FIPSE-6 Short Presentation 2b

Process Systems Engineering in Gene Therapy Drug Development and Manufacturing

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ABSTRACT

Gene therapy is a promising therapeutic approach for genetic and acquired diseases nowadays. Among DNA delivery vectors, recombinant adeno-associated virus (rAAV) is one of the most effective and safest vectors used in commercial drugs and clinical trials. However, the current yield of rAAV biomanufacturing lags the necessary dosages for clinical and commercial use, which embodies a concentrated reflection of low productivity of rAAV from host cells, difficult scalability of the rAAV-producing bioprocess, and high levels of impurities materialized during production. Those issues directly impact the price of gene therapy medicine in the market, limiting most patients' access to gene therapy. In this context, the current practices and several critical challenges associated with rAAV gene therapy bioprocesses are reviewed in the engineering biology content – systems engineering in biology. The talk focuses on how the systems engineering approach can tackle these challenges. These could improve biomanufacturing if these advances are integrated effectively into the current systems.

As a system engineering approach for gene therapy manufacturing, the digital twin model is discussed. Perfusion processes have been closely studied via mathematical modeling for the past decade, leading to more intensified processes. An intensified perfusion process is commonly considered at a steady state with viable cell density controlled at a near-constant level. However, despite this assumption, different metabolites may still accumulate or become depleted during the process. The accumulation of toxic metabolites and the depletion of essential metabolites gradually impact productivity and product quality during the long period of the perfusion process. However, the prediction of the metabolism of cell culture in the extended production process remains challenging, and the perfusion operation for mAb production becomes difficult. The system engineering community can tackle these challenges with a few existing tools, such as multi-scale modeling, model predictive control, flowsheet modeling, and so on. In this presentation, the problems and possible solutions are outlined for further discussion.

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