

the art after considering the following detailed description, appended claims and accompanying drawings.

DESCRIPTION OF THE DRAWING

[0010] FIG. 1 is a schematic drawing of an aseptic sample withdrawal system embodying aspects of the invention.

[0011] FIG. 2 is a schematic drawing of an alternative embodiment of an aseptic sample withdrawal system embodying aspects of the invention.

[0012] FIG. 3 is a schematic drawing of another alternative embodiment of an aseptic sample withdrawal system embodying aspects of the invention.

[0013] FIG. 4 is a flow chart showing steps performed in an aseptic sampling procedure embodying aspects of the invention.

[0014] FIG. 5 is a schematic diagram of a control system for automation of the sample withdrawal system and sampling procedure.

[0015] FIG. 6 is a schematic view of a sample manifold for selectively connecting individual sample containers to a main sampling line in accordance with an embodiment of the invention.

DETAILED DESCRIPTION

[0016] As used herein, unless noted otherwise, the words “a” and “an” mean “one or more.” Furthermore, unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although any methods and materials similar or equivalent to those described herein can be used in the practice of the present invention, the preferred materials and methods are described herein.

[0017] An aseptic withdrawal system embodying aspects of the invention is shown in FIG. 1. The system includes a vessel 20, a dip tube 22 extending into the vessel 20, a sampling line 24, a bi-directional pump 30 placed in line with the sampling line 24, vent lines 32, 34 branching from the sampling line 24, filters 26, 28 disposed on the vent lines 32, 34, respectively, a flow control system which, in the illustrated embodiment, comprises a plurality of valves 1-14, and sample containers B-1-B-5 each connected to a respective secondary line branching from the main sampling line 24. Vessel 20 may be the fluid holding container of a bioreactor for mammalian cell culture, a fermentor or fermentation vessel for microbial cell culture, or fermentation, or a medium batching/holding vessel. A bioreactor with which the aseptic withdrawal system may be incorporated is described by Lee, “Bioreactor Apparatus,” U.S. Patent Publication No. 2009-0269849, the disclosure of which is hereby incorporated by reference. A “medium batching/holding vessel” refers to a tank designated for either batching or holding cell culture medium at a set temperature, pressure, and agitation prior to transfer into a bioreactor or a fermentor. Such batching vessels are used in many biotech facilities to shorten the manufacturing run time, by allowing medium to be batched and held for a few days, up to a week, while a previous batch is still running in the bioreactor or fermentor. Medium batching is typically a non-sterile process, and batched medium is transferred through a sterilizing-grade filter into a medium holding tank, where it is then held under sterile conditions. Samples are typically taken during medium batching to ensure the

medium has the desired pH and dissolved CO₂ level and may be taken after medium hold to ensure it was held as expected.

[0018] Vessel 20 may comprise a bag formed from a suitable plastic film operatively supported by a rigid frame or housing. Valves 1-14 may comprise control pinch valves, but any suitable valve can be used. For example, since valves 1-14 are simply used for automating the opening and closing of tubing, they may be replaced with any number and/or combination of clamps, hemostats, or stopcocks for manually pinching off tubing.

[0019] Pinch valves, if used, may be electronically actuated or pneumatically actuated. Suitable pinch valves are available from BioChem Fluidics Part No. 100P-2-NC-24-05 S Q. A suitable pump is the Watson Marlow 114 pump No. 010. 5E20.00A. Exemplary volumes for sample containers B-1-B-5 are up to 50 mL for R&D applications and up to 1.0 L for cGMP (current good manufacturing practice) applications.

[0020] The sampling system includes the main sampling line 24 with two vent lines 32, 34 that split off from the main sampling line 24 on opposite sides of the pump 30. Each vent line 32, 34 has a vent filter 26, 28, respectively (preferably a sterilizing grade gas filter with, e.g., a 0.2 μm membrane) on its distal end. Filter 26 will be referred to as the “vessel side filter,” and filter 28 will be referred to as the “sample side filter.” Similarly, vent line 32 may be referred to as the “vessel side vent line,” and vent line 34 will be referred to as the “sample side vent line.” With the exception of the vent lines 32, 34, which are open to ambient conditions through filters 26 and 28, respectively, vessel 20, the main sampling line 24, the secondary sampling lines, and the sample containers B-1 through B-5 are preferably closed to ambient conditions (although a filtered gas exhaust may be provided in the vessel), thereby maintaining an aseptic fluid transfer path between the vessel 20 and the sample containers.

[0021] One end of the sampling line 24 is connected to the dip tube 22 that extends into the vessel 20, and the other end of the sampling line 24 is connected to a series of sample containers (e.g., bags) B-1-B-5 attached to the sampling line 24 via secondary sampling lines branching from the main sampling line 24. If the vessel 20 comprises a plastic bag, the dip tube 22 may be inserted into the vessel 20 through a port disc (not shown) heat-sealed to the bag film. If vessel 20 is made out of rigid plastic material, the dip tube 22 may also be inserted into the vessel 20 through plastic port that is molded as part of the top plate of the vessel. In an alternative embodiment, shown in FIG. 2, the end 22' of the sampling line 24 may be connected to the bottom of the vessel 20, for example, through a port disc 36 heat-sealed to the bag film. If vessel 20 is made out of rigid plastic material, the end 22' of the sampling line 24 may also be introduced to the bottom of the vessel 20 as a molded plastic channel that runs vertically on the inside of the vessel 20 from the top plate of the vessel. The number of sample containers is customizable and can be specified ahead of time, but more vessels can be added aseptically by the user through sterile tube welding. To ensure that the sampling system is sterile, i.e., free of live bacteria, other microorganisms, or bioactive DNA, the entire sampling system can be either pre-assembled and pre-sterilized (e.g., by gamma irradiation) with the vessel 20 or sterilized separately and attached to the existing sampling line through sterile tube welding or through aseptic connection devices. Sterilization may also be performed by autoclaving if the sampling system consists of material that can withstand a typical autoclave cycle.