin.

[108] In another aspect, the compound or composition can be a biological fluid, optionally a bodily fluid, for example blood or a blood fraction. In certain aspects of the present invention, the compound or composition can be a product to be administrated to a subject in need thereof, for example a product to be injected, like blood (as in transfusion of blood from a donor to a recipient or reintroduction of blood from a patient back to the patient) or insulin.
[109] A vessel with a passivation layer or pH protective coating as described herein and/or prepared according to a method described herein can further be used for protecting a compound or composition contained in its interior space against mechanical and/or chemical effects of the surface of the vessel material. For example, it can be used for preventing or reducing precipitation and/or clotting or platelet activation of the compound or a component of the composition, for example insulin precipitation or blood clotting or platelet activation.

[110] It can further be used for protecting a compound or composition contained in its interior against the environment outside of the pharmaceutical package or other vessel, for example by preventing or reducing the entry of one or more compounds from the environment surrounding the vessel into the interior space of the vessel. Such environmental compound can be a gas or liquid, for example an atmospheric gas or liquid containing oxygen, air, and/or water vapor.

[111] Referring to the Figures, an aspect of the invention can be a method in which a barrier coating or layer 30 and a passivation layer or pH protective coating 34 are applied directly or indirectly applied to at least a portion of the interior wall 16 of a vessel, such as any of the pharmaceutical packages 210 of FIGS. 7-9, a sample collection tube, for example a blood collection tube and/or a closed-ended sample collection tube; a conduit; a cuvette; or a vessel part, for example a plunger tip, piston, stopper, or seal for contact with and/or storage and/or delivery of a compound or composition.

**Vessel Wall Construction**

[112] Optionally for any of the embodiments of FIGS. 7-9, at least a portion of the internal wall 16 of the pharmaceutical package 210 comprises or consists essentially of a polymer, for example a polyolefin (for example a cyclic olefin polymer, a cyclic olefin copolymer, or polypropylene), a polyester, for example polyethylene terephthalate or polyethylene naphthalate, a polycarbonate, polylactic acid, or any combination, composite or blend of any two or more of the above materials.
Optionally for any of the embodiments of FIGS. 7-9, at least a portion of the internal wall 16 of the pharmaceutical package 210 comprises or consists essentially of glass, for example borosilicate glass.

As an optional feature of any of the foregoing embodiments the polymeric material can be a silicone elastomer or a thermoplastic polyurethane, as two examples, or any material suitable for contact with blood, or with insulin. For example, the use of a coated substrate according to any described embodiment is contemplated for storing insulin.

Optionally, as for the embodiments of FIG. 7, the pharmaceutical package 210 comprises a syringe barrel.

Optionally, the pharmaceutical package comprises a cartridge.

Optionally, as for the embodiments of FIG. 8, the pharmaceutical package 210 comprises a vial.

Optionally, as for the embodiments of FIG. 9, the pharmaceutical package 210 comprises a blister package.

Optionally, the pharmaceutical package comprises an ampoule.

Alternatively, the vessel can be a length of tubing from about 1 cm to about 200 cm, optionally from about 1 cm to about 150 cm, optionally from about 1 cm to about 120 cm, optionally from about 1 cm to about 100 cm, optionally from about 1 cm to about 80 cm, optionally from about 1 cm to about 60 cm, optionally from about 1 cm to about 40 cm, optionally from about 1 cm to about 30 cm long, and processing it with a probe electrode as described below. Particularly for the longer lengths in the above ranges, it is contemplated that relative motion between the PECVD or other chemical vapor deposition probe and the vessel can be useful during passivation layer or pH protective coating formation. This can be done, for example, by moving the vessel with respect to the probe or moving the probe with respect to the vessel.

In these embodiments, it is contemplated that the barrier coating or layer discussed below can be thinner or less complete than would be preferred to provide the high gas barrier integrity needed in an evacuated blood collection tube, and thus the
long shelf life needed to store a liquid material in contact with the barrier coating or layer for an extended period.

[122] As an optional feature of any of the foregoing embodiments the vessel can have a central axis. As an optional feature of any of the foregoing embodiments the vessel wall can be sufficiently flexible to be flexed at least once at 20°C, without breaking the wall, over a range from at least substantially straight to a bending radius at the central axis of not more than 100 times as great as the outer diameter of the vessel.

[123] As an optional feature of any of the foregoing embodiments the bending radius at the central axis can be, for example, not more than 90 times as great as, or not more than 80 times as great as, or not more than 70 times as great as, or not more than 60 times as great as, or not more than 50 times as great as, or not more than 40 times as great as, or not more than 30 times as great as, or not more than 20 times as great as, or not more than 10 times as great as, or not more than 9 times as great as, or not more than 8 times as great as, or not more than 7 times as great as, or not more than 6 times as great as, or not more than 5 times as great as, or not more than 4 times as great as, or not more than 3 times as great as, or not more than 2 times as great as, or not more than the outer diameter of the vessel.

[124] As an optional feature of any of the foregoing embodiments the vessel wall can be a fluid-contacting surface made of flexible material.

[125] As an optional feature of any of the foregoing embodiments the vessel lumen can be the fluid flow passage of a pump.

[126] As an optional feature of any of the foregoing embodiments the vessel can be a blood containing vessel. The passivation layer or pH protective coating can be effective to reduce the clotting or platelet activation of blood exposed to the inner or interior surface, compared to the same type of wall uncoated with a hydrophobic layer.

[127] It is contemplated that the incorporation of a hydrophobic layer will reduce the adhesion or clot forming tendency of the blood, as compared to its properties in contact with an unmodified polymeric or SiOₓ surface. This property is contemplated to reduce or potentially eliminate the need for treating the blood with heparin, as by reducing the necessary blood concentration of heparin in a patient undergoing surgery of a type
requiring blood to be removed from the patient and then returned to the patient, as when using a heart-lung machine during cardiac surgery. It is contemplated that this will reduce the complications of surgery involving the passage of blood through such a pharmaceutical package or other vessel, by reducing the bleeding complications resulting from the use of heparin.

[128] Another embodiment can be a vessel including a wall and having an inner or interior surface defining a lumen. The inner or interior surface can have an at least partial passivation layer or pH protective coating that presents a hydrophobic surface, the thickness of the passivation layer or pH protective coating being from monomolecular thickness to about 1000 nm thick on the inner or interior surface, the passivation layer or pH protective coating being effective to reduce the clotting or platelet activation of blood exposed to the inner or interior surface.

[129] Several non-limiting examples of such a vessel are a blood transfusion bag, a blood sample collection vessel in which a sample has been collected, the tubing of a heart-lung machine, a flexible-walled blood collection bag, or tubing used to collect a patient's blood during surgery and reintroduce the blood into the patient's vasculature. If the vessel includes a pump for pumping blood, a particularly suitable pump can be a centrifugal pump or a peristaltic pump. The vessel can have a wall; the wall can have an inner or interior surface defining a lumen. The inner or interior surface of the wall can have an at least partial passivation layer or pH protective coating of a protective layer, which optionally also presents a hydrophobic surface. The passivation layer or pH protective coating can be as thin as monomolecular thickness or as thick as about 1000 nm. Optionally, the vessel can contain blood viable for return to the vascular system of a patient disposed within the lumen in contact with the hydrophobic layer.

[130] An embodiment can be a blood containing vessel including a wall and having an inner or interior surface defining a lumen. The inner or interior surface can have an at least partial passivation layer or pH protective coating that optionally also presents a hydrophobic surface. The passivation layer or pH protective coating can also comprise or consist essentially of SiO$_x$C$_y$ where x and y are as defined in this specification. The
vessel contains blood viable for return to the vascular system of a patient disposed within the lumen in contact with the hydrophobic coating or layer.

[131] An embodiment can be carried out under conditions effective to form a hydrophobic passivation layer or pH protective coating on the substrate. Optionally, the hydrophobic characteristics of the passivation layer or pH protective coating can be set by setting the ratio of the oxidizing gas to the organosilicon precursor in the gaseous reactant, and/or by setting the electric power used for generating the plasma. Optionally, the passivation layer or pH protective coating can have a lower wetting tension than the uncoated surface, optionally a wetting tension of from 20 to 72 dyne/cm, optionally from 30 to 60 dynes/cm, optionally from 30 to 40 dynes/cm, optionally 34 dyne/cm. Optionally, the passivation layer or pH protective coating can be more hydrophobic than the uncoated surface.

[132] In an optional embodiment, the vessel can have an inner diameter of at least 2 mm, or at least 4 mm.

[133] As an optional feature of any of the foregoing embodiments the vessel can be a tube.

[134] As an optional feature of any of the foregoing embodiments the lumen can have at least two open ends.

**Syringe**

[135] The vessel of FIGS. 1-7 is a syringe, which is a contemplated type of vessel provided with a passivation layer or pH protective coating. The syringe can comprise a syringe barrel 14 and a plunger tip, piston, stopper, or seal 36. The internal wall 16 can define at least a portion of the syringe barrel 250. The plunger tip, piston, stopper, or seal 36 can be a relatively sliding part of the syringe, with respect to the syringe barrel 250. The term "syringe" is broadly defined to include cartridges, injection "pens," and other types of barrels or reservoirs adapted to be assembled with one or more other components to provide a functional syringe. A "syringe" is also broadly defined to include related articles such as auto-injectors, which provide a mechanism for dispensing the contents.
As one non-limiting way to make the syringe, a capped pre-assembly 12 can be provided comprising a barrel 14, a dispensing portion 20, and a shield 28. The capped pre-assembly 12 can be a complete article or it can be a portion of a complete article adapted to dispense fluid, such as a syringe, a cartridge, a catheter, or other article.

The barrel 14 can have an internal wall 16 defining a barrel lumen 18. Optionally in any embodiment, the barrel 14 can further include an opening 32 spaced from the dispensing portion 20 and communicating through the internal wall 16. Such an opening can be conventional, for example, in a syringe or cartridge, where a typical example can be the back opening 32 of a prefilled syringe barrel, through which the plunger tip, piston, stopper, or seal 36 can be inserted after the barrel lumen 18 is filled with a suitable pharmaceutical preparation or other fluid material 40 to be dispensed.

The barrel 14 can be formed, for example, by molding, although the manner of its formation is not critical and it can also be formed, for example, by machining a solid preform. Preferably, the barrel can be molded by injection molding thermoplastic material, although it can also be formed by blow molding or a combined method.

As one preferred example, the barrel 14 can be formed by placing a dispensing portion 20 as described below in an injection mold and injection molding thermoplastic material about the dispensing portion, thus forming the barrel and securing the dispensing portion to the barrel. Alternatively, the dispensing portion and the barrel can be molded or otherwise formed as a single piece, or can be formed separately and joined in other ways. The barrel of any embodiment can be made of any suitable material. Several barrel materials particularly contemplated are COC (cyclic olefin copolymer), COP (cyclic olefin polymer), PET (polyethylene terephthalate), and polypropylene.

The dispensing portion 20 of the capped pre-assembly 12 can be provided to serve as an outlet for fluid dispensed from the barrel lumen 18 of a completed article made from the capped pre-assembly 12. One example of a suitable dispensing portion illustrated in the Figures can be a hypodermic needle 20.
Alternatively, in any embodiment the dispensing portion 20 can instead be a needle-free dispenser. One example of a suitable needle-free dispenser can be a blunt or flexible dispensing portion intended to be received in a complementary coupling to transfer fluid material 40. Such blunt or flexible dispensing portions are well known for use in syringes, intravenous infusion systems, and other systems and equipment to dispense material while avoiding the hazard of working with a sharp needle that may accidentally stick a health professional or other person. Another example of a needle-free dispenser can be a fluid jet or spray injection system that injects a free jet or spray of fluid directly through a patient’s skin, without the need for an intermediate needle. Any type of dispensing portion 20, whether a hypodermic needle or any form of needle-free dispenser, is contemplated for use according to any embodiment of the present invention.

The dispensing portion 20 is or can be secured to the barrel 14 and includes a proximal opening 22, a distal opening 24, and a dispensing portion lumen 26. The proximal opening 22 communicates with the barrel lumen 18. The distal opening 24 can be located outside the barrel 14. The dispensing portion lumen 26 communicates between the proximal and distal openings 22, 24 of the dispensing portion 20. In the illustrated embodiment, the distal opening 24 can be at the sharpened tip of a hypodermic needle 20.

The shield 28 can be secured to the barrel 14 and at least substantially isolates the distal opening 24 of the dispensing portion 20 from pressure conditions outside the shield 28. Optionally in any embodiment, the shield 28 sufficiently isolates portions of the assembly 12 to provide a sufficient bio-barrier to facilitate safe use of the capped pre-assembly 12 for transdermal injections.

The shield 28 can isolate the distal opening 24 in various ways. Effective isolation can be provided at least partially due to contact between the shield 28 and the distal opening 24, as shown in present FIGS. 2, 3, 4, and 7. In the illustrated embodiment, the tip of the dispensing portion 20 can be buried in the material of the shield 28. Alternatively in any embodiment, effective isolation can be provided at least partially due to contact between the shield 28 and the barrel 14, as also shown in
present FIGS. 2, 3, 4, and 7. In the illustrated embodiment, the primary line of contact between the shield 28 and the barrel 14 can be at a rib 42 (best seen in FIG. 3) encircling and seated against a generally cylindrical surface 44 at the nose of the barrel 14. Alternatively in any embodiment, effective isolation can be provided due to both of these types of contact as illustrated in FIGS. 2-3, or in other ways, without limitation.

The shield 28 of any embodiment optionally can have a latching mechanism, best shown in FIG. 3, including a barb 46 and a catch 48 which engage to hold the shield 28 in place. The catch 48 can be made of sufficiently resilient material to allow the shield 28 to be removed and replaced easily.

If the dispensing portion 20 is a hypodermic needle, the shield 28 can be a specially formed needle shield. The original use of a needle shield is to cover the hypodermic needle before use, preventing accidental needle sticks and preventing contamination of the needle before it is injected in a patient or an injection port. A comparable shield preferably is used, even if the dispensing portion 20 is a needle-free dispenser, to prevent contamination of the dispenser during handling.

The shield 28 can be formed in any suitable way. For example, the shield 28 can be formed by molding thermoplastic material. Optionally in any embodiment, the thermoplastic material can be elastomeric material or other material that can be suitable for forming a seal. One suitable category of elastomeric materials is known generically as thermoplastic elastomer (TPE). An example of a suitable thermoplastic elastomer for making a shield 28 is Stelmi® Formulation 4800 (flexible shield formulation). Any other material having suitable characteristics can instead be used in any embodiment.

As another optional feature in any embodiment the shield 28 can be sufficiently permeable to a sterilizing gas to sterilize the portions of the assembly 12 isolated by the shield. One example of a suitable sterilizing gas is ethylene oxide. Shields 28 are available that are sufficiently permeable to the sterilizing gas that parts isolated by the shield can nonetheless be sterilized. An example of a shield formulation sufficiently permeable to accommodate ethylene oxide gas sterilization can be Stelmi® Formulation 4800.
Three embodiments of the invention having many common features are those of FIGS. 7-9. Some of their common features are the following, indicated in many cases by common reference characters or names. The nature of the features of each embodiment can be as described later in the specification.

The pharmaceutical packages of FIGS. 7-9 each include a vessel 210, a fluid composition 40, an SiOₓ barrier coating or layer 30, and a passivation layer or pH protective coating 34. Each vessel 210 can have a lumen 18 defined at least in part by a wall interior portion 16 made of thermoplastic material.

The internal wall 16 can have an interior surface 254 facing the lumen 18 and an outer surface 216.

The fluid composition 40 can be contained in the lumen 18 and can have a pH between 4 and 10, alternatively between 5 and 9.

**Barrier Coating or Layer**

In the filled pharmaceutical package or other vessel 210 the barrier coating or layer 30 can be located between the inner or interior surface of the thermoplastic internal wall 16 and the fluid material 40. The barrier coating or layer 286 of SiOₓ can be supported by the thermoplastic internal wall 16. The barrier coating or layer 286 can have the characteristic of being subject to being measurably diminished in barrier improvement factor in less than six months as a result of attack by the fluid material 40. The barrier coating or layer 286 as described elsewhere in this specification, or in U.S. Patent No. 7,985,188, can be used in any embodiment.

The barrier coating or layer 30 can be effective to reduce the ingress of atmospheric gas into the lumen 18, compared to an uncoated container otherwise the same as the pharmaceutical package or other vessel 210. The barrier coating or layer for any embodiment defined in this specification (unless otherwise specified in a particular instance) is optionally applied by PECVD as indicated in U.S. Pat. No. 7,985,188.

The barrier improvement factor (BIF) of the barrier coating or layer can be determined by providing two groups of identical containers, adding a barrier coating or
layer to one group of containers, testing a barrier property (such as the rate of outgassing in micrograms per minute or another suitable measure) on containers having a barrier coating or layer, doing the same test on containers lacking a barrier coating or layer, and taking a ratio of the properties of the materials with versus without a barrier coating or layer. For example, if the rate of outgassing through the barrier coating or layer is one-third the rate of outgassing without a barrier coating or layer, the barrier coating or layer has a BIF of 3.

[156] The barrier coating or layer optionally can be characterized as an "SiO$_x$" coating, and contains silicon, oxygen, and optionally other elements, in which $x$, the ratio of oxygen to silicon atoms, can be from about 1.5 to about 2.9, or 1.5 to about 2.6, or about 2. These alternative definitions of $x$ apply to any use of the term SiO$_x$ in this specification. The barrier coating or layer can be applied, for example to the interior of a pharmaceutical package or other vessel, for example a sample collection tube, a syringe barrel, a vial, or another type of vessel.

[157] The barrier coating or layer 30 comprises or consists essentially of SiO$_x$, from 2 to 1000 nm thick, the barrier coating or layer 30 of SiO$_x$ having an interior surface facing the lumen 18 and an outer surface facing the internal wall 16. The barrier coating or layer 30 can be effective to reduce the ingress of atmospheric gas into the lumen 18 compared to an uncoated pharmaceutical package 210. One suitable barrier composition can be one where $x$ is 2.3, for example.

[158] For example, the barrier coating or layer such as 30 of any embodiment can be applied at a thickness of at least 2 nm, or at least 4 nm, or at least 7 nm, or at least 10 nm, or at least 20 nm, or at least 30 nm, or at least 40 nm, or at least 50 nm, or at least 100 nm, or at least 150 nm, or at least 200 nm, or at least 300 nm, or at least 400 nm, or at least 500 nm, or at least 600 nm, or at least 700 nm, or at least 800 nm, or at least 900 nm. The barrier coating or layer can be up to 1000 nm, or at most 900 nm, or at most 800 nm, or at most 700 nm, or at most 600 nm, or at most 500 nm, or at most 400 nm, or at most 300 nm, or at most 200 nm, or at most 100 nm, or at most 90 nm, or at most 80 nm, or at most 70 nm, or at most 60 nm, or at most 50 nm, or at most 40 nm, or at most 30 nm, or at most 20 nm, or at most 10 nm, or at most 5 nm thick. Specific
thickness ranges composed of any one of the minimum thicknesses expressed above, plus any equal or greater one of the maximum thicknesses expressed above, are expressly contemplated. The thickness of the SiO<sub>x</sub> 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 passivation layer or pH protective coating described herein can be applied to a variety of pharmaceutical packages or other vessels made from plastic or glass, for example to plastic tubes, vials, and syringes.

**Passivation Layer or pH Protective Coating**

A passivation layer or pH protective coating 34 of SiO<sub>x</sub>C<sub>y</sub> can be applied, for example, by PECVD directly or indirectly to the barrier coating or layer 30 so it can be located between the barrier coating or layer 30 and the fluid material 40 in the finished article. The passivation layer or pH protective coating 34 can have an interior surface facing the lumen 18 and an outer surface facing the interior surface of the barrier coating or layer 30. The passivation layer or pH protective coating 34 can be supported by the thermoplastic internal wall 16. The passivation layer or pH protective coating 34 can be effective to keep the barrier coating or layer 30 at least substantially undissolved as a result of attack by the fluid material 40 for a period of at least six months, in one non-limiting embodiment.

Optionally, the passivation layer or pH protective coating can be composed of Si<sub>w</sub>O<sub>x</sub>C<sub>y</sub>H<sub>z</sub> (or its equivalent SiO<sub>x</sub>C<sub>y</sub>) or Si<sub>w</sub>N<sub>x</sub>C<sub>y</sub>H<sub>z</sub> or its equivalent SiN<sub>x</sub>C<sub>y</sub>, each as defined in this specification. Taking into account the H atoms, the passivation layer or pH protective coating may thus in one aspect have the formula Si<sub>w</sub>O<sub>x</sub>C<sub>y</sub>H<sub>z</sub>, or its equivalent SiO<sub>x</sub>C<sub>y</sub>, 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 (if defined) is from about 2 to about 9.

The atomic ratio can be determined by XPS (X-ray photoelectron spectroscopy). XPS does not detect hydrogen atoms, so it is customary, when determining the atomic ratio by XPS, to omit hydrogen from the stated formulation. The
formulation thus can be typically expressed as \( S_i w O_x Cy \), where \( w \) is 1, \( x \) is from about 0.5 to about 2.4, and \( y \) is from about 0.6 to about 3, with no limitation on \( z \).

[162] The atomic ratios of \( Si, O, \) and \( C \) in the "lubricity and/or passivation layer or pH protective coating" can be, as several options:

[163] \( Si \quad 100 : \quad 0 \quad 50-1 \quad 50 : \quad C \quad 90-200 \quad (i.e. \ w = 1, \ x = 0.5 \ to \ 1.5, \ y = 0.9 \ to \ 2) \);

[164] \( Si \quad 100 : \quad O \quad 70-1 \quad 30 : \quad C \quad 90-200 \quad (i.e. \ w = 1, \ x = 0.7 \ to \ 1.3, \ y = 0.9 \ to \ 2) \);

[165] \( Si \quad 100 : \quad O \quad 80-1 \quad 20 : \quad C \quad 90-150 \quad (i.e. \ w = 1, \ x = 0.8 \ to \ 1.2, \ y = 0.9 \ to \ 1.5) \);

[166] \( Si \quad 100 : \quad O \quad 90-1 \quad 20 : \quad C \quad 90-140 \quad (i.e. \ w = 1, \ x = 0.9 \ to \ 1.2, \ y = 0.9 \ to \ 1.4), \) or

[167] \( Si \quad 100 : \quad O \quad 92-1 \quad 07 : \quad C \quad 116-133 \quad (i.e. \ w = 1, \ x = 0.92 \ to \ 1.07, \ y = 1.16 \ to \ 1.33) \).

[168] Typically, such a coating or layer would contain 36% to 41% carbon normalized to 100% carbon plus oxygen plus silicon. Alternatively, the passivation layer or pH protective coating 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 can be from 25 to 45% carbon, 25 to 65% silicon, and 10 to 35% oxygen. Alternatively, the atomic concentrations can be from 30 to 40% carbon, 32 to 52% silicon, and 20 to 27% oxygen. Alternatively, the atomic concentrations can be from 33 to 37% carbon, 37 to 47% silicon, and 22 to 26% oxygen.

[169] Optionally, the atomic concentration of carbon in the protective 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.

[170] Optionally, the atomic ratio of carbon to oxygen in the passivation layer or pH protective coating 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.
Optionally, the passivation layer or pH protective coating can have an atomic concentration of silicon, normalized to 100% of carbon, oxygen, and silicon, as determined by X-ray photoelectron spectroscopy (XPS), less than the atomic concentration of silicon in the atomic formula for the feed gas. For example, embodiments are contemplated in which the atomic concentration of silicon decreases by from 1 to 80 atomic percent, alternatively by from 10 to 70 atomic percent, alternatively by from 20 to 60 atomic percent, alternatively by from 30 to 55 atomic percent, alternatively by from 40 to 50 atomic percent, alternatively by from 42 to 46 atomic percent.

As another option, a passivation layer or pH protective coating is contemplated that can be characterized by a sum formula wherein the atomic ratio C : O can be increased and/or the atomic ratio Si : O can be decreased in comparison to the sum formula of the organosilicon precursor.

The passivation layer or pH protective coating can have a density between 1.25 and 1.65 g/cm$^3$, alternatively between 1.35 and 1.55 g/cm$^3$, alternatively between 1.4 and 1.5 g/cm$^3$, alternatively between 1.4 and 1.5 g/cm$^3$, alternatively between 1.44 and 1.48 g/cm$^3$, as determined by X-ray reflectivity (XRR). Optionally, the organosilicon compound can be octamethylcyclotetrasiloxane and the passivation layer or pH protective coating can have a density which can be higher than the density of a passivation layer or pH protective coating made from HMDSO as the organosilicon compound under the same PECVD reaction conditions.

The passivation layer or pH protective coating optionally can have an RMS surface roughness value (measured by AFM) of from about 2 to about 9, optionally from about 6 to about 8, optionally from about 6.4 to about 7.8. The $R_a$ surface roughness value of the passivation layer or pH protective coating, measured by AFM, can be from about 4 to about 6, optionally from about 4.6 to about 5.8. The $R_{max}$ surface roughness value of the passivation layer or pH protective coating, measured by AFM, can be from about 70 to about 160, optionally from about 84 to about 142, optionally from about 90 to about 130.
The rate of erosion, dissolution, or leaching (different names for related concepts) of the construction including a passivation layer or pH protective coating 34, if directly contacted by the fluid material 40, can be less than the rate of erosion, dissolution, or leaching of the barrier coating or layer 30, if directly contacted by the fluid material 40.

The passivation layer or pH protective coating 34 can be effective to isolate or protect the barrier coating or layer 30 from the fluid material 40 at least for sufficient time to allow the barrier coating or layer to act as a barrier during the shelf life of the pharmaceutical package or other vessel 210.

Optionally an FTIR absorbance spectrum of the passivation layer or pH protective coating 34 of any embodiment of Figures 7-9 can have 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 assymmetric 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 of the invention of FIGS. 7-9.

Optionally, in any embodiment of Figures 7-9 the passivation layer or pH protective coating, in the absence of the medicament, can have a non-oily appearance. This appearance has been observed in some instances to distinguish an effective passivation layer or pH protective coating from a lubricity layer, which in some instances has been observed to have an oily (i.e. shiny) appearance.

Optionally, in any embodiment of Figures 7-9 the silicon dissolution rate by a 50 mM potassium phosphate buffer diluted in water for injection, adjusted to pH 8 with concentrated nitric acid, and containing 0.2 wt. % polysorbate-80 surfactant, (measured in the absence of the medicament, to avoid changing the dissolution reagent), at 40°C, can be less than 170 ppb/day. (Polysorbate-80 is a common ingredient of pharmaceutical preparations, available for example as Tween®-80 from Uniqema.
Americas LLC, Wilmington Delaware.) As will be seen from the working examples, the silicon dissolution rate can be measured by determining the total silicon leached from the vessel into its contents, and does not distinguish between the silicon derived from the passivation layer or pH protective coating 34, the lubricity layer 287, the barrier coating or layer 30, or other materials present.

Optionally, in any embodiment of Figures 7-9 the silicon dissolution rate can be less than 160 ppb/day, or less than 140 ppb/day, or less than 120 ppb/day, or less than 100 ppb/day, or less than 90 ppb/day, or less than 80 ppb/day. Optionally, in any embodiment of Figures 7-9 the silicon dissolution rate can be more than 10 ppb/day, or more than 20 ppb/day, or more than 30 ppb/day, or more than 40 ppb/day, or more than 50 ppb/day, or more than 60 ppb/day. Any minimum rate stated here can be combined with any maximum rate stated here, as an alternative embodiment of the invention of FIGS. 7-9.

Optionally, in any embodiment of Figures 7-9 the total silicon content of the passivation layer or pH protective coating and barrier coating or layer, upon dissolution into a test composition with a pH of 8 from the vessel, can be less than 66 ppm, or less than 60 ppm, or less than 50 ppm, or less than 40 ppm, or less than 30 ppm, or less than 20 ppm.

Optionally, in any embodiment of Figures 7-9 the calculated shelf life of the package (total Si / Si dissolution rate) can be more than six months, or more than 1 year, or more than 18 months, or more than 2 years, or more than 2½ years, or more than 3 years, or more than 4 years, or more than 5 years, or more than 10 years, or more than 20 years. Optionally, in any embodiment of Figures 7-9 the calculated shelf life of the package (total Si / Si dissolution rate) can be less than 60 years.

Any minimum time stated here can be combined with any maximum time stated here, as an alternative embodiment of the invention of FIGS. 7-9.
O-Parameter or P-Parameters of Passivation Coating or Protective Layer

The passivation layer or pH protective coating optionally can have an O-Parameter measured with attenuated total reflection (ATR) of less than 0.4, measured as:

$$
O-\text{Parameter} = \frac{\text{Intensity at 1253 cm}^{-1}}{\text{Maximum intensity in the range 1000 to 1100 cm}^{-1}}.
$$

The O-Parameter is defined in U.S. Patent No. 8,067,070, which claims an O-parameter value of most broadly from 0.4 to 0.9. It can be measured from physical analysis of an FTIR amplitude versus wave number plot to find the numerator and denominator of the above expression, as shown in Fig. 25, which is the same as Fig. 5 of U.S. Patent No. 8,067,070, except annotated to show interpolation of the wave number and absorbance scales to arrive at an absorbance at 1253 cm$^{-1}$ of .0424 and a maximum absorbance at 1000 to 1100 cm$^{-1}$ of 0.08, resulting in a calculated O-parameter of 0.53. The O-Parameter can also be measured from digital wave number versus absorbance data.

U.S. Patent No. 8,067,070 asserts that its claimed O-parameter range provides a superior passivation layer or pH protective coating, relying on experiments only with HMDSO and HMDSN, which are both non-cyclic siloxanes. Surprisingly, it has been found by the present inventors that if the PECVD precursor is a cyclic siloxane, for example OMCTS, O-parameters outside the ranges claimed in U.S. Patent No. 8,067,070, using OMCTS, can provide better results than are obtained in U.S. Patent No. 8,067,070 with HMDSO.

Alternatively in the embodiment of FIGS. 7-9, the O-parameter can have a value of from 0.1 to 0.39, or from 0.15 to 0.37, or from 0.17 to 0.35.

Even another aspect of the invention can be a composite material as just described, exemplified in FIGS. 7-9, wherein the passivation layer or pH protective coating shows an N-Parameter measured with attenuated total reflection (ATR) of less than 0.7, measured as:

$$
N-\text{Parameter} = \frac{\text{Intensity at 840 cm}^{-1}}{\text{Intensity at 799 cm}^{-1}}.
$$
The N-Parameter is also described in U.S. Patent No. 8,067,070, and can be measured analogously to the O-Parameter except that intensities at two specific wave numbers are used - neither of these wave numbers is a range. U.S. Patent No. 8,067,070 claims a passivation layer or pH protective coating with an N-Parameter of 0.7 to 1.6. Again, the present inventors have made better coatings employing a passivation layer or pH protective coating 34 having an N-Parameter lower than 0.7, as described above. Alternatively, the N-parameter can have a value of 0.3 to lower than 0.7, or from 0.4 to 0.6, or from at least 0.53 to lower than 0.7.

Theory of Operation

The inventors offer the following theory of operation of the passivation layer or pH protective coating described here. The invention is not limited by the accuracy of this theory or to the embodiments predictable by use of this theory.

The dissolution rate of the SiOₓ barrier coating or layer, or of glass, is believed to be dependent on SiO bonding within the layer or glass. Oxygen bonding sites (silanols) are believed to increase the dissolution rate.

It is believed that the OMCTS-based passivation layer or pH protective coating bonds with the silanol sites on the SiOₓ barrier coating or layer, or glass, to "heal" or passivate the SiOₓ surface or glass and thus dramatically reduce the dissolution rate. In this hypothesis, the thickness of the OMCTS layer is not the primary means of protection - the primary means can be passivation of the SiOₓ or glass surface. It is contemplated that a passivation layer or pH protective coating as described in this specification can be improved by increasing the crosslink density of the passivation layer or pH protective coating.

Optional Graded Composite Layers

The passivation layer or pH protective coating 34 and lubricity layers of any embodiment of Figures 7-9 can be either separate layers with a sharp transition or a single, graduated layer that transitions between the passivation layer or pH protective coating 34 and the lubricity layer, without a sharp interface between them. Another
optional expedient contemplated here, for adjacent layers of SiOₓ and a passivation layer or pH protective coating, can be a graded composite of SiOₓ and SiₓOᵧCᵧ, or its equivalent SiOₓCₓ, as defined in the Definition Section.

A graded composite can be separate layers of a lubricity and/or protective and/or barrier coating or layer or coating with a transition or interface of intermediate composition between them, or separate layers of a lubricity and/or protective and/or hydrophobic layer and SiOₓ with an intermediate distinct passivation layer or pH protective coating of intermediate composition between them, or a single coating or layer that changes continuously or in steps from a composition of a lubricity and/or protective and/or hydrophobic layer to a composition more like SiOₓ, going through the passivation layer or pH protective coating in a normal direction.

The grade in the graded composite can go in either direction. For example, the composition of SiOₓ can be applied directly to the substrate and graduate to a composition further from the surface of a passivation layer or pH protective coating, and optionally can further graduate to another type of coating or layer, such as a hydrophobic coating or layer or a lubricity coating or layer. Additionally, in any embodiment an adhesion coating or layer, for example SiₓOₓCᵧ, or its equivalent SiOₓCᵧ, optionally can be applied directly to the substrate before applying the barrier coating or layer.

A graduated passivation layer or pH protective coating is particularly contemplated if a layer of one composition is better for adhering to the substrate than another, in which case the better-adhering composition can, for example, be applied directly to the substrate. It is contemplated that the more distant portions of the graded passivation layer or pH protective coating can be less compatible with the substrate than the adjacent portions of the graded passivation layer or pH protective coating, since at any point the passivation layer or pH protective coating can be changing gradually in properties, so adjacent portions at nearly the same depth of the passivation layer or pH protective coating have nearly identical composition, and more widely physically separated portions at substantially different depths can have more diverse properties. It is also contemplated that a passivation layer or pH protective coating
portion that forms a better barrier against transfer of material to or from the substrate can be directly against the substrate, to prevent the more remote passivation layer or pH protective coating portion that forms a poorer barrier from being contaminated with the material intended to be barred or impeded by the barrier.

The applied coatings or layers, instead of being graded, optionally can have sharp transitions between one layer and the next, without a substantial gradient of composition. Such passivation layer or pH protective coating can be made, for example, by providing the gases to produce a layer as a steady state flow in a non-plasma state, then energizing the system with a brief plasma discharge to form a coating or layer on the substrate. If a subsequent passivation layer or pH protective coating is to be applied, the gases for the previous passivation layer or pH protective coating are cleared out and the gases for the next passivation layer or pH protective coating are applied in a steady-state fashion before energizing the plasma and again forming a distinct layer on the surface of the substrate or its outermost previous passivation layer or pH protective coating, with little if any gradual transition at the interface.

PECVD Apparatus

The low-pressure PECVD process described in U.S. Patent No. 7,985,188 can be used to provide the barrier coating or layer, lubricity coating or layer, and/or passivation layer or pH protective coating described in this specification. A brief synopsis of that process follows, with reference to present FIGS. 4-6.

A PECVD apparatus or coating station 60 suitable for the present purpose includes a vessel holder 50, an inner electrode defined by the probe 108, an outer electrode 160, and a power supply 162. The pre-assembly 12 seated on the vessel holder 50 defines a plasma reaction chamber, which optionally can be a vacuum chamber. Optionally, a source of vacuum 98, a reactant gas source 144, a gas feed (probe 108) or a combination of two or more of these can be supplied.
The PECVD apparatus can be used for atmospheric-pressure PECVD, in which case the plasma reaction chamber defined by the pre-assembly 12 does not need to function as a vacuum chamber.

Referring to FIGS. 4-6, the vessel holder 50 comprises a gas inlet port 104 for conveying a gas into the pre-assembly 12 seated on the opening 82. The gas inlet port 104 can have a sliding seal provided for example by at least one O-ring 106, or two O-rings in series, or three O-rings in series, which can seat against a cylindrical probe 108 when the probe 108 is inserted through the gas inlet port 104. The probe 108 can be a gas inlet conduit that extends to a gas delivery port at its distal end 110. The distal end 110 of the illustrated embodiment can be inserted at an appropriate depth in the pre-assembly 12 for providing one or more PECVD reactants and other precursor feed or process gases.

FIG. 6 shows additional optional details of the coating station 60 that are usable, for example, with all the illustrated embodiments. The coating station 60 can also have a main vacuum valve 574 in its vacuum line 576 leading to the pressure sensor 152. A manual bypass valve 578 can be provided in the bypass line 580. A vent valve 582 controls flow at the vent 404.

Flow out of the PECVD gas or precursor source 144 can be controlled by a main reactant gas valve 584 regulating flow through the main reactant feed line 586. One component of the gas source 144 can be the organosilicon liquid reservoir 588, containing the precursor. The contents of the reservoir 588 can be drawn through the organosilicon capillary line 590, 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 592. Pressure can be applied to the headspace 614 of the liquid reservoir 588, for example a pressure in the range of 0-1.5 psi (0 to 78 cm. Hg), from a pressure source 616 such as pressurized air connected to the headspace 614 by a pressure line 618 to establish repeatable organosilicon liquid delivery that is not dependent on atmospheric pressure (and the fluctuations therein). The reservoir 588 can be sealed and the capillary connection 620 can be at the bottom of the reservoir 588 to ensure that only neat organosilicon liquid (not the pressurized gas from the
headspace 6 1 4) flows through the capillary tube 590. 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 syringe. Preheating can be useful, for example, when feeding OMCTS.

[202] Oxidant gas can be provided from the oxidant gas tank 594 via an oxidant gas feed line 596 controlled by a mass flow controller 598 and provided with an oxidant shut-off valve 600.

[203] Optionally in any embodiment, other precursor, oxidant, and/or carrier gas reservoirs such as 602 can be provided to supply additional materials if needed for a particular deposition process. Each such reservoir such as 602 can have an appropriate feed line 604 and shut-off valve 606.

[204] Referring especially to FIG. 4, the processing station 60 can include an electrode 160 fed by a radio frequency power supply 162 for providing an electric field for generating plasma within the pre-assembly 12 during processing. In this embodiment, the probe 108 can be electrically conductive and can be grounded, thus providing a counter-electrode within the pre-assembly 12. Alternatively, in any embodiment the outer electrode 160 can be grounded and the probe 108 can be directly connected to the power supply 162.

[205] In the embodiment of FIGS. 4-6, the outer electrode 160 can either be generally cylindrical as illustrated in FIGS. 4 and 5 or a generally U-shaped elongated channel as illustrated in FIG. 6 (FIG. 5 being an alternative embodiment of the section taken along section line A—A of FIG. 4). Each illustrated embodiment can have one or more sidewalls, such as 164 and 166, and optionally a top end 168, disposed about the pre-assembly 12 in close proximity.

Application of Barrier Coating or Layer

[206] When carrying out the present method, a barrier coating or layer 30 can be applied directly or indirectly to at least a portion of the internal wall 16 of the barrel 14. In
the illustrated embodiment, the barrier coating or layer 30 can be applied while the pre-
assembly 12 is capped, though this is not a requirement. The barrier coating or layer 30 can be an SiO$_x$ barrier coating or layer applied by plasma enhanced chemical vapor
deposition (PECVD), under conditions substantially as described in U.S. Pat. No.
7,985,188. The barrier coating or layer 30 can be applied under conditions effective to
maintain communication between the barrel lumen 18 and the dispensing portion lumen
26 via the proximal opening 22 at the end of the applying step.
[207]  In any embodiment the barrier coating or layer 30 optionally can be applied
through the opening 32.
[208]  In any embodiment the barrier coating or layer 30 optionally can be applied by
introducing a vapor-phase precursor material through the opening and employing
chemical vapor deposition to deposit a reaction product of the precursor material on the
internal wall of the barrel.
[209]  In any embodiment the precursor material for forming the barrier coating
optionally can be any of the precursors described in U.S. Pat. No. 7,985,188 or in this
specification for formation of the passivating layer or pH protective coating.
[210]  In any embodiment the reactant vapor material optionally can comprise an
oxidant gas.
[211]  In any embodiment the reactant vapor material optionally can comprise
oxygen.
[212]  In any embodiment the reactant vapor material optionally can comprise a
carrier gas.
[213]  In any embodiment the reactant vapor material optionally can include helium,
argon, krypton, xenon, neon, or a combination of two or more of these.
[214]  In any embodiment the reactant vapor material optionally can include argon.
[215]  In any embodiment the reactant vapor material optionally can be a precursor
material mixture with one or more oxidant gases and a carrier gas in a partial vacuum
through the opening and employing chemical vapor deposition to deposit a reaction
product of the precursor material mixture on the internal wall of the barrel.
In any embodiment the reactant vapor material optionally can be passed through the opening at sub-atmospheric pressure.

In any embodiment plasma optionally can be generated in the barrel lumen 18 by placing an inner electrode into the barrel lumen 18 through the opening 32, placing an outer electrode outside the barrel 14 and using the electrodes to apply plasma-inducing electromagnetic energy which optionally can be radio frequency energy, in the barrel lumen 18. If a different arrangement is used, the plasma-inducing electromagnetic energy can be microwave energy or other forms of electromagnetic energy.

In any embodiment the electromagnetic energy optionally can be direct current.

In any embodiment the electromagnetic energy optionally can be alternating current. The alternating current optionally can be modulated at frequencies including audio, or microwave, or radio, or a combination of two or more of audio, microwave, or radio.

In any embodiment the electromagnetic energy optionally can be applied across the barrel lumen (18).

Application of Passivation Layer or pH Protective Coating

In any embodiment, in addition to applying a first coating or layer as described above, the method optionally can include applying second or further coating or layer of the same material or a different material. As one example useful in any embodiment, particularly contemplated if the first coating or layer is an SiO\textsubscript{x} barrier coating or layer, a further coating or layer can be placed directly or indirectly over the barrier coating or layer. One example of such a further coating or layer useful in any embodiment is a passivation layer or pH protective coating 34.
**Precursors**

[222] The organosilicon precursor for any of the processes for forming the barrier coating or layer, the passivation layer or pH protective coating, or a lubricity coating or layer can include any of the following precursors.

[223] The precursor for the passivation layer or pH protective coating of the present invention is broadly defined as an organometallic precursor. An organometallic precursor is defined in this specification as comprehending compounds of metal elements from Group III and/or Group IV of the Periodic Table having organic residues, for example hydrocarbon, aminocarbon or oxycarbon residues. Organometallic compounds as presently defined include any precursor having organic moieties bonded to silicon or other Group III/IV metal atoms directly, or optionally bonded through oxygen or nitrogen atoms. The relevant elements of Group III of the Periodic Table are Boron, Aluminum, Gallium, Indium, Thallium, Scandium, Yttrium, and Lanthanum, Aluminum and Boron being preferred. The relevant elements of Group IV of the Periodic Table are Silicon, Germanium, Tin, Lead, Titanium, Zirconium, Hafnium, and Thorium, with Silicon and Tin being preferred. Other volatile organic compounds can also be contemplated. However, organosilicon compounds are preferred for performing present invention.

[224] An organosilicon precursor is contemplated, where an "organosilicon precursor" is defined throughout this specification most broadly as a compound having at least one of the linkages:

\[
\begin{align*}
\text{O} & \quad \text{Si} \quad \text{C} \quad \text{H} \\
\text{or} & \\
\text{NH} & \quad \text{Si} \quad \text{C} \quad \text{H}
\end{align*}
\]

The first structure immediately above is a tetravalent silicon atom connected to an oxygen atom and an organic carbon atom (an organic carbon atom being a carbon atom
bonded to at least one hydrogen atom). The second structure immediately above is a tetravalent silicon atom connected to an -NH- linkage and an organic carbon atom (an organic carbon atom being a carbon atom bonded to at least one hydrogen atom).

Optionally, the organosilicon precursor can be selected from the group consisting of a linear siloxane, a monocyclic siloxane, a polycyclic siloxane, a polysilsesquioxane, a linear silazane, a monocyclic silazane, a polycyclic silazane, a polysilsesquiazane, and a combination of any two or more of these precursors. Also contemplated as a precursor, though not within the two formulas immediately above, can be an alkyl trimethoxysilane.

If an oxygen-containing precursor (for example a Siloxane) is used, a representative predicted empirical composition resulting from PECVD under conditions forming a hydrophobic or lubricating passivation layer or pH protective coating would be $\text{SiwOxCyHz}$ or its equivalent $\text{SiO}_x\text{C}_y$ as defined in the Definition Section, while a representative predicted empirical composition resulting from PECVD under conditions forming a barrier coating or layer would be $\text{SiO}_x$, where $x$ in this formula is from about 1.5 to about 2.9. If a nitrogen-containing precursor (for example a silazane) is used, the predicted composition would be $\text{S}_{w}^{\text{N}_x^{\text{Cy}}\text{H}_z^{\text{z}}}$, i.e. in $\text{Si}_w\text{OxCyHz}$ or its equivalent $\text{SiO}_x\text{C}_y$ as specified in the Definition Section, $O$ is replaced by $N$ and the indices for $H$ are adapted to the higher valency of $N$ as compared to $O$ (3 instead of 2). The latter adaptation will generally follow the ratio of $w$, $x$, $y$ and $z$ in a Siloxane to the corresponding indices in its aza counterpart. In a particular aspect of the invention, $\text{S}_{w}^{\text{N}_x^{\text{Cy}}\text{H}_z^{\text{z}}}$ (or its equivalent $\text{SiN}_x^{\text{Cy}}\text{y}$) in which $w^+$, $x^+$, $y^+$, and $z^+$ are defined the same as $w$, $x$, $y$, and $z$ for the siloxane counterparts, but for an optional deviation in the number of hydrogen atoms.

One type of precursor starting material having the above empirical formula can be a linear siloxane, for example a material having the following formula:
in which each R can be independently selected from alkyl, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, vinyl, alkyne, or others, and n can be 1, 2, 3, 4, or greater, optionally two or greater. Several examples of contemplated linear siloxanes are hexamethyldisiloxane (HMDSO) (particularly for forming the barrier coating or layer 30 of a vessel), octamethyltrisiloxane, decamethyltetrasiloxane, dodecamethylpentasiloxane, or combinations of two or more of these. The analogous silazanes in which -NH- can be substituted for the oxygen atom in the above structure are also useful for making analogous passivation layers or pH protective coatings or layers. Several examples of contemplated linear silazanes are octamethyltrisilazane, decamethyltetrasilazane, or combinations of two or more of these.

[228] Another type of precursor starting material, among the preferred starting materials in the present context, can be a monocyclic siloxane, for example a material having the following structural formula:
in which $R$ can be defined as for the linear structure and "$a$" can be from 3 to about 10, or the analogous monocyclic silazanes. Several examples of contemplated hetero-substituted and unsubstituted monocyclic siloxanes and silazanes include:

1,3,5-trimethyl-1,3,5-tris(3,3,3-trifluoropropyl)methyl)cyclotrisiloxane
2,4,6,8-tetramethyl-2,4,6,8-tetravinylcyclotetrasiloxane,
pentamethylcyclopentasiloxane,
pentavinypentamethylcyclopentasiloxane,
hexamethylcyclooctasiloxane,
hexaphenylcycloctasiloxane (HMCTS),
octamethylcyclotetrasiloxane (OMCTS),
decamethylcyclopentasiloxane (DMCTS),
2,2,4,4,6,6,8,8-octamethyl-1,5-dimethano-3,7-dioxa-2,4,6,8-tetrasiloxane
octaphenylcyclotetrasiloxane,
decamethylcyclopentasiloxane
dodecamethylcyclohexasiloxane,
methyl(3,3,3-trifluoropropyl)cyclosiloxane,
Cyclic organosilazanes are also contemplated, such as
Octamethylcyclotetrasilazane,
1,3,5,7-tetraethyl-1,3,5,7-tetramethylcyclotetrasilazane hexamethylcycloctasilazane,
octamethylcyclotetrasilazane,
decamethylcyclopentasilazane,
dodecamethylcyclohexasilazane, or combinations of any two or more of these.

[229] Another type of precursor starting material, among the preferred starting materials in the present context, can be a polycyclic siloxane, for example a material having one of the following structural formulas:
in which Y can be oxygen or nitrogen, E is silicon, and Z is a hydrogen atom or an organic substituent, for example alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, vinyl, alkyne, or others. When each Y is oxygen, the respective structures, from left to right, are a Silatrane, a Silquasilatrane, and a Silproatrane. When Y is nitrogen, the respective structures are an azasilatrane, an azasilquasiatrane, and an azasilproatrane.

Another type of polycyclic siloxane precursor starting material, among the preferred starting materials in the present context, can be a polysilsesquioxane, with the empirical formula RSiO$_{1.5}$ and the structural formula:

\[
\begin{array}{c}
\text{T}_8 \text{cube} \\
\end{array}
\]

in which each R is a hydrogen atom or an organic substituent, for example alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, vinyl, alkyne, or others. Two commercial materials of this sort are SST-eM01 poly(methylsilsesquioxane), in which each R can be methyl, and SST-3MH1 poly(Methyl-Hydridosilsesquioxane), in which 90% of the R groups are methyl, 10% are hydrogen atoms. This material is available in
a 10% solution in tetrahydrofuran, for example. Combinations of two or more of these are also contemplated. Other examples of a contemplated precursor are methylsilatrane, CAS No. 2288-13-3, in which each Y is oxygen and Z is methyl, methylazasilatrane, poly(methylsilsesquioxane) (for example SST-eM01 poly(methylsilsesquioxane)), in which each R optionally can be methyl, SST-3MH1.1 poly(Methyl-Hydridosilsesquioxane) (for example SST-3MH1.1 poly(Methyl-Hydridosilsesquioxane)), in which 90% of the R groups are methyl and 10% are hydrogen atoms, or a combination of any two or more of these.

[231] The analogous polysilsesquiazanes in which -NH- can be substituted for the oxygen atom in the above structure are also useful for making analogous passivation layer or pH protective coating. Examples of contemplated polysilsesquiazanes are a poly(methylsilsesquiazane), in which each R can be methyl, and a poly(Methyl-Hydridosilsesquiazane, in which 90% of the R groups are methyl, 10% are hydrogen atoms. Combinations of two or more of these are also contemplated.

[232] One particularly contemplated precursor for the barrier coating or layer according to the present invention can be a linear siloxane, for example hexamethyldisiloxane or HMDSO. One particularly contemplated precursor for the lubricity coating or layer and the passivation layer or pH protective coating according to the present invention can be a cyclic siloxane, for example octamethylcyclotetrasiloxane (OMCTS).

[233] It is believed that the OMCTS or other cyclic siloxane molecule provides several advantages over other siloxane materials. First, its ring structure is believed to result in a less dense passivation layer or pH protective coating (as compared to passivation layer or pH protective coating prepared from HMDSO). The molecule also is believed to allow selective ionization so that the final structure and chemical composition of the passivation layer or pH protective coating can be directly controlled through the application of the plasma power. Other organosilicon molecules are readily ionized (fractured) so that it can be more difficult to retain the original structure of the molecule.
In any of the PECVD methods according to the present invention, the applying step optionally can be carried out by vaporizing the precursor and providing it in the vicinity of the substrate. For example, OMCTS can be vaporized by heating it to about 50°C before applying it to the PECVD apparatus.

Cyclic organosilicon precursors, in particular monocyclic organosilicon precursors (like the monocyclic precursors listed elsewhere in present description), and specifically OMCTS, are particularly suitable to achieve a passivation layer or pH protective coating.

The organosilicon precursor can be delivered at a rate of equal to or less than 10 seem, optionally equal to or less than 6 seem, optionally equal to or less than 2.5 seem, optionally equal to or less than 1.5 seem, optionally equal to or less than 1.25 seem. Larger pharmaceutical packages or other vessels or other changes in conditions or scale may require more or less of the precursor.

Other Components of PECVD Reaction Mixture and Ratios of Components For Passivation Layer or pH Protective Coating

Generally, for a passivation layer or pH protective coating, O₂ can be present in an amount (which can, for example be expressed by the flow rate in seem) which can be less than one order of magnitude greater than the organosilicon amount. In contrast, in order to achieve a barrier coating or layer, the amount of O₂ typically can be at least one order of magnitude higher than the amount of organosilicon precursor.

As some specific examples of suitable proportions of the respective constituents, the volume ratio (in seem) of organosilicon precursor to O₂ for a passivation layer or pH protective coating can be in the range from 0.1 : 1 to 10 : 1, optionally in the range from 0.3 : 1 to 8 : 1, optionally in the range from 0.5 : 1 to 5 : 1, optionally from 1 : 1 to 3 : 1. Some non-exhaustive alternative selections and suitable proportions of the precursor gas, oxygen, and a carrier gas are provided below.

The process gas can contain this ratio of gases for preparing a lubricity and/or passivation layer or pH protective coating:
from 0.5 to 10 standard volumes of the precursor;
from 1 to 100 standard volumes of a carrier gas,
from 0.1 to 10 standard volumes of an oxidizing agent.

alternatively this ratio:
from 1 to 6 standard volumes of the precursor;
from 1 to 80 standard volumes of a carrier gas,
from 0.1 to 2 standard volumes of an oxidizing agent.

alternatively this ratio:
from 2 to 4 standard volumes, of the precursor;
from 1 to 100 standard volumes of a carrier gas,
from 0.1 to 2 standard volumes of an oxidizing agent.

alternatively this ratio:
from 1 to 6 standard volumes of the precursor;
from 3 to 70 standard volumes, of a carrier gas,
from 0.1 to 2 standard volumes of an oxidizing agent.

alternatively this ratio:
from 2 to 4 standard volumes, of the precursor;
from 3 to 70 standard volumes of a carrier gas,
from 0.1 to 2 standard volumes of an oxidizing agent.
alternatively this ratio:

from 1 to 6 standard volumes of the precursor;
from 1 to 100 standard volumes of a carrier gas,
from 0.2 to 1.5 standard volumes of an oxidizing agent.

alternatively this ratio:

from 2 to 4 standard volumes, of the precursor;
from 1 to 100 standard volumes of a carrier gas,
from 0.2 to 1.5 standard volumes of an oxidizing agent.

alternatively this ratio:

from 1 to 6 standard volumes of the precursor;
from 3 to 70 standard volumes of a carrier gas,
from 0.2 to 1.5 standard volumes of an oxidizing agent.

alternatively this ratio:

from 2 to 4 standard volumes of the precursor;
from 3 to 70 standard volumes of a carrier gas,
from 0.2 to 1.5 standard volumes of an oxidizing agent.

alternatively this ratio:

from 1 to 6 standard volumes of the precursor;
from 1 to 100 standard volumes of a carrier gas,
from 0.2 to 1 standard volumes of an oxidizing agent.
alternatively this ratio:

from 2 to 4 standard volumes of the precursor;
from 1 to 100 standard volumes of a carrier gas,
from 0.2 to 1 standard volumes of an oxidizing agent.

alternatively this ratio:

from 1 to 6 standard volumes of the precursor;
from 3 to 70 standard volumes of a carrier gas,
from 0.2 to 1 standard volumes of an oxidizing agent.

alternatively this ratio:

2 to 4 standard volumes, of the precursor;
from 3 to 70 standard volumes of a carrier gas,
from 0.2 to 1 standard volumes of an oxidizing agent.

alternatively this ratio:

from 1 to 6 standard volumes of the precursor;
from 5 to 100 standard volumes of a carrier gas,
from 0.1 to 2 standard volumes of an oxidizing agent.

alternatively this ratio:

from 2 to 4 standard volumes, of the precursor;
from 5 to 100 standard volumes of a carrier gas,
from 0.1 to 2 standard volumes
of an oxidizing agent.
alternatively this ratio:
from 1 to 6 standard volumes of the precursor;
from 10 to 70 standard volumes, of a carrier gas,
from 0.1 to 2 standard volumes of an oxidizing agent.

alternatively this ratio:
from 2 to 4 standard volumes, of the precursor;
from 10 to 70 standard volumes of a carrier gas,
from 0.1 to 2 standard volumes of an oxidizing agent.

alternatively this ratio:
from 1 to 6 standard volumes of the precursor;
from 5 to 100 standard volumes of a carrier gas,
from 0.5 to 1.5 standard volumes of an oxidizing agent.

alternatively this ratio:
from 2 to 4 standard volumes, of the precursor;
from 5 to 100 standard volumes of a carrier gas,
from 0.5 to 1.5 standard volumes of an oxidizing agent.

alternatively this ratio:
from 1 to 6 standard volumes of the precursor;
from 10 to 70 standard volumes, of a carrier gas,
from 0.5 to 1.5 standard volumes of an oxidizing agent.
alternatively this ratio:

from 2 to 4 standard volumes of the precursor;
from 10 to 70 standard volumes of a carrier gas,
from 0.5 to 1.5 standard volumes of an oxidizing agent.

alternatively this ratio:

from 1 to 6 standard volumes of the precursor;
from 5 to 100 standard volumes of a carrier gas,
from 0.8 to 1.2 standard volumes of an oxidizing agent.

alternatively this ratio:

from 2 to 4 standard volumes of the precursor;
from 5 to 100 standard volumes of a carrier gas,
from 0.8 to 1.2 standard volumes of an oxidizing agent.

alternatively this ratio:

from 1 to 6 standard volumes of the precursor;
from 10 to 70 standard volumes of a carrier gas,
from 0.8 to 1.2 standard volumes of an oxidizing agent.

alternatively this ratio:

2 to 4 standard volumes, of the precursor;
from 10 to 70 standard volumes of a carrier gas,
from 0.8 to 1.2 standard volumes of an oxidizing agent.
Exemplary reaction conditions for preparing a passivation layer or pH protective coating according to the present invention in a 3 ml sample size syringe with a 1/8" diameter tube (open at the end) are as follows:

Flow rate ranges:
OMCTS: 0.5 - 10 seem
Oxygen: 0.1 - 10 seem
Argon: 1.0 - 200 seem
Power: 0.1 - 500 watts

In another contemplated embodiment the proportions of precursor, oxygen, and Argon can be, for example:
OMCTS: 0.5 - 5.0 seem
Oxygen: 0.1 - 5.0 seem
Argon: 1.0 - 20 seem

In yet another contemplated embodiment the proportions of precursor, oxygen, and Argon and the power level can be, for example:

Specific Flow rates:
OMCTS: 2.0 seem
Oxygen: 0.7 seem
Argon: 7.0 seem
Power: 3.5 watts

The coatings can vary from the above proportions, however. For example, to provide a coating with lubricity which also serves as a passivation layer or pH protection coating, the following proportions of gases can be used:

- from 0.5 to 10 standard volumes, optionally from 1 to 6 standard volumes,
- optionally from 2 to 4 standard volumes, optionally equal to or less than 6
standard volumes, optionally equal to or less than 2.5 standard volumes, optionally equal to or less than 1.5 standard volumes, optionally equal to or less than 1.25 standard volumes of the precursor, for example OMCTS or one of the other precursors of any embodiment; from 0 to 100 standard volumes, optionally from 1 to 80 standard volumes, optionally from 5 to 100 standard volumes, optionally from 10 to 70 standard volumes, of a carrier gas of any embodiment; from 0.1 to 10 standard volumes, optionally from 0.1 to 2 standard volumes, optionally from 0.2 to 1.5 standard volumes, optionally from 0.2 to 1 standard volumes, optionally from 0.5 to 1.5 standard volumes, optionally from 0.8 to 1.2 standard volumes of an oxidizing agent.

[243] The presence of the precursor and \( O_2 \) in the volume ratios as given in Tables 9-11 can be specifically suitable to achieve a passivation layer or pH protective coating.

[244] In one aspect of the invention, a carrier gas can be absent in the reaction mixture; in another aspect of the invention, it can be present. Suitable carrier gases include any noble gas, for example Argon, Helium, Neon, Xenon or combinations of two or more of these. When the carrier gas is present in the reaction mixture, it is typically present in a volume (in seem) exceeding the volume of the organosilicon precursor. For example, the ratio of the organosilicon precursor to carrier gas can be from 1 : 1 to 1 : 50, optionally from 1 : 5 to 1 : 40, optionally from 1 : 10 to 1 : 30. One function of the carrier gas can be to dilute the reactants in the plasma, encouraging the formation of a coating on the substrate instead of powdered reaction products that do not adhere to the substrate and are largely removed with the exhaust gases.

[245] The addition of Argon gas has been found to improve the performance of the passivation layer or pH protective coating 34. It is believed that additional ionization of the molecule in the presence of Argon contributes to this performance. The Si-O-Si bonds of the molecule have a high bond energy followed by the Si-C, with the C-H bonds being the weakest. Passivation or pH protection appear to be achieved when a portion of the C-H bonds are broken. This allows the connecting (cross-linking) of the
structure as it grows. Addition of oxygen (with the Argon) is understood to enhance this process. A small amount of oxygen can also provide C-O bonding to which other molecules can bond. The combination of breaking C-H bonds and adding oxygen all at low pressure and power leads to a chemical structure that can be solid while providing passivation or pH protection.

[246] In any of the disclosed embodiments, one preferred combination of process gases includes octamethylcyclotetrasiloxane (OMCTS) or another cyclic siloxane as the precursor; O₂, nitrous oxide (N₂O), ozone (O₃), or another oxidizing gas, which means any other gas that oxidizes the precursor during PECVD at the conditions employed, preferably O₂; and a carrier gas, for example a noble carrier gas, for example Argon (Ar). The gaseous reactant or process gas can be at least substantially free of nitrogen. This combination is contemplated to improve the resulting passivation layer or pH protective coating.

**Application Method**

[247] A passivation layer or pH protective coating 34 optionally can be applied directly or indirectly over the barrier coating or layer 30, and optionally can be applied to a pre-assembly such as 12 while the pre-assembly is capped, under conditions effective to maintain communication between the barrel lumen 18 and the dispensing portion lumen 26 via the proximal opening 22 at the end of applying the passivation layer or pH protective coating 34.

**Vessel Made Of Glass**

[248] Optionally in any embodiment, the passivation layer or pH protective coating 34 can be applied as the first or sole vapor-deposited coating or layer 30, instead of or in addition to its application as a further layer. This expedient may be useful, for example, where the barrel is made of glass, as described below. The presently disclosed passivation layer or pH protective coating also can reduce the dissolution of glass by contents having the pH values indicated as attacking SiOₓ coatings or layers.
[249] A pharmaceutical package 210 is contemplated as shown in any embodiment, for example FIGS. 7-9, comprising a vessel or vessel part made of glass; optionally a barrier coating or layer or layer such as 30 on the vessel or vessel part; a passivation layer or pH protective coating such as 34 on the vessel, vessel part, or barrier coating or layer or layer; and a pharmaceutical composition or preparation contained within the vessel.

[250] In this glass embodiment the barrier coating or layer or layer can be optional because a glass vessel wall in itself is an extremely good barrier coating or layer. It is contemplated to optionally provide a barrier coating or layer primarily to provide isolation: in other words, to prevent contact and interchange of material of any kind, such as ions of the glass or constituents of the pharmaceutical composition or preparation between the vessel wall and the contents of the vessel. The protective layer as defined in this specification can be contemplated to perform the isolation function independently, at least to a degree. This passivation coating or pH protection layer can be contemplated to provide a useful function on glass in contact with the pharmaceutical composition or preparation, as the present working examples show that borosilicate glass, commonly used today for pharmaceutical packaging, can be dissolved by a fluid composition having a pH exceeding 5. Particularly in applications where such dissolution can be disadvantageous or perceived to be disadvantageous, the present passivation layers or protective coatings or layers will find utility.

[251] The vessel can be made, for example of glass of any type used in medical or laboratory applications, such as soda-lime glass, borosilicate glass, or other glass formulations. One function of a passivation layer or pH protective coating on a glass vessel can be to reduce the ingress of ions in the glass, either intentionally or as impurities, for example sodium, calcium, or others, from the glass to the contents of the pharmaceutical package or other vessel, such as a reagent or blood in an evacuated blood collection tube. Alternatively, a dual functional protective / lubricity coating or layer can be used on a glass vessel in whole or in part, such as selectively at surfaces contacted in sliding relation to other parts, to provide lubricity, for example to ease the insertion or removal of a stopper or passage of a sliding element such as a piston in a
syringe, as well as to provide the isolation of a passivation layer or pH protective coating. Still another reason to coat a glass vessel, for example with a dual functional hydrophobic and passivation layer or pH protective coating, can be to prevent a reagent or intended sample for the pharmaceutical package or other vessel, such as blood, from sticking to the wall of the vessel or an increase in the rate of coagulation of the blood in contact with the wall of the vessel, as well as to provide the isolation of a passivation layer or pH protective coating.

A related embodiment can be a vessel as described in the previous paragraphs, in which the barrier coating or layer or layer can be made of soda lime glass, borosilicate glass, or another type of glass coating or layer on a substrate.

**Plasma Conditions for Passivation Layer or pH Protective Coating**

The precursor can be contacted with a plasma made by energizing the vicinity of the precursor with electrodes powered at radio frequency, optionally a frequency of 10 kHz to 2.45 GHz, optionally from 10 kHz to less than 300 MHz, optionally from 1 to 50 MHz, optionally from 10 to 15 MHz, alternatively from about 13 to about 14 MHz, optionally at or about 13.56 MHz. Typically, the plasma in the PECVD process can be generated at RF frequency, although microwave or other electromagnetic energy can also be used. For providing a protective layer on the interior of a vessel by a plasma reaction carried out within the vessel, the plasma of any embodiment can be generated with an electric power of from 0.1 to 500 W, optionally from 0.1 to 400 W, optionally from 0.1 to 300 W, optionally from 1 to 250 W, optionally from 1 to 200 W, even optionally from 10 to 150 W, optionally from 20 to 150 W, for example of 40 W, optionally from 40 to 150 W, even optionally from 60 to 150 W.

For any PECVD process in any embodiment herein, PECVD can be initiated by applying an initial higher power level within the stated range, followed by a subsequent lower power level within the stated range. The initial higher power level can be applied, for example, for from 1 to 3 seconds. The subsequent lower power level can applied, for example, for the remainder of PECVD.
For forming a coating intended to provide lubricity in addition to passivation or pH protection, the precursor can be contacted with a plasma made by energizing the vicinity of the precursor with electrodes supplied with electric power at from 0.1 to 25 W, optionally from 1 to 22 W, optionally from 1 to 10 W, even optionally from 1 to 5 W, optionally from 2 to 4 W, for example of 3 W, optionally from 3 to 17 W, even optionally from 5 to 14 W, for example 6 or 7.5 W, optionally from 7 to 11 W, for example of 8 W.

The ratio of the electrode power to the plasma volume can be less than 100 W/ml, optionally can be from 0.1 to 100 W/mL, optionally can be from 5 W/ml to 75 W/ml, optionally can be from 6 W/ml to 60 W/ml, optionally can be from 10 W/ml to 50 W/ml, optionally from 20 W/ml to 40 W/ml. These power levels are suitable for applying passivation layers or protective coatings or layers to syringes and sample tubes and pharmaceutical packages or other vessels of similar geometry having a void volume of 5 ml in which PECVD plasma can be generated. It is contemplated that for larger or smaller objects the power applied, in Watts, should be increased or reduced accordingly to scale the process to the size of the substrate.

For forming a coating intended to provide lubricity in addition to passivation or pH protection, the precursor can be contacted with a plasma made by energizing the vicinity of the precursor with electrodes supplied with electric power density at less than 10 W/ml of plasma volume, alternatively from 6 W/ml to 0.1 W/ml of plasma volume, alternatively from 5 W/ml to 0.1 W/ml of plasma volume, alternatively from 4 W/ml to 0.1 W/ml of plasma volume, alternatively from 2 W/ml to 0.2 W/ml of plasma volume, alternatively from 10 W/ml to 50 W/ml, optionally from 20 W/ml to 40 W/ml.

Optionally, in any embodiment of Figures 7-9 the passivation layer or pH protective coating can be applied by PECVD at a power level per of more than 22,000 kJ/kg of mass of precursor, or more than 30,000 kJ/kg of mass of precursor, or more than 40,000 kJ/kg of mass of precursor, or more than 50,000 kJ/kg of mass of precursor, or more than 60,000 kJ/kg of mass of precursor, or more than 62,000 kJ/kg of mass of precursor, or more than 70,000 kJ/kg of mass of precursor, or more than 80,000 kJ/kg of mass of precursor, or more than 100,000 kJ/kg of mass of precursor, or more than 200,000 kJ/kg of mass of precursor, or more than 300,000 kJ/kg of mass of
precursor, or more than 400,000 kJ/kg of mass of precursor, or more than 500,000 kJ/kg of mass of precursor.

[259] Optionally, in any embodiment of Figures 7-9 the passivation layer or pH protective coating 34 can be applied by PECVD at a power level per of less than 2,000,000 kJ/kg of mass of precursor, or less than 1,000,000 kJ/kg of mass of precursor, or less than 700,000 kJ/kg of mass of precursor, or less than 500,000 kJ/kg of mass of precursor, or less than 100,000 kJ/kg of mass of precursor, or less than 90,000 kJ/kg of mass of precursor, or less than 81,000 kJ/kg of mass of precursor.

[260] For a PECVD process the deposition time can be from 1 to 30 sec, alternatively from 2 to 10 sec, alternatively from 3 to 9 sec. The purposes for optionally limiting deposition time can be to avoid overheating the substrate, to increase the rate of production, and to reduce the use of process gas and its constituents. The purposes for optionally extending deposition time can be to provide a thicker passivation layer or pH protective coating for particular deposition conditions.

[261] Other methods can be used to apply the passivation layer or pH protective coating. 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 layer or pH protective coating treatment is contemplated to be a surface treatment of the SiOₓ barrier coating or layer with HMDZ. It is contemplated that HMDZ will react with the -OH sites that are present in the silicon dioxide coating, resulting in the evolution of NH₃ and bonding of S-(CH₃)₃ to the silicon (it is contemplated that hydrogen atoms will be evolved and bond with nitrogen from the HMDZ to produce NH₃).

[262] It is contemplated that this HMDZ passivation layer or pH protective coating can be accomplished through several possible paths.

[263] One contemplated path can be dehydration/vaporization of the HMDZ at ambient temperature. First, an SiOₓ surface can be deposited, for example using hexamethylene disiloxane (HMDSO). The as-coated silicon dioxide surface then can be reacted with HMDZ vapor. In an embodiment, as soon as the SiOₓ surface is deposited onto the article of interest, the vacuum can be maintained. The HMDSO and
oxygen are pumped away and a base vacuum is achieved. Once base vacuum is achieved, HMDZ vapor can be flowed over the surface of the silicon dioxide (as coated on the part of interest) at pressures from the mTorr range to many Torr. The HMDZ then can be pumped away (with the resulting NH₃ that is a byproduct of the reaction). The amount of NH₃ in the gas stream can be monitored (with a residual gas analyzer -- RGA - as an example) and when there is no more NH₃ detected, the reaction is complete. The part then can be vented to atmosphere (with a clean dry gas or nitrogen). The resulting surface then can be found to have been passivated or protected. It is contemplated that this method optionally can be accomplished without forming a plasma.

[264] Alternatively, after formation of the SiOₓ barrier coating or layer, the vacuum can be broken before dehydration/vaporization of the HMDZ. Dehydration/vaporization of the HMDZ can then be carried out in either the same apparatus used for formation of the SiOₓ barrier coating or layer or different apparatus.

[265] Dehydration/vaporization of HMDZ at an elevated temperature is also contemplated. The above process can alternatively be carried out at an elevated temperature exceeding room temperature up to about 150°C. The maximum temperature can be determined by the material from which the coated part is constructed. An upper temperature should be selected that will not distort or otherwise damage the part being coated.

[266] Dehydration/ vaporization of HMDZ with a plasma assist is also contemplated. After carrying out any of the above embodiments of dehydration/vaporization, once the HMDZ vapor is admitted into the part, plasma can be generated. The plasma power can range from a few watts to 100+ watts (similar powers as used to deposit the SiOₓ). The above is not limited to HMDZ and could be applicable to any molecule that will react with hydrogen, for example any of the nitrogen-containing precursors described in this specification.

[267] Surprisingly, it has been found that the above stated coatings or layers can be applied to the capped pre-assembly 12 with substantially no deposition of the vapor-
deposited coating 30 in the dispensing portion lumen 26. This is shown by a working example below.

[268] In certain embodiments, the generation of uniform plasma throughout the portion of the vessel to be coated is contemplated, as it has been found in certain instances to generate a better passivation layer or pH protective coating. Uniform plasma means regular plasma that does not include a substantial amount of hollow cathode plasma (which has higher emission intensity than regular plasma and can be manifested as a localized area of higher intensity interrupting the more uniform intensity of the regular plasma).

[269] It is further contemplated that any embodiment of the passivation layer or pH protective coating processes described in this specification can also be carried out without using the article to be coated to contain the plasma. For example, external surfaces of medical devices, for example catheters, surgical instruments, closures, and others can be passivated or protected by sputtering the coating, employing a radio frequency target.

**Non-Organosilicon Passivation Layer or pH Protective Coating**

[270] Another way of applying the passivation layer or pH protective coating can be to apply as the passivation layer or pH protective coating an amorphous carbon or fluorinated polymer coating, or a combination of the two.

[271] Amorphous carbon coatings can be formed by PECVD using a saturated hydrocarbon, (e.g. methane, ethane, ethylene or propane), or an unsaturated hydrocarbon (e.g. ethylene, acetylene), or a combination of two or more of these as a precursor for plasma polymerization.

[272] Fluorinated polymer coatings can be applied by chemically modifying a precursor, while on or in the vicinity of the fluid receiving interior surface.

[273] Optionally, the precursor comprises:

- dimeric tetrafluoroparaxylylene,
- difluorocarbene,
- monomeric tetrafluoroethylene,
• oligomeric tetrafluoroethylene having the formula F2C=CF(CF2)xF in which x can be from 1 to 100, optionally 2 to 50, optionally 2-20, optionally 2-10, sodium chlorodifluoroacetate,
• chlorodifluoromethane,
• bromodifluoromethane,
• hexafluoropropylene oxide,
• 1H,1H,2H,2H-perfluorodecyl acrylate (FDA),
• a bromofluoroalkane in which the alkane moiety can have from 1 to 6 carbon atoms,
• an iodofluoroalkane in which the alkane moiety can have from 1 to 6 carbon atoms, or
• a combination of any two or more of these.

[274] The fluorinated polymer is:
• optionally from at least 0.01 micrometer to at most 100 micrometers thick,
• optionally from at least 0.05 micrometers to at most 90 micrometers thick,
• optionally from at least 0.1 micrometers to at most 80 micrometers thick,
• optionally from at least 0.1 micrometers to at most 70 micrometers thick,
• optionally from at least 0.1 micrometers to at most 60 micrometers thick,
• optionally from at least 0.1 micrometers to at most 50 micrometers thick,
• optionally from at least 0.1 micrometers to at most 40 micrometers thick,
• optionally from at least 0.1 micrometers to at most 30 micrometers thick,
• optionally from at least 0.1 micrometers to at most 20 micrometers thick,
• optionally from at least 0.1 micrometers to at most 15 micrometers thick,
• optionally from at least 0.1 micrometers to at most 12 micrometers thick,
• optionally from at least 0.1 micrometers to at most 10 micrometers thick
• optionally from at least 0.1 micrometers to at most 8 micrometers thick,
• optionally from at least 0.1 micrometers to at most 6 micrometers thick,
• optionally from at least 0.1 micrometers to at most 4 micrometers thick,
- optionally from at least 0.1 micrometers to at most 2 micrometers thick,
- optionally from at least 0.1 micrometers to at most 1 micrometers thick,
- optionally from at least 0.1 micrometers to at most 0.9 micrometers thick,
- optionally from at least 0.1 micrometers to at most 0.8 micrometers thick,
- optionally from at least 0.1 micrometers to at most 0.7 micrometers thick,
- optionally from at least 0.1 micrometers to at most 0.6 micrometers thick,
- optionally from at least 0.1 micrometers to at most 0.5 micrometers thick,
- optionally from at least 0.5 micrometers to at most 5 micrometers thick,
- optionally from at least 0.5 micrometers to at most 4 micrometers thick,
- optionally from at least 0.5 micrometers to at most 3 micrometers thick,
- optionally from at least 0.5 micrometers to at most 2 micrometers thick,
- optionally from at least 0.5 micrometers to at most 1 micrometer thick,
- optionally about 10 micrometers thick,
- optionally about 2 micrometers thick.

[275] The fluorinated polymer optionally can be applied by vapor deposition, for example chemical vapor deposition. Optionally, the fluorinated polymer can be applied by chemical vapor deposition of dimeric tetrafluoroparaxylylene. An example of a suitable fluorinated polymer can be polytетrafluoroparaxylylene. Optionally, the fluorinated polymer consists essentially of polytetrafluoroparaxylylene.

[276] Optionally in any embodiment, the fluorinated polymer coating or layer comprises polytetrafluoroethylene. Optionally in any embodiment, the fluorinated polymer coating or layer consists essentially of polytetrafluoroethylene.

[277] For example, in any embodiment, the fluorinated polymer coating or layer can be applied by chemically modifying a precursor, while on or in the vicinity of the fluid receiving interior surface, to produce the fluorinated polymer coating or layer on the fluid receiving interior surface. Optionally in any embodiment, the fluorinated polymer coating or layer can be applied by chemical vapor deposition. For one example, in any embodiment, the fluorinated polymer coating or layer can be applied by heated wire chemical vapor deposition (HWCVD). For another example, in any embodiment, the
fluorinated polymer coating or layer can be applied by plasma enhanced chemical vapor deposition (PECVD). Mixed processes or other processes for applying a suitable coating are also contemplated, in any embodiment.


[279] It is contemplated that that amorphous carbon and/or fluorinated polymer coatings will provide better passivation or protection of an SiO_x barrier coating or layer than a siloxane coating since an amorphous carbon and/or fluorinated polymer coating will not contain silanol bonds.

[280] It is further contemplated that fluorosilicon precursors can be used to provide a passivation layer or pH protective coating over an SiO_x barrier coating or 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.

**Liquid-applied Passivation Layer or pH Protective Coating**

[281] Another example of a suitable barrier or other type of passivation layer or pH protective coating, usable in conjunction with the PECVD-applied passivation layer or pH protective coating or other PECVD treatment as disclosed here, can be a liquid barrier, lubricant, surface energy tailoring, or passivation layer or pH protective coating 90 applied to the inner or interior surface of a pharmaceutical package or other vessel, either directly or with one or more intervening PECVD-applied coatings or layers described in this specification, for example SiO_x, a lubricity coating or layer and/or a passivation layer or pH protective coating, or both.
A suitable liquid barrier, lubricity, or passivation layer or pH protective coating also optionally can be applied, for example, by applying a liquid monomer or other polymerizable or curable material to the inner or interior surface of the vessel and curing, polymerizing, or crosslinking the liquid monomer to form a solid polymer, or by applying a solvent-dispersed polymer to the surface and removing the solvent.

Any of the above methods can include as a step forming a passivation layer or pH protective coating on the interior of a vessel via the vessel port at a processing station or device. One example can be applying a liquid passivation layer or pH protective coating, for example of a curable monomer, prepolymer, or polymer dispersion, to the inner or interior surface 88 of a vessel 80 and curing it to form a film that physically isolates the contents of the vessel from its inner or interior surface. The prior art describes polymer passivation layer or pH protective coating technology as suitable for treating plastic blood collection tubes. For example, the acrylic and polyvinylidene chloride (PVdC) passivation layer or pH protective coating materials and methods described in US Patent 6,165,566, which is hereby incorporated by reference, optionally can be used.

Any of the above methods can also include as a step forming a coating or layer on the exterior outer wall of a vessel. The exterior coating or layer optionally can be a barrier coating or layer or another, optionally an oxygen barrier coating or layer or layer, or optionally a water barrier coating or layer or layer. The exterior coating or layer can also be an armor layer that protects the outer wall of a vessel. One example of a suitable exterior coating or layer can be polyvinylidene chloride, which functions both as a water barrier and an oxygen barrier. Optionally, the exterior coating or layer can be applied as a water-based coating or layer. The exterior coating or layer optionally can be applied by dipping the vessel in it, spraying it on the pharmaceutical package or other vessel, or other expedients.

Yet another coating modality contemplated for protecting or passivating an SiOx barrier coating or layer can be coating the barrier coating or layer using a polyamidoamine epichlorohydrin resin. For example, the barrier coating or layer can be applied by dip coating 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.

[286] 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 an SiO$_x$ barrier coating or 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.

**Fluid Material**

[287] Optionally for any of the embodiments of FIGS. 7-9, the fluid material 40 can have a pH between 5 and 6, optionally between 6 and 7, optionally between 7 and 8, optionally between 8 and 9, optionally between 6.5 and 7.5, optionally between 7.5 and 8.5, optionally between 8.5 and 9.

[288] Optionally for any of the embodiments of FIGS. 7-9, the fluid material 40 can be a liquid at 20°C and ambient pressure at sea level, which is defined as a pressure of 760 mm Hg.

[289] Optionally for any of the embodiments of FIGS. 7-9, the fluid material 40 can be an aqueous liquid.

[290] Optionally for any of the embodiments of FIGS. 7-9, the fluid material 40 comprises a member or a combination of two or more members selected from the group consisting of:

**Inhalation Anesthetics**

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
Xenon

**Injectable Drugs**
Ablavar (Gadofosveset Trisodium Injection)
A barelix Depot
Abobotulinumtoxin A Injection (Dysport)
ABT-263
ABT-869
ABX-EFG
Accrethropin (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-IL1 3
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)
Balin Oil Ampules (Dimercaprol 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-1 023
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 (Maris)
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-1 0 1
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-1 0 1
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 Tartrate
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
Epinephrine
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)
GA1 0 1
Gadobenate Dimeglumine Injection (Multihance)
Gadofosveset Trisodium Injection (Ablavar)
Gadoteridol Injection Solution (ProHance)
Gadoversetamide Injection (OptiMARK)
Gadoxetate Disodium Injection (Eovist)
Ganirelix (Ganirelix Acetate Injection)
Gardasil
GC1 008
GDFD
Gemtuzumab Ozogamicin for Injection (Mylotarg)
Genotropin
Gentamicin Injection
GENZ-1 12638
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)
Maris (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
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 (loversol Injection)
Orencia
Osmiotrol Injection in Aviva (Mannitol Injection in Aviva Plastic Pharmaceutical package 210)
Osmiotrol Injection in Viaflex (Mannitol Injection in Viaflex Plastic Pharmaceutical package 210)
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 Flitop 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 Pharmaceutical package 210)
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)
Recombivax HB
Regadenoson Injection (Lexiscan)
Reglan Injection (Metoclopramide Injection)
Remicade
Renagel
Renvela (Sevelamer Carbonate)
Repronex (Menotropins for Injection)
Retrovir IV (Zidovudine Injection)
rhApo2L/TRAIL
Ringer's and 5% Dextrose Injection (Ringers in Dextrose)
Ringer's Injection (Ringers Injection)
Rituxan
Rituximab
Rocephin (ceftriaxone)
Rocuronium Bromide Injection (Zemuron)
Roferon-A (interferon alfa-2a)
Romazicon (flumazenil)
Romidepsin for Injection (Istodax)
Saizen (Somatropin Injection)
Sandostatin LAR (Octreotide Acetate Injection)
Sclerostin Ab
Sensipar (cinacalcet)
Sensorcaine (Bupivacaine HCl Injections)
Septocaine (Articane HCl and Epinephrine Injection)
Serostim LQ (Somatropin (rDNA origin) Injection)
Simponi Injection (Golimumab Injection)
Sodium Acetate (Sodium Acetate Injection)
Sodium Bicarbonate (Sodium Bicarbonate 5% Injection)
Sodium Lactate (Sodium Lactate Injection in AVIVA)
Sodium Phenylacetate and Sodium Benzoate Injection (Ammonul)
Somatropin (rDNA origin) for Inj (Nutropin)
Sporanox Injection (Itraconazole Injection)
Stelara Injection (Ustekinumab)
Stemgen
Sufenta (Sufentanil Citrate Injection)
Sufentanil Citrate Injection (Sufenta)
Sumavel
Sumatriptan Injection (Alsuma)
Symlin
Symlin Pen
Systemic Hedgehog Antagonist
Synvisc-One (Hylan G-F 20 Single Intra-articular Injection)
Tarceva
Taxotere (Docetaxel for Injection)
Technetium Tc 99m
Telavancin for Injection (Vibativ)
Temsirolimus Injection (Torisel)
Tenormin I.V. Injection (Atenolol Inj)
Teriparatide (rDNA origin) Injection (Forteo)
Testosterone Cypionate
Testosterone Enanthate
Testosterone Propionate
Tev-Tropin (Somatropin, rDNA Origin, for Injection)
tgAAC94
Thallous Chloride
Theophylline
Thiotepa (Thiotepa Injection)
Thymoglobulin (Anti-Thymocyte Globulin (Rabbit)
Thyrogen (Thyrotropin Alfa for Injection)
Ticarcillin Disodium and Clavulanate Potassium Galaxy (Timentin Injection)
Tigan Injection (Trimethobenzamide Hydrochloride Injectable)
Timentin Injection (Ticarcillin Disodium and Clavulanate Potassium Galaxy)
TNKase
Tobramycin Injection (Tobramycin Injection)
Tocilizumab Injection (Actemra)
Torisel (Temsirolimus Injection)
Totect (Dexrazoxane for Injection, Intravenous Infusion Only)
Trastuzumab-DM1
Travasol (Amino Acids (Injection))
Treanda (Bendamustine Hydrochloride Injection)
Trelstar (Triptorelin Pamoate for Injectable Suspension)
Triamcinolone Acetonide
Triamcinolone Diacetate
Triamcinolone Hexacetonide Injectable Suspension (Aristospan Injection 20 mg)
Triesence (Triamcinolone Acetonide Injectable Suspension)
Trimethobenzamide Hydrochloride Injectable (Tigan Injection)
Trimetrexate Glucuronate Inj (Neutrexin)
Triptorelin Pamoate for Injectable Suspension (Trelstar)
Twinject
Trivaris (Triamcinolone Acetonide Injectable Suspension)
Trisenox (Arsenic Trioxide Injection)
Twinrix
Typhoid Vi
Ultravist (lopromide Injection)
Urofollitropin for Injection (Metrodin)
Urokinase Injection (Kinlytic)
Ustekinumab (Stelara Injection)
Ultralente (U)
Valium (diazepam)
Valproate Sodium Injection (Depacon)
Valtropin (Somatropin Injection)
Vancomycin Hydrochloride (Vancomycin Hydrochloride Injection)
Vancomycin Hydrochloride Injection (Vancomycin Hydrochloride)
Vaprisol (Conivaptan Hcl Injection)
VAQTA
Vasovist (Gadofosveset Trisodium Injection for Intravenous Use)
Vectibix (Panitumumab Injection for Intravenous Use)
Venofer (Iron Sucrose Injection)
Verteporfin Inj (Visudyne)
Vibativ (Telavancin for Injection)
Victoza (Liraglutide [rDNA] Injection)
Vimpat (lacosamide Tablet and Injection)
Vinblastine Sulfate (Vinblastine Sulfate Injection)
Vincasar PFS (Vincristine Sulfate Injection)
Victoza
Vincristine Sulfate (Vincristine Sulfate Injection)
Visudyne (Verteporfin Inj)
Vitamin B-12
Vivitrol (Naltrexone XR Inj)
Voluven (Hydroxyethyl Starch in Sodium Chloride Injection)
Xeloda
Xenical (orlistat)
Xeomin (Incobotulinumtoxin A for Injection)
Xolair
Zantac Injection (Ranitidine Hydrochloride Injection)
Zemplar Injection (Paricalcitol Injection Fliptop Vial)
Zemuron (Rocuronium Bromide Injection)
Zenapax (daclizumab)
Zevalin
Zidovudine Injection (Retrovir IV)
Zithromax Injection (Azithromycin)
Zn-DTPA (Pentetate Zinc Trisodium Injection)
Zofran Injection (Ondansetron Hydrochloride Injection)
Zingo
Zoledronic Acid for Inj (Zometa)
Zoledronic Acid Injection (Reclast)
Zometa (Zoledronic Acid for Inj)
Zosyn (Piperacillin and Tazobactam Injection)
Zyprexa Relprevv (Olanzapine Extended Release Injectable Suspension)

**Liquid Drugs (Non-Injectable)**

Ability
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
Aformoterol 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)
Azelaic Acid Hydrochloride Nasal Spray (Astropro)
Azelex (Azelaic Acid Cream)
Azopt (Brinzolamide Ophthalmic Suspension)
Bacteriostatic Saline
Balanced Salt
Bepotastine
Bactroban Nasal
Bactroban
Beclomethasone
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 Ophthalmic 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 (lcodextrin 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)
Kalextra
Lanoxin
Lexiva
Leuprolide Acetate for Depot Suspension (Lupron Depot 11.25 mg)
Levobetaxolol Hydrochloride Ophthalmic Suspension (Betaxon)
Levocarnitine Tablets, Oral Solution, Sugar-Free (Carnitor)
Levofoxacin 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 (Loprednol Etabonate Ophthalmic Suspension)
Loprednol 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)
PENNNSAID (Diclofenac Sodium Topical Solution)
Perforomist (Formoterol Fumarate Inhalation Solution)
Peritoneal Dialysis Solution
Phenylephrine Hydrochloride Ophthalmic Solution (Neo-Synephrine)
Phospholine Iodide (Echotthiophate Iodide for Ophthalmic Solution)
Podofoilox (Podofoilox 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
Serafine
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)
Zymaxid (Gatifloxacin Ophthalmic Solution)

Drug Classes
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
antiarrythmic agents
antiasthmatic combinations
antibiotics/antineoplastics
anticholinergic antiemetics
anticholinergic antiparkinson agents
anticholinergic bronchodilators
anticholinergic chronotropic agents
anticholinergicics/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
antomalarial combinations
antomalarial quinolines
antimetabolites
antimigraine agents
antineoplastic detoxifying agents
antineoplastic interferons
antineoplastic monoclonal antibodies
antineoplastics
antiparkinson agents
antiplatelet agents
antipseudomonal penicillins
antipsoriatrics
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 anhydride inhibitor anticonvulsants
carbonic anhydride 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
genital 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 antimalarial agents
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 anti-histamines 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
vitamins

**Diagnostic Tests**

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)
Alphal -antitrypsin
Alpha-fetoprotein
Alpha-fetoprotein
Ammonia levels
Amylase
ANA (antinuclear antibodies)
ANA (antinuclear antibodies)
Angiotensin-converting enzyme (ACE)
Anion gap
Anticardiolipin antibody
Anticardiolipin antibodies (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)
B 12
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
CH50 Chloride
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 A 1 C
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 (pit)
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)
Widal test

[291] As several examples, the fluid material 40 can be an inhalation anesthetic, a drug, or a diagnostic test material. Any of these fluid materials 40 can be an injectable material, a volatile material capable of being inhaled, or otherwise capable of being introduced into a subject.

Other Uses of the Passivation Layer or pH Protective Coating

[292] A vessel with a passivation layer or pH protective coating as described herein can also be evacuated and stored in an evacuated state. For example, the passivation layer or pH protective coating allows better maintenance of the vacuum in comparison to a corresponding vessel without a passivation layer or pH protective coating. In one aspect of this embodiment, the vessel with a passivation layer or pH protective coating can be a blood collection tube. The tube can also contain an agent for preventing blood clotting or platelet activation, for example EDTA or heparin.

[293] Even another embodiment can be a medical or diagnostic kit including a vessel having a passivation layer or pH protective coating as defined in any embodiment herein on a substrate as defined in any embodiment herein. Optionally, the kit additionally includes a medicament or diagnostic agent as defined in any embodiment herein which is contained in the vessel with a passivation layer or pH protective coating in contact with the coating or layer; and/or a hypodermic needle, double-ended needle, or other delivery conduit; and/or an instruction sheet.

[294] Use of the passivation layer or pH protective coating according to any described embodiment is contemplated for preventing or reducing precipitation and/or clotting or platelet activation of a compound or a component of the composition in contact with the coating or layer.
The use of a coated substrate according to any described embodiment is contemplated for storing insulin. As one option, precipitation of the insulin can be prevented or reduced by providing vessel to contain the insulin having a contact surface including a passivation layer or pH protective coating.

As another option, the compound or a component of the composition can be blood or a blood fraction, and blood clotting or platelet activation can be prevented or reduced by storing the blood in the blood collection tube in contact with a passivation layer or pH protective coating. Optionally, the blood collection tube can contain an agent for preventing blood clotting or platelet activation, for example ethylenediaminetetraacetic acid (EDTA), a sodium salt thereof, or heparin. The blood collection tube can include a passivation layer or pH protective coating for preventing the agent from attacking an SiO\textsubscript{x} barrier coating or layer in the vessel. The use of a coated substrate according to any described embodiment is contemplated for storing blood. Optionally, the stored blood can be viable for return to the vascular system of a patient.

Use of a coating or layer according to any described embodiment can be contemplated as (i) a lubricity coating having a lower frictional resistance than the uncoated surface; and/or (ii) a passivation layer or pH protective coating preventing dissolution of the barrier coating or layer in contact with a fluid, and/or (iii) a hydrophobic layer that can be more hydrophobic than the uncoated surface.

**Measurement of Coating Thickness**

The thickness of a PECVD coating or layer such as the passivation layer or pH protective coating, the barrier coating or layer, the lubricity coating or layer, and/or a composite of any two or more of these layers can be measured, for example, by transmission electron microscopy (TEM). An exemplary TEM image for a lubricity and/or passivation layer or pH protective coating on an SiO\textsubscript{x} barrier coating or layer is shown in Fig. 12. An exemplary TEM image for an SiO\textsubscript{x} barrier coating or layer on a substrate is shown in Fig. 13.
The TEM can be carried out, for example, as follows. Samples can be prepared for Focused Ion Beam (FIB) cross-sectioning in two ways. Either the samples can be first coated with a thin layer of carbon (50-100 nm thick) and then coated with a sputtered coating or layer of platinum (50-100 nm thick) using a K575X Emitech passivation layer or pH protective coating system, or the samples can be coated directly with the protective sputtered Pt layer. The coated samples can be placed in an FEI FIB200 FIB system. An additional coating or layer of platinum can be FIB-deposited by injection of an organometallic gas while rastering the 30kV gallium ion beam over the area of interest. The area of interest for each sample can be chosen to be a location half way down the length of the syringe barrel. Thin cross sections measuring approximately 15 µm ("micrometers") long, 2 µm wide and 15 µm deep can be extracted from the die surface using an in-situ FIB lift-out technique. The cross sections can be attached to a 200 mesh copper TEM grid using FIB-deposited platinum. One or two windows in each section, measuring about 5 µm wide, can be thinned to electron transparency using the gallium ion beam of the FEI FIB.

Cross-sectional image analysis of the prepared samples can be performed utilizing either a Transmission Electron Microscope (TEM), or a Scanning Transmission Electron Microscope (STEM), or both. All imaging data can be recorded digitally. For STEM imaging, the grid with the thinned foils can be transferred to a Hitachi HD2300 dedicated STEM. Scanning transmitted electron images can be acquired at appropriate magnifications in atomic number contrast mode (ZC) and transmitted electron mode (TE). The following instrument settings can be used.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Scanning Transmission Electron Microscope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer/Model</td>
<td>Hitachi HD2300</td>
</tr>
<tr>
<td>Accelerating Voltage</td>
<td>200kV</td>
</tr>
<tr>
<td>Objective Aperture</td>
<td>#2</td>
</tr>
<tr>
<td>Condenser Lens 1 Setting</td>
<td>1.672</td>
</tr>
<tr>
<td>Condenser Lens 2 Setting</td>
<td>1.747</td>
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</tbody>
</table>
### Instrument Table

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Settings</th>
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</thead>
<tbody>
<tr>
<td>Approximate Objective Lens Setting</td>
<td>5.86</td>
</tr>
<tr>
<td>ZC Mode Projector Lens</td>
<td>1.149</td>
</tr>
<tr>
<td>TE Mode Projector Lens</td>
<td>0.7</td>
</tr>
<tr>
<td>Image Acquisition</td>
<td></td>
</tr>
<tr>
<td>Pixel Resolution</td>
<td>1280x960</td>
</tr>
<tr>
<td>Acquisition Time</td>
<td>20 sec. (x4)</td>
</tr>
</tbody>
</table>

For TEM analysis the sample grids can be transferred to a Hitachi HF2000 transmission electron microscope. Transmitted electron images can be acquired at appropriate magnifications. The relevant instrument settings used during image acquisition can be those given below.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Transmission Electron Microscope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer/Model</td>
<td>Hitachi HF2000</td>
</tr>
<tr>
<td>Accelerating Voltage</td>
<td>200 kV</td>
</tr>
<tr>
<td>Condenser Lens 1</td>
<td>0.78</td>
</tr>
<tr>
<td>Condenser Lens 2</td>
<td>0</td>
</tr>
<tr>
<td>Objective Lens</td>
<td>6.34</td>
</tr>
<tr>
<td>Condenser Lens Aperture</td>
<td>#1</td>
</tr>
<tr>
<td>Objective Lens Aperture for imaging</td>
<td>#3</td>
</tr>
<tr>
<td>Selective Area Aperture for SAD</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Basic Protocols for Forming and Coating Syringe Barrels

The pharmaceutical packages or other vessels tested in the subsequent working examples were formed and coated according to the following exemplary protocols, except as otherwise indicated in individual examples. Particular parameter
values given in the following basic protocols, for example the electric power and
gaseous reactant or process gas flow, are typical values. When parameter values were
changed in comparison to these typical values, this will be indicated in the subsequent
working examples. The same applies to the type and composition of the gaseous
reactant or process gas.

[303] In some instances, the reference characters and Figures mentioned in the
following protocols and additional details can be found in U.S. Patent No. 7,985,188.

Protocol for Coating Syringe Barrel Interior with \( \text{SiO}_x \)

[304] The apparatus and protocol generally as found in U.S. Patent No. 7,985,188
were used for coating syringe barrel interiors with an \( \text{SiO}_x \) barrier coating or layer, in
some cases with minor variations. A similar apparatus and protocol were used for
coating vials with an \( \text{SiO}_x \) barrier coating or layer, in some cases with minor variations.

Protocol for Coating Syringe Barrel Interior with OMCTS Passivation Layer or pH
Protective Coating

[305] Syringe barrels already interior coated with a barrier coating or layer of \( \text{SiO}_x \),
as previously identified, are further interior coated with a passivation layer or pH
protective coating as previously identified, generally following the protocols of U.S.
Patent No. 7,985,188 for applying the lubricity coating or layer, except with modified
conditions in certain instances as noted in the working examples. The conditions given
here are for a COC syringe barrel, and can be modified as appropriate for syringe
barrels made of other materials. The apparatus as generally shown in FIG. 4 can be
used to hold a syringe barrel with butt sealing at the base of the syringe barrel.

[306] The syringe barrel is carefully moved into the sealing position over the
extended probe or counter electrode 108 and pushed against a plasma screen. The
plasma screen is fit snugly around the probe or counter electrode 108 insuring good
electrical contact. The probe or counter electrode 108 is grounded to the casing of the
RF matching network.
The gas delivery port 110 is connected to a manual ball valve or similar apparatus for venting, a thermocouple pressure gauge and a bypass valve connected to the vacuum pumping line. In addition, the gas system is connected to the gas delivery port 110 allowing the gaseous reactant or process gas, octamethylcyclotetrasiloxane (OMCTS) (or the specific gaseous reactant or process gas reported for a particular example) to be flowed through the gas delivery port 110 (under process pressures) into the interior of the syringe barrel.

The gas system is comprised of a commercially available heated mass flow vaporization system that heats the OMCTS to about 100°C. The heated mass flow vaporization system is connected to liquid octamethylcyclotetrasiloxane (Alfa Aesar® Part Number A12540, 98%). The OMCTS flow rate is set to the specific organosilicon precursor flow reported for a particular example. To ensure no condensation of the vaporized OMCTS flow past this point, the gas stream is diverted to the pumping line when it is not flowing into the interior of the COC syringe barrel for processing.

Once the syringe barrel is installed, the vacuum pump valve is opened to the vessel holder 50 and the interior of the COC syringe barrel. A vacuum pump and blower comprise the vacuum pump system. The pumping system allows the interior of the COC syringe barrel to be reduced to pressure(s) of less than 100 mTorr while the gaseous reactant or process gases is flowing at the indicated rates.

Once the base vacuum level is achieved, the vessel holder 50 assembly is moved into the electrode 160 assembly. The gas stream (OMCTS vapor) is flowed into the gas delivery port 110 (by adjusting the 3-way valve from the pumping line to the gas delivery port 110. The plasma for PECVD, if used, can be generated at reduced pressure and the reduced pressure can be less than 300 mTorr, optionally less than 200 mTorr, even optionally less than 100 mTorr. Pressure inside the COC syringe barrel can be, as one example, approximately 140 mTorr as measured by a capacitance manometer (MKS) installed on the pumping line near the valve that controls the vacuum. In addition to the COC syringe barrel pressure, the pressure inside the gas delivery port 110 and gas system is also measured with the thermocouple vacuum gauge that is connected to the gas system. This pressure is typically less than 6 Torr.
Once the gas is flowing to the interior of the COC syringe barrel, the RF power supply is turned on to its fixed power level or as otherwise indicated in a specific example or description. The physical and chemical properties of the passivation layer or pH protective coating can be set by setting the ratio of oxidizing gas to the organosilicon precursor in the gaseous reactant, and/or by setting the electric power used for generating the plasma. A 600 Watt RF power supply is used (at 13.56 MHz) at a fixed power level or as otherwise indicated in a specific example or description. The RF power supply is connected to an auto match which matches the complex impedance of the plasma (to be created in the vessel) to the output impedance of the RF power supply. The forward power is as stated and the reflected power is 0 Watts so that the stated power is delivered to the interior of the vessel. The RF power supply is controlled by a laboratory timer and the power on time set to 10 seconds (or a different time stated in a given example).

Upon initiation of the RF power, uniform plasma is established inside the interior of the vessel. The plasma is maintained for the entire passivation layer or pH protective coating time, until the RF power is terminated by the timer. The plasma produces a passivation layer or pH protective coating on the interior of the vessel.

After applying the passivation layer or pH protective coating, the gas flow is diverted back to the vacuum line and the vacuum valve is closed. The vent valve is then opened, returning the interior of the COC syringe barrel to atmospheric pressure (approximately 760 Torr). The treated vessel is then carefully removed from the vessel holder 50 assembly (after moving the vessel holder 50 assembly out of the electrode 160 assembly).

A similar protocol is used, except using apparatus generally like that of FIG. 1, for applying a passivation layer or pH protective coating to vials.

Protocol for Total Silicon Measurement

This protocol is used to determine the total amount of silicon coatings present on the entire vessel wall. A supply of 0.1 N potassium hydroxide (KOH) aqueous solution is prepared, taking care to avoid contact between the solution or ingredients
and glass. The water used is purified water, 18 MΩ quality. A Perkin Elmer Optima Model 7300DV ICP-OES instrument is used for the measurement except as otherwise indicated.

[31.6] Each device (vial, syringe, tube, or the like) to be tested and its cap and crimp (in the case of a vial) or other closure are weighed empty to 0.001 g, then filled completely with the KOH solution (with no headspace), capped, crimped, and reweighed to 0.001 g. In a digestion step, each vial is placed in a sonicating water bath at 40°C for a minimum of 8-10 hours. The digestion step is carried out to quantitatively remove the silicon coatings from the vessel wall into the KOH solution. After this digestion step, the vials are removed from the sonicating water bath and allowed to cool to room temperature. The contents of the vials are transferred into 15 ml ICP tubes. The total Si concentration is run on each solution by ICP/OES following the operating procedure for the ICP/OES.

[31.7] The total Si concentration is reported as parts per billion of Si in the KOH solution. This concentration represents the total amount of silicon coatings that were on the vessel wall before the digestion step was used to remove it.

[31.8] The total Si concentration can also be determined for fewer than all the silicon layers on the vessel, as when an SiOₓ barrier coating or layer is applied, an SiOₓCy second layer (for example, a lubricity layer or a passivation layer or pH protective coating) is then applied, and it is desired to know the total silicon concentration of just the SiOxCy layer. This determination is made by preparing two sets of vessels, one set to which only the SiOₓ layer is applied and the other set to which the same SiOₓ layer is applied, followed by the SiOₓCy layer or other layers of interest. The total Si concentration for each set of vessels is determined in the same manner as described above. The difference between the two Si concentrations is the total Si concentration of the SiOxCy second layer.

**Protocol for Measuring Dissolved Silicon in a Vessel**

[31.9] In some of the working examples, the amount of silicon dissolved from the wall of the vessel by a test solution is determined, in parts per billion (ppb), for example
to evaluate the dissolution rate of the test solution. This determination of dissolved silicon is made by storing the test solution in a vessel provided with an SiO$_x$ and/or SiOxC$_y$ coating or layer under test conditions, then removing a sample of the solution from the vessel and testing the Si concentration of the sample. The test is done in the same manner as the Protocol for Total Silicon Measurement, except that the digestion step of that protocol is replaced by storage of the test solution in the vessel as described in this protocol. The total Si concentration is reported as parts per billion of Si in the test solution.

**Protocol for Determining Average Dissolution Rate**

[320] The average dissolution rates reported in the working examples are determined as follows. A series of test vessels having a known total silicon measurement are filled with the desired test solution analogous to the manner of filling the vials with the KOH solution in the Protocol for Total Silicon Measurement. (The test solution can be a physiologically inactive test solution as employed in the present working examples or a physiologically active pharmaceutical preparation intended to be stored in the vessels to form a pharmaceutical package). The test solution is stored in respective vessels for several different amounts of time, then analyzed for the Si concentration in parts per billion in the test solution for each storage time. The respective storage times and Si concentrations are then plotted. The plots are studied to find a series of substantially linear points having the steepest slope.

[321] The plot of dissolution amount (ppb Si) versus days decreases in slope with time. It is believed that the dissolution rate is not flattening out because the Si layer has been fully digested by the test solution.

[322] For the PC194 test data in Table 10 below, linear plots of dissolution versus time data are prepared by using a least squares linear regression program to find a linear plot corresponding to the first five data points of each of the experimental plots. The slope of each linear plot is then determined and reported as representing the average dissolution rate applicable to the test, measured in parts per billion of Si dissolved in the test solution per unit of time.
Protocol for Determining Calculated Shelf Life

[323] The calculated shelf life values reported in the working examples below are determined by extrapolation of the total silicon measurements and average dissolution rates, respectively determined as described in the Protocol for Total Silicon Measurement and the Protocol for Determining Average Dissolution Rate. The assumption is made that under the indicated storage conditions the SiO_xC_y passivation layer or pH protective coating will be removed at the average dissolution rate until the coating is entirely removed. Thus, the total silicon measurement for the vessel, divided by the dissolution rate, gives the period of time required for the test solution to totally dissolve the SiO_xC_y coating. This period of time is reported as the calculated shelf life. Unlike commercial shelf life calculations, no safety factor is calculated. Instead, the calculated shelf life is the calculated time to failure.

[324] It should be understood that because the plot of ppb Si versus hours decreases in slope with time, an extrapolation from relatively short measurement times to relatively long calculated shelf lives is believed to be a "worst case" test that tends to underestimate the calculated shelf life actually obtainable.

SEM Procedure

[325] SEM Sample Preparation: Each syringe sample was cut in half along its length (to expose the inner or interior surface). The top of the syringe (Luer end) was cut off to make the sample smaller.

[326] The sample was mounted onto the sample holder with conductive graphite adhesive, then put into a Denton Desk IV SEM Sample Preparation System, and a thin (approximately 50 Å) gold passivation layer or pH protective coating was sputtered onto the inner or interior surface of the syringe. The gold passivation layer or pH protective coating is required to eliminate charging of the surface during measurement.

[327] The sample was removed from the sputter system and mounted onto the sample stage of a Jeol JSM 6390 SEM (Scanning Electron Microscope). The sample was pumped down to at least 1 x 10^-6 Torr in the sample compartment. Once the
sample reached the required vacuum level, the slit valve was opened and the sample was moved into the analysis station.

The sample was imaged at a coarse resolution first, then higher magnification images were accumulated. The SEM images provided in the Figures are 5 \textmu m edge-to-edge (horizontal and vertical).

**AFM (Atomic Force Microscopy) Procedure.**

AFM images were collected using a NanoScope III Dimension 3000 machine (Digital Instruments, Santa Barbara, California, USA). The instrument was calibrated against a NIST traceable standard. Etched silicon scanning probe microscopy (SPM) tips were used. Image processing procedures involving auto-flattening, plane fitting or convolution were employed. One 10 \textmu m x 10 \textmu m area was imaged. Roughness analyses were performed and were expressed in: (1) Root-Mean-Square Roughness, RMS; 2 Mean Roughness, Ra; and (3) Maximum Height (Peak-to-Valley), \( R_{\text{max}} \), all measured in nm (see Table 5). For the roughness analyses, each sample was imaged over the 10 \textmu m x 10 \textmu m area, followed by three cross sections selected by the analyst to cut through features in the 10 \textmu m x 10 \textmu m images. The vertical depth of the features was measured using the cross section tool. For each cross section, a Root-Mean-Square Roughness (RMS) in nanometers was reported. These RMS values along with the average of the three cross sections for each sample are listed in Table 5.

Additional analysis of the 10 \textmu m x 10 \textmu m images represented by Examples Q, T and V was carried out. For this analysis three cross sections were extracted from each image. The locations of the cross sections were selected by the analyst to cut through features in the images. The vertical depth of the features was measured using the cross section tool.

The Digital Instruments Nanoscope III AFM/STM acquires and stores 3-dimensional representations of surfaces in a digital format. These surfaces can be analyzed in a variety of ways.

The Nanoscope III software can perform a roughness analysis of any AFM or STM image. The product of this analysis is a single page reproducing the selected
image in top view. To the upper right of the image is the "Image Statistics" box, which lists the calculated characteristics of the whole image minus any areas excluded by a stopband (a box with an X through it). Similar additional statistics can be calculated for a selected portion of the image and these are listed in the "Box Statistics" in the lower right portion of the page. What follows is a description and explanation of these statistics.

[333] Image Statistics:
[334] Z Range (R_p): The difference between the highest and lowest points in the image. The value is not corrected for tilt in the plane of the image; therefore, plane fitting or flattening the data will change the value.
[335] Mean: The average of all of the Z values in the imaged area. This value is not corrected for the tilt in the plane of the image; therefore, plane fitting or flattening the data will change this value.
[336] RMS (R_q): This is the standard deviation of the Z values (or RMS roughness) in the image. It is calculated according to the formula:

\[ R_q = \left( \frac{1}{N} \sum (Z_1 - Z_{avg})^2 \right)^{1/2} \]

where \( Z_{avg} \) is the average Z value within the image; \( Z_1 \) is the current value of Z; and \( N \) is the number of points in the image. This value is not corrected for tilt in the plane of the image; therefore, plane fitting or flattening the data will change this value.
[339] Mean roughness (R_d): This is the mean value of the surface relative to the Center plane and is calculated using the formula:

\[ R_d = \frac{1}{L_x L_y} \int \int f(x,y) \, dx \, dy \]

where \( f(x,y) \) is the surface relative to the Center plane, and \( L_x \) and \( L_y \) are the dimensions of the surface.
[340] Max height (R_{max}): This is the difference in height between the highest and lowest points of the surface relative to the Mean Plane.
[341] Surface area: (Optical calculation): This is the area of the 3-dimensional surface of the imaged area. It is calculated by taking the sum of the areas of the triangles formed by 3 adjacent data points throughout the image.
Surface area diff: (Optional calculation) This is the amount that the Surface area is in excess of the imaged area. It is expressed as a percentage and is calculated according to the formula:

\[ \text{Surface area diff} = 100 \left( \frac{\text{Surface area}}{\text{Si}^2} - 1 \right) \]

where Si is the length (and width) of the scanned area minus any areas excluded by stopbands.

Center Plane: A flat plane that is parallel to the Mean Plane. The volumes enclosed by the image surface above and below the center plane are equal.

Mean Plane: The image data has a minimum variance about this flat plane. It results from a first order least squares fit on the Z data.

**WORKING EXAMPLES**

The working examples follow. While much of the testing is carried out using thermoplastic vessels, instead of glass vessels, and protecting barrier coatings, instead of preventing glass delamination, the testing of the passivation layer or pH protective coating is analogous in either type of vessel.

**Examples A-D**

Syringe samples were produced as follows. A COC 8007 extended barrel syringe was produced according to the Protocol for Forming COC Syringe Barrel. An SiO\textsubscript{x} coating or layer was applied to some of the syringes according to the Protocol for coating COC Syringe Barrel Interior with SiO\textsubscript{x}. A lubricity and/or passivation layer or pH protective coating was applied to the SiO\textsubscript{x} coated syringes according to the Protocol for Coating COC Syringe Barrel Interior with OMCTS Lubricity Coating, modified as follows. The OMCTS was supplied from a vaporizer, due to its low volatility. Argon carrier gas was used. The process conditions were set to the following:

- OMCTS - 3 seem
- Argon gas - 65 seem
- Power - 6 watts
- Time - 10 seconds
The coater was later determined to have a small leak while producing the L2 samples identified in the Table, which resulted in an estimated oxygen flow of 1.0 seem. The L3 samples were produced without introducing oxygen.

Several syringes were then tested for lubricity using a Genesis Packaging Plunger Force Tester (Model SFT-01 Syringe Force Tester, manufactured by Genesis Machinery, Lionville, PA) according to the Protocol for Lubricity Testing. Both the initiation force and maintenance forces (in Newtons) were noted relative to an uncoated sample, and are reported in Table 1.

Syringes coated with silicone oil were included as a reference since this is the current industry standard.

The lubricity coatings produced according to these working examples are also contemplated to function as passivation layers or pH protective coatings or layers to increase the shelf life of the vessels, compared to similar vessels provided with a barrier coating or layer but no lubricity coating or layer.

Examples E-H

Syringe samples were produced as follows. A COC 8007 extended barrel syringe was produced according to the Protocol for Forming COC Syringe Barrel. An SiOx passivation layer or pH protective coating was applied to the syringe barrels according to the Protocol for Coating COC Syringe Barrel Interior with SiOx. A lubricity and/or passivation layer or pH protective coating was applied to the SiOx coated syringes according to the Protocol for Coating COC Syringe Barrel Interior with OMCTS, modified as follows. Argon carrier gas and oxygen were used where noted in Table 2. The process conditions were set to the following, or as indicated in Table 2:

- OMCTS - 3 seem (when used)
- Argon gas -7.8 seem (when used)
- Oxygen 0.38 seem (when used)
- Power - 3 watts
- Power on time - 10 seconds
Syringes E and F prepared under these conditions, Syringes G prepared under these conditions except without a lubricity layer or a passivation layer or pH protective coating, and Syringes H (a commercial syringe coated with silicone oil) were then tested for lubricity using a Genesis Packaging Plunger Force Tester according to the Protocol for Lubricity Testing. Both the initiation force and maintenance forces (in Newtons) were noted relative to an uncoated sample, and are reported in Table 2. Syringes coated with silicone oil were included as a reference since this is the current industry standard.

The lubricity results are shown in Table 2 (Initiation Force and Maintenance Force), illustrating under these test conditions as well that the lubricity and/or passivation layer or pH protective coating on Syringes E and F markedly improved their lubricity compared to Syringes G which lacked any lubricity and/or passivation layer or pH protective coating. The lubricity and/or passivation layer or pH protective coating on Syringes E and F also markedly improved their lubricity compared to Syringes H which contained the standard lubricity coating or layer in the industry.

Syringes E, F, and G were also tested to determine total extractable silicon levels (representing extraction of the organosilicon-based PECVD passivation layer or pH protective coating) using the Protocol for Measuring Dissolved Silicon in a Vessel, modified and supplemented as shown in this example.

The silicon was extracted using saline water digestion. The tip of each syringe plunger tip, piston, stopper, or seal was covered with PTFE tape to prevent extracting material from the elastomeric tip material, then inserted into the syringe barrel base. The syringe barrel was filled with two milliliters of 0.9% aqueous saline solution via a hypodermic needle inserted through the Luer tip of the syringe. This is an appropriate test for extractables because many prefilled syringes are used to contain and deliver saline solution. The Luer tip was plugged with a piece of PTFE beading of appropriate diameter. The syringe was set into a PTFE test stand with the Luer tip facing up and placed in an oven at 50°C for 72 hours.

Then, either a static or a dynamic mode was used to remove the saline solution from the syringe barrel. According to the static mode indicated in Table 2, the
syringe plunger tip, piston, stopper, or seal was removed from the test stand, and the fluid in the syringe was decanted into a vessel. According to the dynamic mode indicated in Table 2, the Luer tip seal was removed and the plunger tip, piston, stopper, or seal was depressed to push fluid through the syringe barrel and expel the contents into a vessel. In either case, the fluid obtained from each syringe barrel was brought to a volume of 50ml using 18.2MQ-cm deionized water and further diluted 2x to minimize sodium background during analysis. The CVH barrels contained two milliliters and the commercial barrels contained 2.32 milliliters.

Next, the fluid recovered from each syringe was tested for extractable silicon using the Protocol for Measuring Dissolved Silicon in a Vessel. The instrument used was a Perkin Elmer Elan DRC II equipped with a Cetac ASX-520 autosampler. The following ICP-MS conditions were employed:

- Nebulizer: Quartz Meinhardt
- Spray Chamber: Cyclonic
- RF (radio frequency) power: 1550 Watts
- Argon (Ar) Flow: 15.0 L/min
- Auxiliary Ar Flow: 1.2 L/min
- Nebulizer Gas Flow: 0.88 L/min
- Integration time: 80 sec
- Scanning mode: Peak hopping
- RPq (The RPq is a rejection parameter) for Cerium as CeO (m/z 156: < 2 %)

Aliquots from aqueous dilutions obtained from Syringes E, F, and G were injected and analyzed for Si in concentration units of micrograms per liter. The results of this test are shown in Table 2. While the results are not quantitative, they do indicate that extractables from the lubricity and/or passivation layer or pH protective coating are not clearly higher than the extractables for the SiOx barrier coating or layer only. Also, the static mode produced far less extractables than the dynamic mode, which was expected.
Examples I-K

[361] Syringe samples I, J, and K, employing three different lubricity and/or passivation layers or pH protective coatings or layers, were produced in the same manner as for Examples E-H except as follows or as indicated in Table 3:
- OMCTS -2.5 seem
- Argon gas -7.6 seem (when used)
- Oxygen 0.38 seem (when used)
- Power - 3 watts
- Power on time - 10 seconds

[362] Syringe I had a three-component passivation layer or pH protective coating employing OMCTS, oxygen, and carrier gas. Syringe J had a two component passivation layer or pH protective coating employing OMCTS and oxygen, but no carrier gas. Syringe K had a one-component passivation layer or pH protective coating (OMCTS only). Syringes I, J, and K were then tested for lubricity as described for Examples E-H.

[363] The lubricity results are shown in Table 3 (Initiation Force and Maintenance Force). Syringe I with a three-component passivation layer or pH protective coating employing OMCTS, oxygen, and carrier gas provided the best lubricity results for both initiation force and maintenance force. Syringe J omitting the carrier gas yielded intermediate results. Syringe K had a one-component passivation layer or pH protective coating (OMCTS only), and provided the lowest lubricity. This example shows that the addition of both a carrier gas and oxygen to the process gas improved lubricity under the tested conditions.

[364] The lubricity coatings produced according to these working examples are also contemplated to function as passivation layers or pH protective coatings or layers to increase the shelf life of the vessels, compared to similar vessels provided with a barrier coating or layer but no lubricity coating or layer.
Examples L-N

[365] Examples L-K using an OMCTS precursor gas were repeated in Examples L-N, except that HMDSO was used as the precursor in Examples L-N. The results are shown in Table 3. The results show that for the tested three-component, two-component, and one-component lubricity coating or layer, the OMCTS passivation layer or pH protective coating provided lower resistance, thus better lubricity, than the HMDSO passivation layer or pH protective coating, demonstrating the value of OMCTS as the precursor gas for lubricity.

[366] The lubricity coatings produced according to these working examples are also contemplated to function as passivation layers or pH protective coatings or layers to increase the shelf life of the vessels, compared to similar vessels provided with a barrier coating or layer but no lubricity coating or layer.

Examples O-Y

[367] In these examples the surface roughness of the lubricity and/or passivation layer or pH protective coating was correlated with lubricity and/or protective performance.

[368] OMCTS lubricity coatings or layers were applied with previously described equipment with the indicated specific process conditions (Table 5) onto one milliliter COC 6013 molded syringe barrels. Plunger force measurements ($F_1$, $F_m$) (Table 5) were performed with previously described equipment under the same protocols. Scanning electron spectroscopy (SEM) photomicrographs (Table 5, Figs. 10 and 11) and atomic force microscopy (AFM) Root Mean Square (RMS) and other roughness determinations (Tables 5 and 6) were made using the procedures indicated below. Average RMS values are taken from three different RMS readings on the surface. The plunger force tests, AFM and SEM tests reported in table 5 were performed on different samples due to the nature of the individual tests which prohibited a performance of all tests on one sample.
Comparison of $F_j/F_m$ to SEM photomicrograph to AFM Average RMS values clearly indicates that lower plunger forces are realized with non-continuous, rougher OMCTS plasma-coated surfaces (cf. Samples O to Q vs. R to V).

Further testing was carried out on sister samples Examples W, X, and Y, respectively made under conditions similar to Example Q, T, and V, to show the $F_j$ and $F_m$ values corresponding to the AFM roughness data. Example W which has a higher surface roughness (compare Example Q in Table 5) has much lower $F_j$ and $F_m$ friction values (Table 6) than Example X or Y. The $F_m$ test shown in Table 6 was interrupted before reaching the measured value of $F_m$ for Examples X and Y because the $F_m$ value was too high.

The lubricity coatings produced according to these working examples are also contemplated to function as passivation layers or pH protective coatings or layers to increase the shelf life of the vessels, compared to similar vessels provided with a barrier coating or layer but no lubricity coating or layer.

**Summary of Lubricity and/or Protective Measurements**

Table 8 shows a summary of the above OMCTS coatings or layers and their $F_j$ and $F_m$ values. It should be understood that the initial lubricity and/or passivation layer or pH protective coating work (C-K; roughness not known) was to identify the lowest possible plunger tip, piston, stopper, or seal advancing force attainable. From subsequent market input, it was determined that the lowest achievable force was not necessarily most desirable, for reasons explained in the generic description (for example premature release). Thus, the PECVD reaction parameters were varied to obtain a plunger tip, piston, stopper, or seal force of practical market use.
Example Z: Lubricity and/or passivation layer or pH protective coating Extractables

[373] Silicon extractables from syringes were measured using ICP-MS analysis as described in the Protocol for Measuring Dissolved Silicon in a Vessel. The syringes were evaluated in both static and dynamic situations. The Protocol for Measuring Dissolved Silicon in a Vessel, modified as follows, describes the test procedure:

[374] · Syringe filled with 2 ml of 0.9% saline solution
[375] · Syringe placed in a stand - stored at 50°C for 72 hours.
[376] · After 72 hours saline solution test for dissolved silicon
[377] · Dissolved silicon measured before and after saline solution expelled through syringe.

[378] The extractable Silicon Levels from a silicone oil coated glass syringe and a Lubricity and/or protective coated and SiO_x coated COC syringe are shown in Table 7. Precision of the ICP-MS total silicon measurement is +/- 3%.

Comparative Example AA: Dissolution of SiO_x Coating Versus pH

[379] The Protocol for Measuring Dissolved Silicon in a Vessel is followed, except as modified here. Test solutions - 50 mM buffer solutions at pH 3, 6, 7, 8, 9, and 12 are prepared. Buffers are selected having appropriate pH values to provide the pH values being studied. A potassium phosphate buffer is selected for pH 3, 7, 8 and 12, a sodium citrate buffer is utilized for pH 6 and tris buffer is selected for pH 9. 3 ml of each test solution is placed in borosilicate glass 5 ml pharmaceutical vials and SiO_x coated 5 ml thermoplastic pharmaceutical vials. The vials are all closed with standard coated stoppers and crimped. The vials are placed in storage at 20 - 25°C and pulled at various time points for inductively coupled plasma spectrometer (ICP) analysis of Si content in the solutions contained in the vials, in parts per billion (ppb) by weight, for different storage times.

[380] The Protocol for Determining Average Dissolution Rate Si content is used to monitor the rate of glass dissolution, except as modified here. The data is plotted to
determine an average rate of dissolution of borosilicate glass or SiO$_x$ coating at each pH condition. Representative plots at pH 6 through 8 are Figs. 14-16.

The rate of Si dissolution in ppb is converted to a predicted thickness (nm) rate of Si dissolution by determining the total weight of Si removed, then using a surface area calculation of the amount of vial surface (11.65 cm$^2$) exposed to the solution and a density of SiO$_x$ of 2.2 g/cm$^3$. FIG. 17 shows the predicted initial thickness of the SiO$_x$ coating required, based on the conditions and assumptions of this example (assuming a residual SiO$_x$ coating of at least 30 nm at the end of the desired shelf life of two years, and assuming storage at 20 to 25°C). As FIG. 17 shows, the predicted initial thickness of the coating is about 36 nm at pH 5, about 80 nm at pH 6, about 230 nm at pH 7, about 400 nm at pH 7.5, about 750 nm at pH 8, and about 2600 nm at pH 9.

The coating thicknesses in FIG. 17 represent atypically harsh case scenarios for pharma and biotech products. Most biotech products and many pharma products are stored at refrigerated conditions and none are typically recommended for storage above room temperature. As a general rule of thumb, storage at a lower temperature reduces the thickness required, all other conditions being equivalent.

The following conclusions are reached, based on this test. First, the amount of dissolved Si in the SiO$_x$ coating or glass increases exponentially with increasing pH. Second, the SiO$_x$ coating dissolves more slowly than borosilicate glass at a pH lower than 8. The SiO$_x$ coating shows a linear, monophasic dissolution over time, whereas borosilicate glass tends to show a more rapid dissolution in the early hours of exposure to solutions, followed by a slower linear dissolution. This may be due to surface accumulation of some salts and elements on borosilicate during the forming process relative to the uniform composition of the SiO$_x$ coating. This result incidentally suggests the utility of an SiO$_x$ coating on the wall of a borosilicate glass vial to reduce dissolution of the glass at a pH lower than 8. Third, PECVD applied barrier coatings or layers for vials in which pharmaceutical preparations are stored will need to be adapted to the specific pharmaceutical preparation and proposed storage conditions (or vice versa), at least in some instances in which the pharmaceutical preparation interacts with the barrier coating or layer significantly.
Example BB

[384] An experiment is conducted with vessels coated with SiO$_x$ coating + OMCTS lubricity layer, to test the lubricity layer for its functionality as a passivation layer or pH protective coating. The vessels are 5 mL vials (the vials are normally filled with product to 5 mL; their capacity without headspace, when capped, is about 7.5 mL) composed of cyclic olefin co-polymer (COC, Topas® 601 3M-07).

[385] Sixty vessels are coated on their interior surfaces with an SiO$_x$ coating produced in a plasma enhanced chemical vapor deposition (PECVD) process using a HMDSO precursor gas according to the Protocol for Coating Tube Interior with SiO$_x$ set forth above, except that equipment suitable for coating a vial is used. The following conditions are used.

- HMDSO flow rate: 0.47 seem
- Oxygen flow rate: 7.5 seem
- RF power: 70 Watts
- Coating time: 12 seconds (includes a 2-sec RF power ramp-up time)

[386] Next the SiO$_x$ coated vials are coated over the SiO$_x$ with an SiO$_x$C$_y$ coating produced in a PECVD process using an OMCTS precursor gas according to the Protocol for Coating COC Syringe Barrel Interior with OMCTS Lubricity Coating set forth above, except that the same coating equipment is used as for the SiO$_x$ coating. Thus, the special adaptations in the protocol for coating a syringe are not used. The following conditions are used.

- OMCTS flow rate: 2.5 seem
- Argon flow rate: 10 seem
- Oxygen flow rate: 0.7 seem
- RF power: 3.4 Watts
- Coating time: 5 seconds
Eight vials are selected and the total deposited quantity of PECVD coating (SiO_x + SiO_{x+y}) is determined with a Perkin Elmer Optima Model 7300DV ICP-OES instrument, using the Protocol for Total Silicon Measurement set forth above. This measurement determines the total amount of silicon in both coatings, and does not distinguish between the respective SiO_x and SiO_xC_y coatings. The results are shown below.

<table>
<thead>
<tr>
<th>Vial</th>
<th>Total Silicon ug/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13844</td>
</tr>
<tr>
<td>2</td>
<td>14878</td>
</tr>
<tr>
<td>3</td>
<td>14387</td>
</tr>
<tr>
<td>4</td>
<td>13731</td>
</tr>
<tr>
<td>5</td>
<td>15260</td>
</tr>
<tr>
<td>6</td>
<td>15017</td>
</tr>
<tr>
<td>7</td>
<td>15118</td>
</tr>
<tr>
<td>8</td>
<td>12736</td>
</tr>
<tr>
<td>Mean</td>
<td>14371</td>
</tr>
<tr>
<td>StdDev</td>
<td>877</td>
</tr>
</tbody>
</table>

*Quantity of SiO_x + Lubricity layer on Vials*

In the following work, except as indicated otherwise in this example, the Protocol for Determining Average Dissolution Rate is followed. Two buffered pH test solutions are used in the remainder of the experiment, respectively at pH 4 and pH 8 to test the effect of pH on dissolution rate. Both test solutions are 50 mM buffers using potassium phosphate as the buffer, diluted in water for injection (WFI) (0.1 um sterilized, filtered). The pH is adjusted to pH 4 or 8, respectively, with concentrated nitric acid.

25 vials are filled with 7.5 ml per vial of pH 4 buffered test solution and 25 other vials are filled with 7.5 ml per vial of pH 4 buffered test solution (note the fill level is to the top of the vial - no head space). The vials are closed using prewashed butyl stoppers and aluminum crimps. The vials at each pH are split into two groups. One group at each pH containing 12 vials is stored at 4°C and the second group of 13 vials is stored at 23°C.

The vials are sampled at Days 1, 3, 6, and 8. The Protocol for Measuring Dissolved Silicon in a Vessel is used, except as otherwise indicated in this example.
The analytical result is reported on the basis of parts per billion of silicon in the buffered test solutions of each vial. A dissolution rate is calculated in terms of parts per billion per day as described above in the Protocol for Determining Average Dissolution Rate. The results at the respective storage temperatures follow:

<table>
<thead>
<tr>
<th>Shelf Life Conditions 23°C</th>
<th>Vial SiOx + Lubricity Coating at pH 4</th>
<th>Vial SiOx + Lubricity Coating at pH 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si Dissolution Rate (PPB/day)</td>
<td>31</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Shelf Life Conditions 4°C</th>
<th>Vial SiOx + Lubricity Coating at pH 4</th>
<th>Vial SiOx + Lubricity Coating at pH 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si Dissolution Rate (PPB/day)</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>

The observations of Si dissolution versus time for the OMCTS-based coating at pH8 and pH 4 indicate the pH 4 rates are higher at ambient conditions. Thus, the pH 4 rates are used to determine how much material would need to be initially applied to leave a coating of adequate thickness at the end of the shelf life, taking account of the amount of the initial coating that would be dissolved. The results of this calculation are:

<table>
<thead>
<tr>
<th>Vial with SiOx + Lubricity Coating at pH 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si Dissolution Rate (PPB/day)</td>
</tr>
<tr>
<td>Mass of Coating Tested (Total Si)</td>
</tr>
<tr>
<td>Shelf Life (days) at 23°C</td>
</tr>
<tr>
<td>Shelf Life (years) at 23°C</td>
</tr>
<tr>
<td>Required Mass of Coating (Total Si) -- 2-years</td>
</tr>
<tr>
<td>Required Mass of Coating (Total Si) -- 3-years</td>
</tr>
</tbody>
</table>

*Shelf Life Calculation*
Based on this calculation, the OMCTS lubricity layer needs to be about 2.5 times thicker - resulting in dissolution of 33945 ppb versus the 14,371 ppb representing the entire mass of coating tested - to achieve a 3-year calculated shelf life.

**Example CC**

The results of Comparative Example AA and Example BB above can be compared as follows, where the "lubricity layer" is the coating of SiO$_x$C$_y$ referred to in Example BB.

<table>
<thead>
<tr>
<th>Si Dissolution Rate (PPB/day)</th>
<th>Shelf Life Conditions -- pH 8 and 23° C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vial with SiOx</td>
</tr>
<tr>
<td>1,250</td>
<td>7</td>
</tr>
</tbody>
</table>

This data shows that the silicon dissolution rate of SiO$_x$ alone is reduced by more than 2 orders of magnitude at pH 8 in vials also coated with SiO$_x$C$_y$ coatings.

Another comparison is shown by the following data from several different experiments carried out under similar accelerated dissolution conditions, of which the 1-day data is also presented in Fig. 18.

<table>
<thead>
<tr>
<th>Silicon Dissolution with pH 8 at 40°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ug/L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vial Coating Description</th>
<th>1 day</th>
<th>2 days</th>
<th>3 days</th>
<th>4 days</th>
<th>7 days</th>
<th>10 days</th>
<th>15 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. SiO$_x$ made with HMDSO Plasma + Si$_w$O$_x$C$_y$ or its equivalent SiO$_x$C$_y$ made</td>
<td>165</td>
<td>211</td>
<td>226</td>
<td>252</td>
<td>435</td>
<td>850</td>
<td>1,364</td>
</tr>
<tr>
<td>Vial Coating Description</td>
<td>1 day</td>
<td>2 days</td>
<td>3 days</td>
<td>4 days</td>
<td>7 days</td>
<td>10 days</td>
<td>15 days</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>with OMCTS Plasma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. SiwOxCy Or its equivalent SiOxCy made with OMCTS Plasma</td>
<td>109</td>
<td>107</td>
<td>76</td>
<td>69</td>
<td>74</td>
<td>158</td>
<td>198</td>
</tr>
<tr>
<td>C. SiOx made with HMDSO Plasma</td>
<td>2,504</td>
<td>4,228</td>
<td>5,226</td>
<td>5,650</td>
<td>9,292</td>
<td>10,177</td>
<td>9,551</td>
</tr>
<tr>
<td>D. SiOx made with HMDSO Plasma + SiwOxCy or its equivalent SiOxCy made with HMDSO Plasma</td>
<td>1,607</td>
<td>1,341</td>
<td>3,927</td>
<td>10,182</td>
<td>18,148</td>
<td>20,446</td>
<td>21,889</td>
</tr>
<tr>
<td>E. SiwOxCy Or its equivalent SiOxCy made with HMDSO Plasma</td>
<td>1,515</td>
<td>1,731</td>
<td>1,813</td>
<td>1,743</td>
<td>2,890</td>
<td>3,241</td>
<td>3,812</td>
</tr>
</tbody>
</table>

[396] Fig. 18 and Row A (SiOₓ with OMCTS coating) versus C (SiOₓ without OMCTS coating) show that the OMCTS lubricity layer is also an effective passivation
layer or pH protective coating to the SiO_x coating at pH 8. The OMCTS coating reduced the one-day dissolution rate from 2504 ug/L ("u" or μ or the Greek letter "mu" as used herein are identical, and are abbreviations for "micro") to 165 ug/L. This data also shows that an HMDSO-based Si_wO_xC_y (or its equivalent SiO_xC_y) overcoat (Row D) provided a far higher dissolution rate than an OMCTS-based Si_wO_xC_y (or its equivalent SiO_xC_y) overcoat (Row A). This data shows that a substantial benefit can be obtained by using a cyclic precursor versus a linear one.

Example DD

[397] Samples 1-6 as listed in Table 9 were prepared as described in Example AA, with further details as follows.

[398] A cyclic olefin copolymer (COC) resin was injection molded to form a batch of 5ml vials. Silicon chips were adhered with double-sided adhesive tape to the internal walls of the vials. The vials and chips were coated with a two layer coating by plasma enhanced chemical vapor deposition (PECVD). The first layer was composed of SiO_x with barrier coating or layer properties as defined in the present disclosure, and the second layer was an SiO_xC_y passivation layer or pH protective coating.

[399] A precursor gas mixture comprising OMCTS, argon, and oxygen was introduced inside each vial. The gas inside the vial was excited between capacitively coupled electrodes by a radio-frequency (13.56 MHz) power source as described in connection with FIGS. 4-6. The monomer flow rate (F_m) in units of seem, oxygen flow rate (F_o) in units of seem, argon flowrate in seem, and power (W) in units of watts are shown in Table 9.

[400] A composite parameter, W/FM in units of kJ/kg, was calculated from process parameters W, F_m, F_o and the molecular weight, M in g/mol, of the individual gas species. W/FM is defined as the energy input per unit mass of polymerizing gases. Polymerizing gases are defined as those species that are incorporated into the growing coating such as, but not limited to, the monomer and oxygen. Non-polymerizing gases, by contrast, are those species that are not incorporated into the growing coating, such as but not limited to argon, helium and neon.
In this test, PECVD processing at high W/FM is believed to have resulted in higher monomer fragmentation, producing organosiloxane coatings with higher cross-link density. PECVD processing at low W/FM, by comparison, is believed to have resulted in lower monomer fragmentation producing organosiloxane coatings with a relatively lower cross-link density.

The relative cross-link density of samples 5, 6, 2, and 3 was compared between different coatings by measuring FTIR absorbance spectra. The spectra of samples 5, 6, 2, and 3 are provided in Figs. 21-24. In each spectrum, the ratio of the peak absorbance at the symmetric stretching mode (1000-1040 cm⁻¹) versus the peak absorbance at the asymmetric stretching mode (1060-1100 cm⁻¹) of the Si-O-Si bond was measured, and the ratio of these two measurements was calculated, all as shown in Table 9. The respective ratios were found to have a linear correlation to the composite parameter W/FM as shown in Figs. 19 and 20.

A qualitative relation - whether the coating appeared oily (shiny, often with iridescence) or non-oily (non-shiny) when applied on the silicon chips - was also found to correlate with the W/FM values in Table 9. Oily appearing coatings deposited at lower W/FM values, as confirmed by Table 9, are believed to have a lower crosslink density, as determined by their lower sym/asym ratio, relative to the non-oily coatings that were deposited at higher W/FM and a higher cross-link density. The only exception to this general rule of thumb was sample 2 in Table 9. It is believed that the coating of sample 2 exhibited a non-oily appearance because it was too thin to see. Thus, an oilyness observation was not reported in Table 9 for sample 2. The chips were analyzed by FTIR in transmission mode, with the infrared spectrum transmitted through the chip and sample coating, and the transmission through an uncoated null chip subtracted.

Non-oily organosiloxane layers produced at higher W/FM values, which protect the underlying SiOₓ coating from aqueous solutions at elevated pH and temperature, were preferred because they provided lower Si dissolution and a longer shelf life, as confirmed by Table 9. For example, the calculated silicon dissolution by contents of the vial at a pH of 8 and 40°C was reduced for the non-oily coatings, and the
resulting shelf life was 1381 days in one case and 1147 days in another, as opposed to the much shorter shelf lives and higher rates of dissolution for oily coatings. Calculated shelf life was determined as shown for Example AA. The calculated shelf life also correlated linearly to the ratio of symmetric to asymmetric stretching modes of the Si-O-Si bond in organosiloxane passivation layers or pH protective coatings.

[405] Sample 6 can be particularly compared to Sample 5. An organosiloxane, pH passivation layer or pH protective coating was deposited according to the process conditions of sample 6 in Table 9. The coating was deposited at a high W/FM. This resulted in a non-oily coating with a high Si-O-Si sym/asym ratio of 0.958, which resulted in a low rate of dissolution of 84.1 ppb/day (measured by the Protocol for Determining Average Dissolution Rate) and long shelf life of 1147 days (measured by the Protocol for Determining Calculated Shelf Life). The FTIR spectra of this coating is shown in Figure 35, which exhibits a relatively similar asymmetric Si-O-Si peak absorbance compared to the symmetric Si-O-Si peak absorbance. This is an indication of a higher cross-link density coating, which is a preferred characteristic for pH protection and long shelf life.

[406] An organosiloxane pH passivation layer or pH protective coating was deposited according to the process conditions of sample 5 in Table 9. The coating was deposited at a moderate W/FM. This resulted in an oily coating with a low Si-O-Si sym/asym ratio of 0.673, which resulted in a high rate of dissolution of 236.7 ppb/day (following the Protocol for Determining Average Dissolution Rate) and shorter shelf life of 271 days (following the Protocol for Determining Calculated Shelf Life). The FTIR spectrum of this coating is shown in FIG. 21, which exhibits a relatively high asymmetric Si-O-Si peak absorbance compared to the symmetric Si-O-Si peak absorbance. This is an indication of a lower cross-link density coating, which is contemplated to be an unfavorable characteristic for pH protection and long shelf life.

[407] Sample 2 can be particularly compared to Sample 3. A passivation layer or pH protective coating was deposited according to the process conditions of sample 2 in Table 9. The coating was deposited at a low W/FM. This resulted in a coating that exhibited a low Si-O-Si sym/asym ratio of 0.582, which resulted in a high rate of
dissolution of 174ppb/day and short shelf life of 107 days. The FTIR spectrum of this coating is shown in Figure 36, which exhibits a relatively high asymmetric Si-O-Si peak absorbance compared to the symmetric Si-O-Si peak absorbance. This is an indication of a lower cross-link density coating, which is an unfavorable characteristic for pH protection and long shelf life.

[408] An organosiloxane, pH passivation layer or pH protective coating was deposited according to the process conditions of sample 3 in Table 9. The coating was deposited at a high W/FM. This resulted in a non-oily coating with a high Si-O-Si sym/asym ratio of 0.947, which resulted in a low rate of Si dissolution of 79.5ppb/day (following the Protocol for Determining Average Dissolution Rate) and long shelf life of 1381 days (following the Protocol for Determining Calculated Shelf Life). The FTIR spectrum of this coating is shown in Figure 37, which exhibits a relatively similar asymmetric Si-O-Si peak absorbance compared to the symmetric Si-O-Si peak absorbance. This is an indication of a higher cross-link density coating, which is a preferred characteristic for pH protection and long shelf life.

Example EE

[409] An experiment similar to Example BB was carried out, modified as indicated in this example and in Table 10 (where the results are tabulated). 100 5 mL COP vials were made and coated with an SiOx barrier coating or layer and an OMCTS-based passivation layer or pH protective coating as described previously, except that for Sample PC1.94 only the passivation layer or pH protective coating was applied. The coating quantity was again measured in parts per billion extracted from the surfaces of the vials to remove the entire passivation layer or pH protective coating, as reported in Table 10.

[410] In this example, several different coating dissolution conditions were employed. The test solutions used for dissolution contained either 0.02 or 0.2 wt.% polysorbate-80 surfactant, as well as a buffer to maintain a pH of 8. Dissolution tests were carried out at either 23°C or 40°C.
Multiple syringes were filled with each test solution, stored at the indicated temperature, and analyzed at several intervals to determine the extraction profile and the amount of silicon extracted. An average dissolution rate for protracted storage times was then calculated by extrapolating the data obtained according to the Protocol for Determining Average Dissolution Rate. The results were calculated as described previously and are shown in Table 10. Of particular note, as shown on Table 10, were the very long calculated shelf lives of the filled packages provided with a PC 194 passivation layer or pH protective coating:

- 21045 days (over 57 years) based on storage at a pH of 8, 0.02 wt.% polysorbate-80 surfactant, at 23°C;
- 38768 days (over 100 years) based on storage at a pH of 8, 0.2 wt.% polysorbate-80 surfactant, at 23°C;
- 8184 days (over 22 years) based on storage at a pH of 8, 0.02 wt.% polysorbate-80 surfactant, at 40°C; and
- 14732 days (over 40 years) based on storage at a pH of 8, 0.2 wt.% polysorbate-80 surfactant, at 40°C.

Referring to Table 10, the longest calculated shelf lives corresponded with the use of an RF power level of 150 Watts and a corresponding high W/FM value. It is believed that the use of a higher power level causes higher cross-link density of the passivation layer or pH protective coating.

Example FF

Another series of experiments similar to those of Example EE are run, showing the effect of progressively increasing the RF power level on the FTIR absorbance spectrum of the passivation layer or pH protective coating. The results are tabulated in Table 11, which in each instance shows a symmetric / assymmetric 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 assymmetric stretch peak normally located between about 1060 and about 1100 cm⁻¹. Thus, the symmetric / assymmetric ratio is 0.79 at a power level of 20
W, 1.21 or 1.22 at power levels of 40, 60, or 80 W, and 1.26 at 100 Watts under otherwise comparable conditions.

[418] The 150 Watt data in Table 11 is taken under somewhat different conditions than the other data, so it is not directly comparable with the 20 - 100 Watt data discussed above. The FTIR data of samples 6 and 8 of Table 11 was taken from the upper portion of the vial and the FTIR data of samples 7 and 9 of Table 11 was taken from the lower portion of the vial. Also, the amount of OMCTS was cut in half for samples 8 and 9 of Table 11, compared to samples 6 and 7. Reducing the oxygen level while maintaining a power level of 150 W raised the symmetric / asymmetric ratio still further, as shown by comparing samples 6 and 7 to samples 8 and 9 in Table 11.

[419] It is believed that, other conditions being equal, increasing the symmetric / asymmetric ratio increases the shelf life of a vessel filled with a material having a pH exceeding 5.

[420] Table 12 shows the calculated O-Parameters and N-Parameters (as defined in U.S. Pat. No. 8,067,070) for the experiments summarized in Table 11. As Table 12 shows, the O-Parameters ranged from 0.134 to 0.343, and the N-Parameters ranged from 0.408 to 0.623 - all outside the ranges claimed in U.S. Pat. No. 8,067,070.

**Example GG - Measurement of Contact Angle**

[421] The test purpose was to determine the contact angle or surface energy on the inside surface of two kinds of plastic vials and one kind of glass vial.

[422] The specimens that underwent testing and analysis reported here are three kinds of vials. The specimens are (A) an uncoated COP vial, (B) an SiO$_x$ + passivation layer or pH protective coating on a COP vial prepared according to the above Protocol for Coating Syringe Barrel Interior with SiO$_x$, followed by the Protocol for Coating Syringe Barrel Interior with OMCTS Passivation layer or pH protective coating, and (C) a glass vial. Small pieces were obtained by cutting the plastic vials or crushing the glass vial in order to test the inside surface.

[423] The analysis instrument for the contact angle tests is the Contact Angle Meter model DM-701, made by Kyowa Interface Science Co., Ltd. (Tokyo, Japan). To obtain
the contact angle, five water droplets were deposited on the inside surface of small pieces obtained from each specimen. The testing conditions and parameters are summarized below. Both plastic vials were cut and trimmed, while the glass vial needed to be crushed. The best representative pieces for each specimen were selected for testing. A dropsize of 1 µl (one microliter) was used for all samples. Due to the curvature of the specimens, a curvature correction routine was used to accurately measure the contact angle. The second table below contains the values for the radius of curvature used for each specimen.

[424] Contact Angle Testing Conditions and Parameters
Test instrument - DM-701 Contact Angle Meter
Liquid Dispenser - 22 gauge stainless steel needle
Drop Size - 1 µl
Test liquid Distilled water
Environment Ambient air, room temperature

[425] Radius of Curvature for each Vial Specimen
Specimen Radius of Curvature
(µ m, micrometers)
COP 9240
COP plus passivation layer or pH protective coating 9235
Glass 9900

[426] The contact angle results for each specimen are provided below.
[427] The specimen made from COP plus passivation layer or pH protective coating had the highest average contact angle of all tested specimens. The average contact angle for specimen made from COP plus passivation layer or pH protective coating was 99.1°. The average contact angle for the uncoated COP specimen was 90.5°. The glass specimen had a significantly lower average contact angle at 10.6°. This data shows the utility of the passivation layer or pH protective coating to raise the contact angle of the
uncoated COP vessel. It is expected that an SiO$_x$ coated vessel without the passivation layer or pH protective coating would exhibit a result similar to glass, which shows a hydrophilic coating relative to the relative to the passivation layer or pH protective coating.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
<th>Test 4</th>
<th>Test 5</th>
<th>Ave.</th>
<th>Std.Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>COP</td>
<td>88.9</td>
<td>91.9</td>
<td>89.1</td>
<td>91.4</td>
<td>91.1</td>
<td>90.5</td>
<td>1.4</td>
</tr>
<tr>
<td>COP/Pass.</td>
<td>98.9</td>
<td>96.8</td>
<td>102.2</td>
<td>98.3</td>
<td>99.5</td>
<td>99.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Glass</td>
<td>11.6</td>
<td>10.6</td>
<td>10.1</td>
<td>10.4</td>
<td>10.4</td>
<td>10.6</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Note: "Pass." means passivation layer or pH protective coating.

Example HH -

[428] The purpose of this example was to evaluate the recoverability or drainage of a slightly viscous aqueous solution from glass, COP and coated vials.

[429] This study evaluated the recovery of a 30 cps (centipoise) carbohydrate solution in water-for-injection from (A) an uncoated COP vial, (B) an SiO$_x$ + passivation layer or pH protective coating on a COP vial prepared according to the above Protocol for Coating Syringe Barrel Interior with SiO$_x$, followed by the Protocol for Coating Syringe Barrel Interior with OMCTS Passivation layer or pH protective coating, and (C) a glass vial.

[430] 2.0 ml of the carbohydrate solution was pipetted into 30 vials each of glass, COP and vials coated with a passivation layer or pH protective coating. The solution was aspirated from the vials with a 10 ml syringe, through a 23 gauge, 1.5" needle. The vials were tipped to one side as the solution was aspirated to maximize the amount recovered. The same technique and similar withdrawal time was used for all vials. The vials were weighed empty, after placing 2.0 ml of the solution to the vial and at the conclusion of aspirating the solution from the vial. The amount delivered to the vial (A) was determined by subtracting the weight of the empty vial from the weight of the vial with the 2.0 ml of solution. The weight of solution not recovered (B) was determined by
subtracting the weight of the empty vial from the weight of the vials after aspirating the solution from the vial. The percent unrecovered was determined by dividing B by A and multiplying by 100.

[431] It was observed during the aspiration of drug product that the glass vials remained wetted with the solution. The COP vial repelled the liquid and as the solution was aspirated from the vials. This helped with recovery but droplets were observed to bead on the sidewalls of the vials during the aspiration. The vials coated with a passivation layer or pH protective coating also repelled the liquid during aspiration but no beading of solution on the sidewalls was observed.

[432] The conclusion was that vials coated with a passivation layer or pH protective coating do not wet with aqueous solutions as do glass vials, leading to superior recovery of drug product relative to glass. Vials coated with a passivation layer or pH protective coating were not observed to cause beading of solution on sidewall during aspiration of aqueous products therefore coated vials performed better than uncoated COP vials in product recovery experiments.

Example II - Glass Delamination

[433] Bi-layer coated (SiO_x barrier coating or layer plus passivation layer or pH protective coating) glass vials were subjected to a wide range of chemical and physical challenges:

- pH 2.5 to 9.5
- Water for Injection (WFI) contained in the vial;
- Variety of buffers - acetate, citrate, phosphate and HEPES contained in the vial;
- 4-(2-hydroxyethyl)-1-piperazinethanesulfonic acid contained in the vial.
- Ionic strengths from 0 to 600 milliosmoles per kilogram
- Tween 80 concentrations up to 2%
- Temperatures up to 40°C

No delamination events were observed in these tests. The bi-layer coating also did not delaminate when subjected to a liquid nitrogen (-200°C) freeze - thaw temperature
cycle. The bi-layer coating further did not delaminate when scratched and then subjected to a liquid nitrogen (-200 °C) freeze-thaw temperature cycle.
<table>
<thead>
<tr>
<th>Example</th>
<th>Lubricity, passivation layer or pH protective coating Type</th>
<th>Monomer</th>
<th>Coating Time (sec)</th>
<th>OMCTS Flow Rate (seem)</th>
<th>02 Flow Rate (seem)</th>
<th>Carrier Gas (Ar) Flow Rate (seem)</th>
<th>Power (Watts)</th>
<th>Initiation Force, $F_i$ (N, Kg.)</th>
<th>Maintenance Force, $F_m$ (N, Kg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Control)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>&gt; 11 N</td>
<td>&gt; 11 N</td>
</tr>
<tr>
<td>B (Industry Standard)</td>
<td>Silicone oil on COC</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>8.2 N 0.84 Kg.</td>
<td>6.3 N 0.64 Kg.</td>
</tr>
<tr>
<td>C (without Oxygen)</td>
<td>L3 lubricity coating or layer over SiO$_x$ on COC</td>
<td>OMCTS</td>
<td>10 sec</td>
<td>3</td>
<td>0</td>
<td>65</td>
<td>6</td>
<td>4.6 N 0.47 Kg.</td>
<td>4.6 N 0.47 Kg.</td>
</tr>
<tr>
<td>D (with Oxygen)</td>
<td>L2 lubricity and/or passivation layer or pH protective coating over SiO$_x$ on COC</td>
<td>OMCTS</td>
<td>10 sec</td>
<td>3</td>
<td>1</td>
<td>65</td>
<td>6</td>
<td>4.8 N 0.49 Kg.</td>
<td>3.5 N 0.36 Kg.</td>
</tr>
</tbody>
</table>
### TABLE 2: OMCTS Lubricity and/or passivation layer or pH protective coating (E and F)

<table>
<thead>
<tr>
<th>Example</th>
<th>OMCTS (sccm)</th>
<th>O₂ (sccm)</th>
<th>Ar (sccm)</th>
<th>Initiation Force, Fᵢ (N)</th>
<th>Maintenance Force, Fₘ (N)</th>
<th>ICPMS (µg./liter)</th>
<th>ICPMS Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>3.0</td>
<td>0.38</td>
<td>7.8</td>
<td>4.8</td>
<td>3.5</td>
<td>&lt;5</td>
<td>static</td>
</tr>
<tr>
<td>F</td>
<td>3.0</td>
<td>0.38</td>
<td>7.8</td>
<td>5.4</td>
<td>4.3</td>
<td>38</td>
<td>dynamic</td>
</tr>
<tr>
<td>G (SiOₓ only)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>13</td>
<td>11</td>
<td>&lt;5</td>
<td>static</td>
</tr>
<tr>
<td>H (silicone oil)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>8.2</td>
<td>6.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 3: OMCTS Lubricity and/or passivation layer or pH protective coating

<table>
<thead>
<tr>
<th>Example</th>
<th>OMCTS (sccm)</th>
<th>O₂ (sccm)</th>
<th>Ar (sccm)</th>
<th>Initiation Force, Fᵢ (N)</th>
<th>Maintenance Force, Fₘ (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2.5</td>
<td>0.38</td>
<td>7.6</td>
<td>5.1</td>
<td>4.4</td>
</tr>
<tr>
<td>J</td>
<td>2.5</td>
<td>0.38</td>
<td>-</td>
<td>7.1</td>
<td>6.2</td>
</tr>
<tr>
<td>K</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
<td>8.2</td>
<td>7.2</td>
</tr>
</tbody>
</table>

### TABLE 4: HMDSO passivation layer or pH protective coating

<table>
<thead>
<tr>
<th>Example</th>
<th>HMDSO (sccm)</th>
<th>O₂ (sccm)</th>
<th>Ar (sccm)</th>
<th>Initiation Force, Fᵢ (N)</th>
<th>Maintenance Force, Fₘ (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>2.5</td>
<td>0.38</td>
<td>7.6</td>
<td>9</td>
<td>8.4</td>
</tr>
<tr>
<td>M</td>
<td>2.5</td>
<td>0.38</td>
<td>-</td>
<td>&gt;11</td>
<td>&gt;11</td>
</tr>
<tr>
<td>N</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
<td>&gt;11</td>
<td>&gt;11</td>
</tr>
<tr>
<td>Example</td>
<td>OMCTS (seem)</td>
<td>Ar/0₂ (seem)</td>
<td>Power (Watts)</td>
<td>Dep. Time (sec)</td>
<td>F₁ (lbs, Kg)</td>
</tr>
<tr>
<td>---------</td>
<td>--------------</td>
<td>--------------</td>
<td>--------------</td>
<td>----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>O</td>
<td>Baseline OMCTS Lubricity</td>
<td>2.0 10/0.38</td>
<td>3.5</td>
<td>10</td>
<td>4.66, 2.11 (ave)</td>
</tr>
<tr>
<td>P</td>
<td>OMCTS Lubricity</td>
<td>2.0 10/0.38</td>
<td>3.5</td>
<td>10</td>
<td>4.9, 2.2</td>
</tr>
<tr>
<td>Q</td>
<td>19.6, 9.9, 9.4 (Average=6.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>High Power OMCTS Lubricity</td>
<td>2.0 10/0.38</td>
<td>4.5</td>
<td>10</td>
<td>4.9, 2.2</td>
</tr>
<tr>
<td>S</td>
<td>OMCTS Lubricity</td>
<td>2.0 10/0.38</td>
<td>3.4</td>
<td>10</td>
<td>4.9, 2.2</td>
</tr>
<tr>
<td>T</td>
<td>No 0₂ OMCTS Lubricity</td>
<td>2.0</td>
<td>10/0</td>
<td>3.4</td>
<td>4.9, 2.2</td>
</tr>
<tr>
<td>U</td>
<td>1.9, 2.6, 3.0 (Average=2.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>No 0₂ OMCTS Lubricity</td>
<td>2.0</td>
<td>10/0</td>
<td>3.4</td>
<td>4.9, 2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SiO₂/Lub</td>
<td>Coater</td>
<td>Mode</td>
<td>Siloxane Feed</td>
<td>Ar/O₂</td>
<td>Power (W)</td>
</tr>
<tr>
<td>--------------</td>
<td>--------</td>
<td>------</td>
<td>---------------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Example W</td>
<td>SiO₂₂</td>
<td>Auto-Tube</td>
<td>Auto</td>
<td>HMDSO 52.5 in, 133.4 cm.</td>
<td>0 sccm Ar, 90 sccm O₂</td>
</tr>
<tr>
<td>Lubricity:</td>
<td>Auto-S</td>
<td>same</td>
<td>OMCTS, 2.0 sccm</td>
<td>10 sccm Ar, 0.38 sccm O₂</td>
<td>3.4</td>
</tr>
<tr>
<td>Example X</td>
<td>SiO₂₂</td>
<td>same</td>
<td>same</td>
<td>same</td>
<td>same</td>
</tr>
<tr>
<td>Lubricity:</td>
<td>same</td>
<td>same</td>
<td>same</td>
<td>same</td>
<td>same</td>
</tr>
<tr>
<td>Example Y</td>
<td>SiO₂₂</td>
<td>Auto-Tube</td>
<td>same</td>
<td>same</td>
<td>0 sccm Ar, 90 sccm O₂</td>
</tr>
<tr>
<td>Lubricity:</td>
<td>Auto-S</td>
<td>same</td>
<td>same</td>
<td>10 sccm Ar, 0 sccm O₂</td>
<td>3.4</td>
</tr>
</tbody>
</table>
### TABLE 7

<table>
<thead>
<tr>
<th>Package Type</th>
<th>Static (µg/L)</th>
<th>Dynamic (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclic Olefin Syringe with CV Holdings SiOCH Lubricity Coating</td>
<td>70</td>
<td>81</td>
</tr>
<tr>
<td>Borocilicate Glass Syringe with silicone oil</td>
<td>825</td>
<td>835</td>
</tr>
</tbody>
</table>

### TABLE 8: Summary Table of OMCTS passivation layer or pH protective coating from Tables 1, 2, 3 and 5

<table>
<thead>
<tr>
<th>Example</th>
<th>OMCTS (sccm)</th>
<th>O₂ (sccm)</th>
<th>Ar (sccm)</th>
<th>Power (Watt)</th>
<th>Dep Time (sec)</th>
<th>F₁ (lbs)</th>
<th>F₂ (lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>3.0</td>
<td>0.00</td>
<td>65</td>
<td>6</td>
<td>10</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>D</td>
<td>3.0</td>
<td>1.00</td>
<td>65</td>
<td>6</td>
<td>10</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>E</td>
<td>3.0</td>
<td>0.38</td>
<td>7.8</td>
<td>6</td>
<td>10</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td>F</td>
<td>3.0</td>
<td>0.38</td>
<td>7.8</td>
<td>6</td>
<td>10</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>I</td>
<td>2.5</td>
<td>0.38</td>
<td>7.6</td>
<td>6</td>
<td>10</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>J</td>
<td>2.5</td>
<td>0.38</td>
<td>0.0</td>
<td>6</td>
<td>10</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
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While the invention has been illustrated and described in detail in the drawings and foregoing description, such illustration and description are to be considered illustrative or exemplary and not restrictive; the invention is not limited to the disclosed embodiments. Other variations to the disclosed embodiments can be understood and effected by those skilled in the art and practicing the claimed invention, from a study of the drawings, the disclosure, and the appended claims. In the claims, the word "comprising" does not exclude other elements or steps, and the indefinite article "a" or "an" does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.
CLAIMS

1. A filled package comprising:
   • a vessel having a lumen defined at least in part by a wall, the wall having an interior surface facing the lumen and an outer surface;
   • a barrier coating or layer of SiO\(_x\) wherein \(x\) is from 1.5 to 2.9, from 2 to 1000 nm thick, the barrier coating or layer of SiO\(_x\) having an interior surface facing the lumen and an outer surface facing the wall interior surface, the barrier coating or layer being effective to reduce the ingress of atmospheric gas into the lumen compared to a vessel without a barrier coating or layer;
   • a passivation layer or pH protective coating of SiO\(_x\)C\(_y\) or SiN\(_x\)C\(_y\) wherein \(x\) is from about 0.5 to about 2.4 and \(y\) is from about 0.6 to about 3, the passivation layer or pH protective coating having an interior surface facing the lumen and an outer surface facing the interior surface of the barrier coating or layer, the passivation layer or pH protective coating being effective to increase the calculated shelf life of the package (total Si / Si dissolution rate); and
   • a fluid composition contained in the lumen and having a pH between 4 and 10, optionally 5 and 9;

wherein the calculated shelf life of the package is more than six months at a storage temperature of 4°C.

2. A filled package comprising:
   • a vessel having a lumen defined at least in part by a wall, the wall having an interior surface comprising glass facing the lumen and an outer surface;
   • a passivation layer or pH protective coating of SiO\(_x\)C\(_y\) or SiN\(_x\)C\(_y\) wherein \(x\) is from about 0.5 to about 2.4 and \(y\) is from about 0.6 to about 3, the passivation layer or pH protective coating having an interior surface facing the lumen and an outer surface facing the interior surface comprising glass, the passivation layer or pH protective coating being effective to decrease the Si dissolution rate of the interior surface comprising glass; and
• a fluid composition contained in the lumen and having a pH between 4 and 10, optionally between 5 and 9.

3. An article comprising:
• a wall having a surface;
• a barrier coating or layer of SiO$_x$, wherein $x$ is from 1.5 to 2.9, from 2 to 1000 nm thick, the barrier coating or layer of SiO$_x$ having an interior surface facing the lumen and an outer surface facing the wall interior surface, the barrier coating or layer being effective to reduce the ingress of atmospheric gas through the wall compared to an uncoated wall; and
• a passivation layer or pH protective coating of SiO$_x$C$_y$ or SiN$_x$C$_y$ wherein $x$ is from about 0.5 to about 2.4 and $y$ is from about 0.6 to about 3, on the barrier coating or layer, the passivation layer or pH protective coating being formed by chemical vapor deposition of a precursor selected from a a linear siloxane, a monocyclic siloxane, a polycyclic siloxane, a polysilsesquioxane, a linear silazane, a monocyclic silazane, a polycyclic silazane, a polysilsesquiazane, a silatrane, a silquasilatrane, a silproatrane, an azasilatrane, an azasilquasilatrane, an azasilproatrane, or a combination of any two or more of these precursors; in which the rate of erosion of the passivation layer or pH protective coating, if directly contacted by a fluid composition having a pH at some point between 5 and 9, is less than the rate of erosion of the barrier coating or layer, if directly contacted by the fluid composition.

4. A vessel comprising:
• a thermoplastic wall having an interior surface enclosing a lumen;
• a fluid contained in the lumen having a pH greater than 5 disposed in the lumen;
• a barrier coating or layer of SiO$_x$, in which $x$ is between 1.5 and 2.9, the barrier coating or layer applied by PECVD, positioned between the interior surface of the thermoplastic wall and the fluid, and supported by the thermoplastic wall, the barrier coating or layer having the characteristic of being subject to being measurably diminished in barrier improvement factor in less than six months as a result of attack by the fluid; and

• a passivation layer or pH protective coating of SiO$_x$C$_y$, in which $x$ is between 0.5 and 2.4 and $y$ is between 0.6 and 3, the passivation layer or pH protective coating applied by PECVD, positioned between the barrier coating or layer and the fluid, and supported by the thermoplastic wall, the passivation layer or pH protective coating being effective to keep the barrier coating or layer at least substantially undissolved as a result of attack by the fluid for a period of at least six months.

5. The invention of any preceding claim, in which at least a portion of the wall of the vessel comprises or consists essentially of a polyolefin, optionally polypropylene, a cyclic olefin polymer, a cyclic olefin copolymer, a polyester, optionally polyethylene terephthalate, a polycarbonate, polylactic acid, glass, optionally borosilicate glass, or a combination or copolymer of these.

6. The invention of any preceding claim, in which the vessel comprises a syringe barrel, a cartridge, a vial, or a blister package.

7. The invention of any preceding claim 1, 2, or 4-6, in which the fluid composition has a pH between 4 and 10, alternatively between 5 and 9, alternatively between 5 and 6, alternatively between 6 and 7, alternatively between 7 and 8, alternatively between 8 and 9, alternatively between 6.5 and 7.5, alternatively between 7.5 and 8.5, alternatively between 8.5 and 9.
8. The invention of any preceding claim 1, 2, or 4-7, in which the fluid composition is a liquid at 20°C and 760 mm Hg. atmospheric pressure.

9. The invention of any preceding claim 1 or 3-8, in which the barrier coating or layer is from 4 nm to 500 nm thick, alternatively from 7 nm to 400 nm thick, alternatively from 10 nm to 300 nm thick, alternatively from 20 nm to 200 nm thick, alternatively from 30 nm to 100 nm thick.

10. The invention of any preceding claim, in which the passivation layer or pH protective coating comprises SiO$_x$C$_y$.

11. The invention of any preceding claim, in which the passivation layer or pH protective coating comprises SiN$_x$C$_y$.

12. The invention of any preceding claim, in which the passivation layer or pH protective coating is applied by PECVD of a precursor feed comprising a linear siloxane, for example hexamethyldisiloxane, a linear silazane, for example hexamethyldisilazane, a monocyclic siloxane, for example octamethylcyclotetrasiloxane (OMCTS), a polycyclic siloxane, a polysilsesquioxane, a monocyclic silazane, a polycyclic silazane, a polysilsesquiazane, a silatrane, a silquasilatrane, a silproatrane, an azasilatrine, an azasilquasilatrane, an azasilproatrane, or a combination of any two or more of these precursors.

13. The invention of any preceding claim, in which the passivation layer or pH protective coating is applied by PECVD of a precursor feed comprising octamethylcyclotetrasiloxane (OMCTS).

14. The invention preceding claim 13, in which the precursor feed further comprises an oxidizing gas, for example oxygen.
15. The invention of any preceding claim 12-14, in which the precursor feed further comprises a noble gas, for example argon.

16. The invention of any preceding claim 12-15, in which the precursor feed comprises:
   • from 0.5 to 10 standard volumes of the organosilicon precursor, for example octamethylenecycloptetrasiloxane (OMCTS);
   • from 0.1 to 10 standard volumes of an oxidizing gas, for example oxygen; and
   • from 1 to 100 seem of a carrier gas, for example Argon.

17. The invention of any preceding claim, in which the passivation layer or pH protective coating as applied is between 10 and 1000 nm thick, alternatively between 50 and 800 nm thick, alternatively between 100 and 700 nm thick, alternatively between 300 and 600 nm thick.

18. The invention of any preceding claim 1, 2, or 4-17, in which the passivation layer or pH protective coating contacting the fluid composition is between 10 and 1000 nm thick, alternatively between 20 and 700 nm thick, alternatively between 50 and 500 nm thick, alternatively between 100 and 400 nm thick, alternatively between 150 and 300 nm thick two years after the invention is assembled.

19. The invention of any preceding claim 1 or 3-18, in which the rate of erosion of the passivation layer or pH protective coating, if directly contacted by a fluid composition having a pH of 8, is less than 20%, alternatively less than 15%, alternatively less than 10%, alternatively less than 7%, alternatively from 5% to 20%, alternatively 5% to 15%, alternatively from 5% to 10%, alternatively from 5% to 7% of the rate of erosion of the barrier coating or layer, if directly contacted by the same fluid composition under the same conditions.
20. The invention of any preceding claim 1 or 3-19, in which the passivation layer or pH protective coating is at least coextensive with the barrier coating or layer.

21. The invention of any preceding claim 1, 2, or 4-20, having a minimum shelf life, after the invention is assembled, of at least one year, alternatively at least two years, alternatively at least three years, alternatively at least four years, alternatively at least five years, alternatively at least six years, alternatively at least seven years, alternatively at least eight years, alternatively at least nine years.

22. The invention of claim 21, having a shelf life of up to ten years.

23. The invention of any preceding claim 21-22, in which the shelf life is determined at 3°C, alternatively at 4°C, alternatively at 20°C, alternatively at 23°C, alternatively 40°C.

24. The invention of any preceding claim 21 to 23, in which the pH of the fluid composition is between 5 and 6, alternatively between 6 and 7, alternatively between 7 and 8, alternatively between 8 and 9, and the thickness of the passivation layer or pH protective coating is at least 80 nm, alternatively at least 150 nm at the end of the shelf life.

25. The invention of any preceding claim, in which the fluid composition removes the passivation layer or pH protective coating at a rate of 1 nm or less of passivation layer or pH protective coating thickness per 44 hours of contact, alternatively per 88 hours of contact, alternatively per 350 hours of contact with the fluid composition.

26. The invention of any preceding claim, in which the passivation layer or pH protective coating is effective to provide a lower frictional resistance than the uncoated interior surface.
27. The invention of claim 26 wherein the frictional resistance is reduced by at least 25%, alternatively least 45%, alternatively at least 60% in comparison to the uncoated interior surface.

28. The invention of any preceding claim, in which the passivation layer or pH protective coating is effective to reduce the frictional resistance between a portion of the wall contacted by the fluid composition and a relatively sliding part after the invention is assembled, alternatively at least two years after the invention is assembled.

29. The invention of claim 28, in which the invention is a syringe.

30. The invention of claim 29, in which the syringe comprises a syringe barrel and a plunger tip, piston, stopper, or seal and the wall defines at least a portion of the syringe barrel.

31. The invention of claim 30, in which the relatively sliding part comprises the plunger tip, piston, stopper, or seal.

32. The invention of any preceding claim, further comprising
• a lubricity coating applied between the passivation layer or pH protective coating and the lumen;
• optionally, a further coating applied adjacent to the inner surface of the passivation layer or pH protective coating, the further coating having an outer surface facing the interior surface of the thermoplastic wall and an inner surface facing the lumen; and
• fluid in contact with the passivation layer or pH protective coating.

33. The invention of any preceding claim, in which an FTIR absorbance spectrum of the passivation layer or pH protective coating has a ratio greater than 0.75,
alternatively at least 0.8, alternatively, at least 0.9 alternatively at least 1, alternatively at least 1.1, alternatively at least 1.2 between:
  • the maximum amplitude of the Si-O-Si symmetrical stretch peak between about 1000 and 1040 cm⁻¹, and
  • the maximum amplitude of the Si-O-Si asymmetric stretch peak between about 1060 and about 1100 cm⁻¹.

34. The invention of claim 33, in which the FTIR absorbance spectrum of the passivation layer or pH protective coating has a ratio of at most 1.7, alternatively at most 1.6, alternatively at most 1.5, alternatively at most 1.4, alternatively at most 1.3.

35. The invention of any preceding claim, in which the passivation layer or pH protective coating has a non-oily appearance.

36. The invention of any preceding claim, in which the silicon dissolution rate by a 50 mM potassium phosphate buffer diluted in water for injection, adjusted to pH 8 with concentrated nitric acid, and containing 0.2 wt. % polysorbate-80 surfactant from the vessel is less than 170 ppb/day, alternatively less than 160 ppb/day, alternatively less than 140 ppb/day, alternatively less than 120 ppb/day, alternatively less than 100 ppb/day, alternatively less than 90 ppb/day, alternatively less than 80 ppb/day.

37. The invention of any preceding claim 1 or 3-36, in which the total silicon content of the passivation layer or pH protective coating and barrier coating or layer, upon dissolution into 0.1 N potassium hydroxide aqueous solution at 40°C from the vessel, is less than 66 ppm, alternatively less than 60 ppm, alternatively less than 50 ppm, alternatively less than 40 ppm, alternatively less than 30 ppm, alternatively less than 20 ppm.

38. The invention of any preceding claim 1, 2, or 4-37, in which the calculated shelf life (total Si / Si dissolution rate) is more than 1 year, alternatively more than 18
months, alternatively more than 2 years, alternatively more than 2½ years, alternatively more than 3 years.

39. The invention of any preceding claim 1, 2, or 4-38, in which the calculated shelf life (total Si / Si dissolution rate) is less than 4 years, alternatively less than 5 years.

40. The invention of any preceding claim, in which the passivation layer or pH protective coating is applied by PECVD at a power level per of more than 22,000 kJ/kg, alternatively more than 30,000 kJ/kg, alternatively more than 40,000 kJ/kg, alternatively more than 50,000 kJ/kg, alternatively more than 60,000 kJ/kg, alternatively more than 70,000 kJ/kg, alternatively more than 80,000 kJ/kg of mass of polymerizing gases in the PECVD reaction chamber.

41. The invention of any preceding claim, in which the passivation layer or pH protective coating is applied by PECVD at a power level per of less than 100,000 kJ/kg, alternatively less than 90,000 kJ/kg of mass of polymerizing gases in the PECVD reaction chamber.

42. The invention of any preceding claim, in which the passivation layer or pH protective coating is applied by PECVD at a power level of from 0.1 to 500 W, alternatively 0.1 to 400 W, alternatively 1 to 250 W, alternatively 1 to 200 W, alternatively 10 to 150 W, alternatively 20 to 150 W, alternatively 40 to 150 W, alternatively 60 to 150 W.

43. The invention of any preceding claim, in which the ratio of the electrode power to the plasma volume is from 1 W/ml to 100 W/ml, alternatively 5 W/ml to 75 W/ml, alternatively 6 W/ml to 60 W/ml, alternatively 10 W/ml to 50 W/ml, alternatively 20 W/ml to 40 W/ml.
44. The invention of any preceding claim, in which the passivation layer or pH protective coating has an RMS surface roughness value (measured by AFM) of from about 2 to about 9, alternatively about 6 to about 8, alternatively about 4 to about 6, alternatively from about 4.6 to about 5.8.

45. The invention of any preceding claim, in which the passivation layer or pH protective coating has an $R_{max}$ surface roughness value of the passivation layer or pH protective coating, measured by AFM, from about 70 to about 160, alternatively about 84 to about 142, alternatively about 90 to about 130.

46. The invention of any preceding claim, comprising a syringe barrel coated on its interior wall with a passivation layer or pH protective coating, the invention further comprising a plunger tip, piston, stopper, or seal positioned for sliding in the barrel and a lubricity coating or layer on at least a portion of the plunger tip, piston, stopper, or seal.

47. The invention of claim 46, in which the lubricity coating or layer is configured to provide a lower plunger tip, piston, stopper, or seal sliding force or breakout force than the uncoated substrate.

48. The invention of claim 46 or 47, in which the lubricity coating or layer has one of the following atomic ratios, measured by X-ray photoelectron spectroscopy (XPS), $Si_{w}O_{x}C_{y}$ (or its equivalent $SiO_{x}C_{y}$) or $Si_{w}N_{x}C_{y}$ (or its equivalent $SiN_{x}C_{y}$) where $w$ is 1, $x$ in this formula is from about 0.5 to 2.4, and $y$ is from about 0.6 to about 3.

49. The invention of any preceding claim 46-48, in which the lubricity coating or layer the lubricity layer having a thickness by transmission electron microscopy (TEM) between 10 and 500 nm;
50. The invention of claim any claim 46-49, in which the lubricity coating or layer the lubricity layer deposited by plasma enhanced chemical vapor deposition (PECVD).

51. The invention of claim any preceding claim 46-50, in which the lubricity coating or layer is deposited under conditions effective to form a coating from a precursor selected from a linear siloxane, a monocyclic siloxane, optionally octamethylcyclotetrasiloxane (OMCTS), a polycyclic siloxane, a polysilsesquioxane, a linear silazane, 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.

52. The invention of any preceding claim, wherein the passivation coating or pH protection layer shows an O-Parameter measured with attenuated total reflection (ATR) of less than 0.4, alternatively 0.1 to 0.39, alternatively 0.15 to 0.37, alternatively 0.17 to 0.35, measured as:

\[
O\text{-Parameter} = \frac{\text{Intensity at } 1253 \text{ cm}^{-1}}{\text{Maximum intensity in the range } 1000 \text{ to } 1100 \text{ cm}^{-1}}.
\]

53. The invention of any preceding claim, wherein the passivation coating or pH protection layer shows an N-Parameter measured with attenuated total reflection (ATR) of less than 0.7, alternatively 0.4 to 0.6, alternatively at least 0.3 measured as:

\[
N\text{-Parameter} = \frac{\text{Intensity at } 840 \text{ cm}^{-1}}{\text{Intensity at } 799 \text{ cm}^{-1}}.
\]

54. The invention of claim 53, wherein the passivation coating or pH protection layer shows an N-Parameter of at least 0.3.
55. A composite material comprising:

- a substrate,
- a barrier coating or layer over the substrate, and
- a passivation layer or pH protective coating over the barrier coating or layer,

wherein the passivation layer or pH protective coating shows an FTIR absorbance ratio of greater than 0.75 between:

- the maximum amplitude of the Si-O-Si symmetrical stretch peak of an FTIR spectrum between about 1000 and 1040 cm\(^{-1}\), and
- the maximum amplitude of the Si-O-Si asymmetric stretch peak of the FTIR spectrum between about 1060 and about 1100 cm\(^{-1}\).

56. The invention of claim 55, in which the maximum amplitude of the Si-O-Si symmetrical stretch peak of an FTIR spectrum between about 1000 and 1040 cm\(^{-1}\) is between 0.5 and 1.5 and the maximum amplitude of the Si-O-Si asymmetric stretch peak of the FTIR spectrum between about 1060 and about 1100 cm\(^{-1}\) is between 0.9 and 2.

57. The invention of claim 55 or 56, in which the maximum amplitude of the Si-O-Si symmetrical stretch peak of an FTIR spectrum between about 1000 and 1040 cm\(^{-1}\) is between 0.7 and 1.3 and the maximum amplitude of the Si-O-Si asymmetric stretch peak of the FTIR spectrum between about 1060 and about 1100 cm\(^{-1}\) is between 0.9 and 2.

58. The invention of any preceding claim 55-57, in which the maximum amplitude of the Si-O-Si symmetrical stretch peak of an FTIR spectrum between about 1000 and 1040 cm\(^{-1}\) is between 0.8 and 1.2 and the maximum amplitude of the Si-O-Si asymmetric stretch peak of the FTIR spectrum between about 1060 and about 1100 cm\(^{-1}\) is between 0.9 and 1.5.
59. The invention of any preceding claim 55-58, in which the maximum amplitude of the Si-O-Si symmetrical stretch peak of an FTIR spectrum between about 1000 and 1040 cm⁻¹ is between 0.9 and 1.2 and the maximum amplitude of the Si-O-Si asymmetric stretch peak of the FTIR spectrum between about 1060 and about 1100 cm⁻¹ is between 0.9 and 1.4.

60. The invention of any preceding claim 55-59, in which the maximum amplitude of the Si-O-Si symmetrical stretch peak of an FTIR spectrum between about 1000 and 1040 cm⁻¹ is between 0.92 and 1.07 and the maximum amplitude of the Si-O-Si asymmetric stretch peak of the FTIR spectrum between about 1060 and about 1100 cm⁻¹ is between 1.16 and 1.33.

61. The invention of any preceding claim,, in which the RMS surface roughness value of the passivation layer or pH protective coating, measured by atomic force microscopy, is from about 2 to about 9, optionally from about 6 to about 8, optionally from about 6.4 to about 7.8.

62. The invention of any preceding claim,, in which the Ra surface roughness value of the passivation layer or pH protective coating, measured by atomic force microscopy, is from about 4 to about 6, optionally from about 4.6 to about 5.8.

63. The invention of any preceding claim,, in which the R_max surface roughness value of the passivation layer or pH protective coating, measured by atomic force microscopy, is from about 70 to about 160, optionally from about 84 to about 142, optionally from about 90 to about 130.

64. The invention of any preceding claim, in which the fluid composition comprises a member selected from the group consisting of:
Inhalation Anesthetics
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
Xenon

Injectable Drugs
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)
Adrenacllick
AdreView (lobenguane 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-IL1 3
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)
Bai ni 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-1 023
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 (Maris)
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-1 0 1
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)
Clofarabine (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-1 0 1
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)
Dexorubicin 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)
GA1 01
Gadobenate Dimeglumine Injection (Multihance)
Gadofosveset Trisodium Injection (Ablavar)
Gadoteridol Injection Solution (ProHance)
Gadoversetamide Injection (OptiMARK)
Gadoxetate Disodium Injection (Eovist)
Ganirelix (Ganirelix Acetate Injection)
Gardasil
GC1 008
GDFD
Gemtuzumab Ozogamicin for Injection (Mylotarg)
Genotropin
Gentamicin Injection
GENZ-1 12638
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)
Maris (Canakinumab Injection)
Imipenem and Cilastatin for Injection (Primaxin I.V.)
Imitrex
Imcotobulinumtoxin 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)
Ilobenguane 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 A Q
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 (loversol 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
Remicade
Renagel
Renvela (Sevelamer Carbonate)
Repronex (Menotropins for Injection)
Retrovir IV (Zidovudine Injection)
rhApo2L/TRAIL
Ringer’s and 5% Dextrose Injection (Ringers in Dextrose)
Ringer’s Injection (Ringers Injection)
Rituxan
Rituximab
Rocephin (ceftriaxone)
Rocuronium Bromide Injection (Zemuron)
Roferon-A (interferon alfa-2a)
Romazicon (flumazenil)
Romidepsin for Injection (Istodax)
Saizen (Somatropin Injection)
Sandostatin LAR (Octreotide Acetate Injection)
Sclerostin Ab
Sensipar (cinacalcet)
Sensorcaine (Bupivacaine HCl Injections)
Septocaine (Articane HCl and Epinephrine Injection)
Serostim LQ (Somatropin (rDNA origin) Injection)
Simponi Injection (Golimumab Injection)
Sodium Acetate (Sodium Acetate Injection)
Sodium Bicarbonate (Sodium Bicarbonate 5% Injection)
Sodium Lactate (Sodium Lactate Injection in AVIVA)
Sodium Phenylacetate and Sodium Benzoate Injection (Ammonul)
Somatropin (rDNA origin) for Inj (Nutropin)
Sporanox Injection (Itraconazole Injection)
Stelara Injection (Ustekinumab)
Stemgen
Sufenta (Sufentanil Citrate Injection)
Sufentanil Citrate Injection (Sufenta )
Sumavel
Sumatriptan Injection (Alsuma)
Symlin
Symlin Pen
Systemic Hedgehog Antagonist
Synvisc-One (Hylan G-F 20 Single Intra-articular Injection)
Tarceva
Taxotere (Docetaxel for Injection)
Technetium Tc 99m
Telavancin for Injection (Vibativ)
Temsirolimus Injection (Torisel)
Tenormin I.V. Injection (Atenolol Inj)
Teriparatide (rDNA origin) Injection (Forteo)
Testosterone Cypionate
Testosterone Enanthate
Testosterone Propionate
Tev-Tropin (Somatropin, rDNA Origin, for Injection)
tgAAC94
Thallous Chloride
Theophylline
Thiotepa (Thiotepa Injection)
Thymoglobulin (Anti-Thymocyte Globulin (Rabbit)
Thyrogen (Thyrotropin Alfa for Injection)
Ticarcilllin 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)
Victeza
Vincristine Sulfate (Vincristine Sulfate Injection)
Visudyne (Verteporfin Inj)
Vitamin B-1 2
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)
Zemuron (Rocuronium Bromide Injection)
Zenapax (daclizumab)
Zevalin
Zidovudine Injection (Retrovir IV)
Zithromax Injection (Azithromycin)
Zn-DTPA (Pentetate Zinc Trisodium Injection)
Zofran Injection (Ondansetron Hydrochloride Injection)
Zingo
Zoledronic Acid for Inj (Zometa)
Zoledronic Acid Injection (Reclast)
Zometa (Zoledronic Acid for Inj)
Zosyn (Piperacillin and Tazobactam Injection)
Zyprexa Relprevv (Olanzapine Extended Release Injectable Suspension)

Liquid Drugs (Non-Injectable)

Ability
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)
Cultivate
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 (Ocuven)
FML
Foradii
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
Sepran
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 \( \text{K}\text{1} \) (Fluid Colloidal Solution of Vitamin \( \text{K}\text{1} \))
Voltaren Ophthalmic (Diclofenac Sodium Ophthalmic Solution)
Zarontin Oral Solution (Ethosuximide Oral Solution)
Ziagen
Zyvox
Zymar (Gatifloxacin Ophthalmic Solution)
Zymaxid (Gatifloxacin Ophthalmic Solution)

Drug Classes
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
anorexians
tantacids
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/antineoplasticas
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
antipsoriatrics
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
cardiopausal 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
fibracic 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 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
serotonergic 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 antipsoriatrics
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
vitamins

**Diagnostic Tests**
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)
Alphal -antitrypsin
Alpha-fetoprotein
Alpha-fetoprotien
Ammonia levels
Amylase
ANA (antinuclear antibodies)
ANA (antinuclear antibodies)
Angiotensin-converting enzyme (ACE)
Anion gap
Anticardiolipin antibody
Anticardiolipin antibodies (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
CH50 Chloride
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 (pit)
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)
Widal test

65. The invention of any preceding claim, wherein said fluid composition comprises an inhalation anesthetic.

66. The invention of any preceding claim, wherein said fluid composition comprises a drug.

67. The invention of any preceding claim, wherein said fluid composition comprises a diagnostic test material.

68. The invention of any preceding claim 2, 5-8, 10-18, or 21-67, the passivation layer or pH protective coating being effective to reduce delamination of the glass interior surface.

69. The invention of any preceding claim, in which the passivation layer or pH protective coating is applied by PECVD of a precursor feed comprising hexamethylcyclotrisiloxane (HMCTS).

70. The invention of any preceding claim, in which the passivation layer or pH protective coating is applied by PECVD of a precursor feed comprising decamethylcyclopentasiloxane (DMCPS).
71. The invention of any preceding claim, in which the passivation layer or pH protective coating is applied by PECVD of a precursor feed comprising 2,2,4,4,6,6,8,8-octamethyl-1,5-dimethano-3,7-dioxo-2,4,6,8-tetrasiloxane.

72. The invention of any preceding claim 42-71, in which PECVD is initiated by applying an initial higher power level within the stated range, followed by a subsequent lower power level within the stated range.

73. The invention of claim 72, in which the initial higher power level is applied for from 1 to 3 seconds.

74. The invention of claim 72 or 73, in which the subsequent lower power level is applied for the remainder of PECVD.
Si dissolution, pH 6

FIG. 13

Si dissolution, pH 7

FIG. 14
Sample 2

FIG. 20

Sample 3

FIG. 21
Sample 5

[Graph with wave number (cm⁻¹) on the x-axis and absorbance on the y-axis, showing peaks at certain wave numbers.]

FIG. 22

Sample 6

[Graph with wave number (cm⁻¹) on the x-axis and absorbance on the y-axis, showing a different pattern of peaks.]

FIG. 23
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8)- C23C 16/40 (2013.01)
USPC - 427/579

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - B05B 13/06; C23C 16/00, 30, 40 (2013.01)
USPC - 427/489, 569, 579; 428/447; 438/788

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CPC- B05B 13/06; C23C 16/00, 40, 401, 402

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Orbit.com, Google Patents, ProQuest, Google

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>US 2010/0132762 A1 (GRAHAM, JR et al) 03 June 2010 (03.06.2010) entire document</td>
<td>55-57, 1, 5</td>
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<tr>
<td>Y</td>
<td>US 2008/0109017 A1 (HERWECZ et al) 08 May 2008 (08.05.2008) entire document</td>
<td>4</td>
</tr>
</tbody>
</table>

Date of the actual completion of the international search: 03 January 2013

Date of mailing of the international search report: 25 JAN 2013

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
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Authorized officer: Blaine R. Copenhagen
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/2 10 (second sheet) (July 2009)
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. [ ] Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [x] Claims Nos.: 6-54, 58-74
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
[ ] No protest accompanied the payment of additional search fees.