

INTENSIFICATION OF A MULTI-PRODUCT PERFUSION PLATFORM – MANAGING GROWTH CHARACTERISTICS AT HIGH CELL DENSITY FOR MAXIMIZED VOLUMETRIC PRODUCTIVITY

Shawn Barrett, Continuous Manufacturing Skill Center, BioPharmaceutics Development, Sanofi
shawn.barrett@sanofi.com

Wenqin He, Continuous Manufacturing Skill Center, BioPharmaceutics Development, Sanofi
Jared Franklin, Continuous Manufacturing Skill Center, BioPharmaceutics Development, Sanofi

Mara Stangl, Continuous Manufacturing Skill Center, BioPharmaceutics Development, Sanofi

Aleksandar Cvetkovic, Continuous Manufacturing Skill Center, BioPharmaceutics Development, Sanofi

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Integrated Continuous Biomanufacturing (ICB) provides many important strategic advantages for therapeutic protein production through process intensification, simplification and integration. Dramatic reductions in cost of goods manufactured can be achieved by pushing perfusion culture towards high productivity at moderate perfusion rate and integrating with multi-column capture. We have demonstrated that an in-house chemically defined medium designed for high volumetric productivity (VPR) can support clones producing different monoclonal antibodies in perfusion bioreactors at cell densities >100 million viable cells/mL and VPR from 4 to 6 g/L/day. However, for other cell lines tested productivity could not be consistently sustained due to declining growth rate at high cell density. It was demonstrated that increased bleed rates could extend the culture duration for these clones but only with substantially lower cell density and productivity, and reverting to a less productive perfusion medium improved culture longevity to a certain degree. It was shown that continuous addition of a concentrated supplement to this medium could improve productivity to levels comparable to the high-VPR medium, but this appeared to be less effective for clones with lower specific productivity. Some clones producing the same biologic were observed to exhibit either sustained or declining growth rate at high cell density, indicating clonal variability should be considered as another factor that can affect this growth phenotype. Potential strategies to mitigate declining growth rate in high cell density perfusion culture will be discussed and additional case studies on the application of intensified perfusion will be examined.