to be installed. The sealing member may include a clip or a ledge. In some embodiments, the sealing member includes an o-ring.

[0005] The carrier may be disk shaped with the peripheral having an exposed sensing surface on a flat side of the carrier. In some embodiments, the carrier includes two or more peripherals having exposed sensing surfaces on a flat side of the carrier. In various embodiments, the carrier may be generally sheath shaped with the peripheral having an exposed sensing surface on an end of the carrier.

[0006] The peripheral may be configured or designed to detect an optical response. In some embodiments, the peripheral is an electrochemical peripheral, or a temperature peripheral, or a pH peripheral, or an oxygen peripheral. In some embodiments, the carrier includes an oxygen peripheral, a pH peripheral, ~~a pH peripheral,~~ and a temperature peripheral. In various embodiments, the peripheral is a single use peripheral. The carrier may include two or more peripherals.

[0007] The applicator includes a sleeve and vessel-facing opening adjacent to an applicator connector configured to temporarily connect to the aseptic vessel connector on the bio-processing vessel. In some embodiments, the applicator includes a sleeve and component-facing opening adjacent to an applicator connector configured to temporarily connect to the aseptic connector on the bio-processing component. The applicator may be configured to be removed from the carrier and the bio-processing vessel or component after the carrier is installed in the bio-processing vessel. The applicator sleeve may be constructed of a rigid material. In some embodiments, the applicator sleeve has a tubular shape and the plunger has a substantially circular shape that forms a seal with an interior surface of the applicator.

[0008] The applicator connector may include a clip or a ledge. In some embodiments, the applicator connector may include an o-ring. The applicator connector may be configured to provide a hermetic seal with the aseptic connector or aseptic vessel connector while the plunger inserts the carrier into the aseptic connector or aseptic vessel connector. In some embodiments, the applicator is composed of polycarbonates, polysulfone, polyvinylidene fluoride, or co-polyester. In various embodiments, the applicator is composed of USP Class VI material that is animal derived component free, latex free, phthalate free, and capable of being sterilized by

is a filter with a flow path. The bio-processing component housing may be a filter including a ~~containing~~ container packed with material for product separation.

[0012] Yet another aspect is a method of fabricating an aseptic peripheral connection assembly for installing a sterilized peripheral in a bio-processing vessel via an aseptic connector affixed to the vessel by (a) placing the carrier in an applicator; (b) sterilizing the aseptic peripheral connection assembly such that the sterilizing does not employ exposure to radiation at a level of greater than about 15 kGy; and (c) packaging the aseptic peripheral connection assembly in a hermetically sealed package. The aseptic peripheral connection assembly includes (i) a carrier including the peripheral and a sealing member configured to form a leak-tight seal with the aseptic vessel connector on the bio-processing vessel at a location where the carrier is to be installed; and (ii) the applicator including a sleeve and vessel-facing opening adjacent to an applicator connector configured to temporarily connect to the aseptic vessel connector on the bio-processing vessel. The method may further include sending the packaged aseptic peripheral connection assembly to a site for installation in the bio-processing vessel. In alternative embodiments, the bio-processing vessel described with respect to the disclosed embodiments may instead be a flow path or filter path.

[0013] In some embodiments, the method may include, prior to (a), applying the peripheral to a carrier structure. The method may include, prior to (a): treating a carrier structure, which does not include the complete peripheral, by a process that reduces colony forming units (CFUs) on the carrier structure; and subsequently applying the peripheral to a carrier structure. In some embodiments, the method may further include calibrating the peripheral in the carrier; and storing information from the calibrating.

[0014] The sterilizing further includes exposing the aseptic peripheral connection assembly and packaging to gamma, beta, and/or x-ray radiation. In some embodiments, the sterilizing includes plasma cleaning the aseptic peripheral connection assembly. In some embodiments, the plasma cleaning is performed prior to (c). In some embodiments, plasma cleaning performed prior to (c) may involve packaging prior to sterilizing with ethylene oxide. In some embodiments, the plasma cleaning includes sterilizing using atmospheric plasma at a temperature less than

[0066] Sensors could also be used in single-use fill-and-finish skids for measurement of liquid flow, syringe filling, and final product purity verification (e.g. spectroscopy such as Raman). Thus, the ability to insert single-use sensors into a single-use process unit operation will be a ubiquitous requirement for the successful implementation of any single-use production facility. As the number of sensors multiplies, the ability to connect them to the process in a robust manner that does not increase the risk of contamination will become paramount.

[0067] Disclosed embodiments may be used for bio-processing components such as vessels or flow paths. The term "vessel" generally refers to a self-contained and sterilized liquid container, of whatever shape or configuration, e.g., a cylindrically shaped bioreactor or mixer. Some embodiments involve a flow path with multiple junctions and made of pressure-resistant plastic tubing. Here, flow path is any tubing set, filter, or single-use component used in bio-processing (typically downstream processing) that may be connected using an aseptic connector system; though tube welding is also employed to connect systems. The tubing diameters generally range from about 1/8" ID to 3/4" ID.

[0068] Most of this description focuses on single-use bioreactors, but the principals apply generically to any of the aforementioned single-use equipment used in bioprocessing, both in the upstream processing (USP) and downstream ~~(DSP)~~ processing (DSP) arenas. Examples of USP units include mixers and bioreactors, and examples of DSP tools include chromatography assemblies and filtration skids which may use films similar to those used in USP. DSP tools may implement single-use sensors to replace traditional sensors and/or enable new additional analytical capability. "Smart" sensors for DSP and USP tools may have the capability of being pre-calibrated and gamma- or beta-irradiation sterilized along with the bio-process vessel itself.

[0069] Although a number of different styles of single-use bioreactors have been conceived and introduced into the marketplace, two types currently predominate: the "pillow" or "rocker" bag and the stirred tank. The first type of single-use bioreactor to become commercially popular is generally referred to as the pillow or rocker bag style, and is described, for example, in US Patent No. 6,190,913 the teaching of which is incorporated herein by this reference in its entirety. The pillow or rocker type of

single-use bioreactor utilizes a wave motion induced by movement of a bag support platform which generally rocks about a single axis to both mix and sparge (aerate) the contents of the bioreactor. Another of disposable bioreactor is a single-use implementation of the traditional (e.g.: stainless steel and/or glass) stirred tank reactor and utilizes an impeller and a sparger just as its traditional counterpart. The single-use stirred tank implementations include single-use polymeric hard shell bioreactors that functionally imitate small scale glass vessels, and also larger scale single-use versions that generally utilize plastic liner bags that fit inside rigid containers which hold the agitation motors etc. (e.g., US Patent No. 7,384,783 the teaching of which is incorporated herein in its entirety by this reference). The larger liner bags are typically constructed of multi-layer film laminates that also utilize some form of low or ultra-low density polyethylene (LDPE or ULDPE), ethylene vinyl-acetate (EVA), or similar material generally considered to be inert for the contact layer. The liner type single-use bioreactor vessels (bioreactors or mixers or holding cells for liquids) can be constructed from a variety of different polymeric materials, but as mentioned above, are constructed with an inner layer (i.e., the bag surface which is in contact with the aqueous growth medium) made of LDPE or EVA copolymers. Other materials sometimes used in the construction of the single-use bioreactor vessels include but are not limited to high density polyethylene (HDPE) and Kevlar (Poly-paraphenylene terephthalamide). By way of example, Figure 1 shows the construction of the CX-14 film used by Thermo Fisher Scientific for flexible bioreactor vessels~~)~~. Figure 1 is obtained from *Thermo Scientific Hyclone BPC Products and Capabilities 2008/2009*. The figure shows Thermo Fisher CX-14 film where the layer in contact with the bio process liquid is A1 (low density polyethylene, 10.4 mil thick) followed by layer A2 (a 0.9 mil thick "tie layer" which bonds A1 and A3), and layer A3 (Ethylene- vinyl alcohol copolymer "EVOH", 1.0 mil thick), and layer A4 (another 0.9 mil thick "tie layer" which bonds A3 and A5), and finally A5 (polyester, 0.8 mil thick).

[0070] While single-use bioreactor bags and single-use bioreactor vessels are enjoying popularity, all single use bioprocess vessels (e.g. single-use bioreactors, single-use mixing vessels, single-use liquid holding/storage vessels) are in general seeing increasing market acceptance. To date one major issue has been the lack of robust, single-use sensors that can be readily and reliably integrated into the single-

surface tension allowing the construction to occur is typically isopropyl alcohol and water (70%/30%) mix or pure isopropanol. Pure isopropanol is typically viewed less by manufacturing organizations as it is flammable, must be transported on the ground (e.g. trucking) and the vapors can be dangerous making it difficult to deal with in a controlled environment. The use of isopropanol water mixes and/or isopropanol in the construction of single-use bioprocess containers is a standard and ubiquitous practice. There is often a sizable accumulation (tens of milliliters or more) of these substances inside the container when the construction process is complete. As single-use (flexible or not) vessels are then double wrapped within 2 or more bags for use in cGMP (Good Manufacturing Practice) qualified applications, the bags are clearly hermetically sealed and the isopropanol/water mix or isopropanol is locked into the vessel during the gamma sterilization process.

[0075] The subsequent gamma sterilization of the closed container with these substances locked inside creates other more chemically active substances. For example, when water is exposed to Gamma radiation (Gamma Hydrolysis) it is broken down and forms hydrogen, hydroxyl radicals, and H_2O_2 (hydrogen peroxide) and peroxide radicals (LaVerne, J.A., Radiation Research 153, 196-200, (2000)). It is also clear that the exposure of isopropanol (C_3H_8O or C_3H_7OH) to Gamma radiation will lead to an even greater formation of highly reactive OH^- radicals (J. Environmental Eng. Management, 20(30, 151-156 (2010)). This means that there are reactive agents (e.g.: solvents) inside the single-use vessel that were never considered, let alone tested in the USP Class VI (United States Pharmacopia) testing regimen or considered by the BPSA, Bio-processing Systems Alliance, (bpsalliance.org) sub-committees on single-use vessels or sensors. Neither H_2O_2 nor the post gamma isopropanol compounds are conducive to cell growth and are likely detrimental to any active element (e.g. an opto-chemical sensor) inside the bioprocess container.

[0076] These reactive compounds have implications to sensing elements that are introduced into the single-use vessels. Potentially detrimental reactive compounds are formed in all or the majority of the currently employed single-use vessels where water vapor, oxygen, and plastics are present. While the concentration of these reactive compounds created in each material and how these levels scale with surface area and

Hammond et al., PDA Journal of Pharmaceutical Science and Technology, Vol. 67, No. 2, March-April 2013, incorporated herein by reference in its entirety) shows without equivocation that the aforementioned CX-514 film exhibits detrimental characteristics to cell growth following exposure to gamma radiation. The paper identifies compounds such as anti-oxidants (e.g. tris(2,4-di-tert-butylphenyl) phosphite) which are present in many formulations of polyethylene as responsible for at least some of the issues noted in the field. The paper identifies byproducts (e.g: (bis(2,4-di-tert-butylphenyl)phosphate (bDtBPP)) of these anti-oxidants that are created by gamma radiation process. The gamma radiation breaks down the anti-oxidant that remains in the LDPE; often the anti-oxidant is not completely consumed during the rolling of the films. Hammond et al. showed that bDtBPP can inhibit cell growth for many lines of commonly used cells in biotech drug development. Another byproduct of the gamma radiation exposure of the anti-oxidant noted in Hammond's paper is Phosphoric Acid. It is clear that depending on the surface area of the vessel and the sensitivity of the active elements introduced, many deleterious effects will be endured. However, even before this paper by Hammond et al. was published, it was commonly known that polyethylene films can give off hydrogen when gamma irradiated and that this could interact with ozone that is also created when oxygen is present during the gamma process. As most bio-process containers/bioreactors are closed vessels that are not under vacuum during the sterilization process it is quite possible for Phosphoric Acid, Hydrogen, ozone, and Hydrogen Peroxide to exist simultaneously in the same volume. It is also likely that aggressive free radicals are also present in the single-use vessels immediately following gamma sterilization depending on the exact materials used and the conditions in the vessel during gamma exposure.

[0080] In addition to the titer or viability of the cells being directly reduced by the presence of free radicals and radiation byproducts, these byproducts can also affect active elements (e.g. sensors) introduced into the single-use bags prior to gamma exposure. In fact, has been noted by many in the field that single-use optical sensors for analytes such as dissolved oxygen (DO), pH, dissolved CO_2 (dCO_2), and others are deleteriously affected by exposure to gamma radiation in single-use bioprocess containers. The gamma exposure affects the sensors via two distinct readily delineated mechanisms. The first is the chain scissioning

use of welding or suitable adhesives or retention/attachment processes. In a conventional approach, if this were to be welded to a flexible single-use bio-processing vessel, the material on the base of sleeve 13-2 would either have to be compatible with the inner layer of the bag or sealingly affixed to a flange made of such a material. The carrier 13-1 may be disk shaped with the sensor having an exposed sensing surface on the flat ~~size~~ side of the carrier 13-1. As described below, in some embodiments, the carrier may be generally sheath shaped with the sensor having an exposed sensing surface on an end of the carrier. In some embodiments, two or more sensors in carrier 13-1 have exposed sensing surfaces on a flat side of the carrier 13-1.

[0094] While the following examples show sensor-containing assemblies, this disclosure is not limited to sensors. Other peripherals such as filter flow tubes, sample ports, etc. may be used in place of sensors in the following examples. Figure 14 shows an aseptic sensor connection assembly for installing a sterilized sensor in a bio-processing vessel via an aseptic vessel connector or aseptic connector 14-3 affixed to the vessel. The Figure depicts a full cross-sectional view of both halves of the aseptic sensor connection assembly prior to the connection being made. Shown is an example of an optical carrier 13-1 as shown in Figure 6. Here the carrier depicted in Figure 13 as 13-1 is labeled as 14-1 and as before, holds the opto-chemical sensors spots and the stainless steel window for temperature sensing.

[0095] The sleeve 14-2 is a substantially tubular part of the top portion of the aseptic connector that encloses the carrier 14-1 and its sealing flange 14-10; this entire assembly holding the sensor will be referred to as the sensor applicator or applicator, having an applicator connector 14-4. The applicator may be composed of a polycarbonate, polysulfone, polyvinylidene fluoride, co-polyester, or a combination of any of these. The sleeve 14-2 may be constructed of rigid material. The applicator may be configured to be removed from the carrier 14-1 and the bio-processing vessel after the carrier is installed in the bio-processing vessel. The lower half or aseptic connector 14-3 is attached to the single-use bio-processing vessel so that the sensor carrier 14-1 can be aseptically connected to the vessel at a later date and processed independently and will be referred to as the aseptic vessel connector or aseptic connector 14-3. The two halves are sterilized independently prior to the time when