CHALLENGES IN THE DEVELOPMENT AND SCALE-UP OF A PURIFICATION PROCESS FOR AN ATTENUATED LIVE VIRUS VACCINE CANDIDATE

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Key Words: Live Attenuated Virus, Single-Use Bioreactor, Purification, Closed Sterile Processing

Prophylactic live attenuated vaccines (LAV) have been successfully developed for multiple viral disease targets, offering an advantage over subunit vaccine approaches by simultaneously stimulating innate, humoral and cellular immune responses. However, the development of manufacturing processes for robust production of LAVs at commercially viable scales can be challenging, particularly because of the need to use novel and/or adherent cell lines, the inefficient performance of conventional chromatography for processing large viral particles, and the complexity of product characterization. Further adding to these challenges, closed-system aseptic processes are required for those viruses too large for terminal sterile filtration, thereby limiting processing options and complicating process logistics at commercial scale. Highlighting these challenges, we present here on the development of a scalable, fully sterile, purification process for a large, enveloped, live attenuated virus having multiple glycoprotein complexes. During the development of this vaccine the process was changed from a static cell culture process to one that is amenable to scaling in a stirred tank single-use bioreactor. This change presented challenges for the purification process, requiring modifications of the process separation techniques including evaluation of new unit operations of various separation modes such as membrane and monolith absorbers, resin chromatography, selective precipitation, large pore tangential flow filtration, and centrifugation. Critical to this evaluation was the understanding of the adaptability of these unit operations to closed sterile processing, with a premium placed on industry ready, single-use technologies. Through this process development effort, a scalable, sterile, purification process was defined that met targets for purity and yield.