AUTOMATABLE ASEPTIC SAMPLE WITHDRAWAL SYSTEM

PRIORITY CLAIM

[0001] This application claims the benefit under 35 U.S.C. 119(e) of U.S. Provisional Application No. 61/161,831, filed Mar. 20, 2009, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The invention relates to mammalian cell culture or microbial fermentation and, more particularly, to systems and methods for aseptically withdrawing discrete samples of culture material from a vessel containing such material.

BACKGROUND

[0003] Cell culture (mammalian cell culture) procedures using a bioreactor or fermentation (microbial cell culture) procedures using a fermentor or fermentation vessel embody techniques for growing and proliferating unit cells separate from an organism and is widely used in biology, medical science, pharmacy, and agriculture. Additionally, the use of biological cultivation procedures has expanded into other disciplines, such as the treatment of waste water or oil.

[0004] Apparatuses designed for cultivation of microbial organisms or eukaryotic cells, known as bioreactors or fermentors, have been used for production of various biological or chemical products in the pharmaceutical, biotechnological and beverage industry. A typical bioreactor includes a vessel for containing culture medium in a sterile environment that provides the various nutrients required to support growth of the homogeneous biological agents of interest.

[0005] Effective cell culture process requires appropriate supplies of nutrient substances, such as glutamine, glucose, and other medium components, and gas, such as oxygen and carbon dioxide, for the growing cells in a bioreactor. In addition, timely control of physiological conditions, such as appropriate pH, temperature, and osmolarity is required for mass cell culture production. In order to provide optimal culture conditions in a bioreactor, rapid and effective mixing in the culture medium is prerequisite, and cells should be uniformly dispersed throughout the culture medium without aggregation in any portion of the cultivation vessel.

[0006] During a cell culture process, aseptic withdrawal of a culture broth sample that is representative of the overall cell culture condition is critical for monitoring the performance of the cell culture or fermentation process and for troubleshooting any process problems. The aseptic sampling step is also applicable in medium batching and holding vessels, for which maintaining the desired dissolved carbon dioxide level can be critical to ensuring the proper pH of the cell culture medium. Conventional sample withdrawal from a bioreactor, fermentor, or medium holding vessel, however, is typically performed by a series of manual operations, including purging the sampling line, connecting a sample device aseptically to the line, removing the sample from the bioreactor, and closing the line. The purge step is usually required at the beginning of each sampling step to flush the residual sample in the sampling line from the previous sampling into a waste reservoir. The conventional sample withdrawal procedure results in waste of sample held up in the main sampling line and requires an additional step to switch the sampling line between the waste reservoir and the actual sample container. The conventional sampling procedure also creates the additional step of properly disposing the flushed material.

SUMMARY

[0007] Aspects of the invention are embodied in a system for withdrawing discrete fluid samples from a vessel. The system includes a main sampling line in fluid communication with the vessel, a pump in fluid communication with the main sampling line and adapted to selectively pump fluid from in the main sampling line in a first direction away from the vessel or a second direction toward the vessel, a first vent port in fluid communication with the main sampling line and disposed on a first side of the pump, a second vent port in fluid communication with the main sampling line and disposed on a second side of the pump, one or more sample containers in fluid communication with a portion of the main sampling line on the second side of the pump, and a flow control system adapted to be selectively configured to open or close each of the first and second vent ports, open or close one or more portions of the main sampling line, and open or close each sample container. When the flow control system is in a first configuration, the first and second vent ports are closed, the main sampling line is open on the first and second sides of the pump, and at least one sample container is open, so that the pump can be operated in a first direction to move an amount of fluid from the vessel, through a portion of the main sampling line, and into the open sample container. When the flow control system is in a second configuration, the first vent port is closed, the second vent port is open, each of the one or more sample containers is closed, and a portion of the main sampling line on the first side of the pump is open so that the pump can be operated in a second direction to move fluid disposed in the main sampling line into the vessel without withdrawing fluid from the at least one sample container. When the flow control system is in a third configuration, the first vent port is open, the second vent port is closed, the main sampling line is closed on the first side of the pump and opened on the second side of the pump, and the at least one sample container is open so that the pump can be operated in the first direction to move fluid disposed in the main sampling line and into the open sample container without withdrawing additional fluid from the main sample container.

[0008] Other aspects of the invention are embodied in a method for aseptically removing a sample portion of a fluid from a vessel containing the fluid. A fluid flow connection is provided between the vessel and a sample container, and fluid is pumped in a first direction from the vessel to the sample container through the fluid flow connection. The vessel is then disconnected from the fluid flow connection, a vent is opened upstream from the pump, and fluid is pumped in the first direction through the fluid flow connection into the sample container without pumping any additional fluid from the vessel. The upstream vent is then closed, the vessel is reconnected to the fluid flow connection, the sample container is disconnected from the fluid flow connection, a vent is opened downstream from the pump, and fluid is pumped in a second direction opposite the first direction through the fluid flow connection and into the vessel without pumping any fluid from the sample container.

[0009] These and other features, aspects, and advantages of the present invention will become apparent to those skilled in