NEXT GENERATION MANUFACTURING FOR BIOLOGICS: INTEGRATION OF A HYBRID MODEL FOR CONTINUOUS MANUFACTURING CONCEPTS INTO A CLINICAL FACILITY

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The “one size fits all” concept is rarely applicable in life, this is also true for the concept of continuous manufacturing where specific applications will differ based upon the requirements of the end user. This is the scenario we describe here in which aspects of continuous manufacturing for both upstream and downstream biologics manufacturing are being incorporated to address the current pipeline needs within Bristol-Myers Squibb. The application is for stable, easily expressed monoclonal antibody processes that require moderate volumes and throughputs, such as for most oncology or immuno-oncology therapies. However, this is countered by challenges of an expanding pipeline that necessitates looking beyond the current platform philosophy for how to modify the process with the goal to increase overall productivity in a flexible manner.

BMS recently constructed a clinical biologics manufacturing facility on the Devens, Massachusetts campus with operations being initiated in two phases. The first phase start-up aligned with a traditional, but flexible (i.e., based upon disposable technologies) upstream and downstream processes and was rapidly brought on line. The second phase is the design and construction within that same manufacturing building purposely left unfinished to allow for the process development group to design and demonstrate a next generation concept for manufacturing. With respect to the upstream process, the decision was made to maintain a fed-batch production bioreactor philosophy, but to employ much higher inoculation densities through use of perfusion culture at the seed bioreactor stage generating the inoculum. This results in cultures with shorter durations and opportunities for increased titer. Selection of the overall cycle time is an optimization between cadence and bioreactor throughput. With respect to the downstream processes, numerous continuous manufacturing technologies were evaluated to handle the increased titers being generated in the bioreactors. These downstream technologies include continuous harvest technologies, multicolumn continuous chromatography for capture, integrated pool-less polishing steps, automated viral inactivation, single pass TFF and in-line diafiltration. The advantages for manufacturing cadence and overall throughput, as well as other outcomes including efforts to decrease perfusion media usage, and a significant reduction in downstream resin costs will be presented. Once the second phase is implemented, the facility will accommodate both traditional as well as this hybrid model for continuous manufacturing interchangeably. The overall benefit to support multiple clinical products and the higher titer/throughputs are expected to reduce the number of batches as well as eliminate resupply batches for clinical supply.