DEVELOPMENT OF A HIGH-YIELD PURIFICATION PROCESS FOR THE PRODUCTION OF INFLUENZA VIRUS VACCINES

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Key Words: Influenza virus vaccine, Animal cells, Hemagglutinin (HA), Benzonase, Column chromatography

Production of influenza virus in animal cells has emerged as an alternative to conventional platforms such as egg-based production system. Animal cells, especially MDCK and VERO cell lines, are widely used as the primary production cell for influenza virus vaccine because of their high susceptibility to infection with various influenza viruses. Recently, a robust and reliable purification process was successfully developed for the production of quadri-valent HA proteins (from two strains of the type A virus and two strains of the type B virus) by using animal cell-based production system in Green Cross Corp., Korea. The UF/DF process, Benzonase treatment at high temperature as well as column chromatography strategy was optimized to maximize the final HA production yields. Benzonase treatment was conducted to reduce in hcDNA (host cell DNA) because hcDNA was main impurity for cell-based influenza virus vaccine. A simple and stable UF/DF process has been tested with membrane molecular weight cutoffs of 100 and 300 kDa as well as 0.2 and 0.45 um microfiltration membrane. Anion exchange chromatography (AEC) and size exclusion chromatography (SEC) were selected for acceptable reduction in hcDNA and HCP. AEC was used to separate hcDNA from virus at a salt concentration of 0.5 M sodium chloride. The HA yield through AEC & SEC combination process was sufficiently achieved under specific purification process condition. Overall, the amount of residual hcDNA was reduced to an acceptable level (10ng/dose) and the increased HA yield was maintained throughout the whole process. The performance, productivity and scalability of the purification process were successfully demonstrated in over 30 GMP batches using 4 different influenza virus strains.