INTENSIFIED CELL CULTURE USING A LINKED BIOREACTOR SYSTEM

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As manufacturing capacity becomes limited and demand and competition increases in the biologics space, the need for more flexible, cost effective, and productive biomanufacturing processes grows. We will describe a novel, intensified cell culture process that uses the cell-bleed of an N-1 (or seed) perfusion bioreactor to continuously feed a production-stage continuous-flow stirred-tank bioreactor. This continuously-linked bioreactor system effectively separates cells into two cultures, one a high growth phase, and the second a highly productive stationary phase. The design of the system allows it to operate indefinitely under steady-state conditions with volumetric productivities exceeding 1.0 gram/liter/day, regardless of any cell-specific productivity loss due to cell line instability. Multiple modes of system start-up will be discussed as part of the optimization work performed to date. Due to the unique design of the linked bioreactor system it may be effectively operated at very large scales typically deemed impractical for more conventional perfusion processes, potentially enabling more efficient use of installed production capacity. The linked bioreactor system attained productivities up to 2.4-fold those achieved in the respective commercial-ready, fed-batch processes, while drastically reducing overall process media consumption. Finally, since the production bioreactor operates as a continuous-flow stirred-tank bioreactor the system creates additional flexibility for downstream operations. Cell culture could be harvested continuously, or intermittently on a potentially variable cycle, depending upon facility fit and maximum efficiency using existing large-volume disc-stacked centrifuges. The resulting integrated continuous biomanufacturing system could operate under very nearly true steady-state conditions uninterrupted for months at a time.