PROCESS DEVELOPMENT APPROACHES FOR EXPANSION OF ADHERENT STEM CELLS IN MICROCARRIER-BASED BIOREACTOR CULTURE

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Key words: MSC, bioreactor, single-use

Industry trends in regenerative medicine show an increased need for scalable and closed manufacturing of cell therapies. Single-use bioreactor systems have proven suitable as a platform to meet the industry's needs. Key process parameters for cell culture performance in these systems include pH, dissolved oxygen (DO) and agitation rates. Especially important is the understanding and application of appropriate solid-liquid mixing, which is essential for microcarrier-based cultures used for adherent stem cells. Agitation rates that are too high in microcarrier-based cultures can be correlated with smaller eddy lengths that impact cellular shear. Conversely, agitation rates that are low do not support the consistent microcarrier turnover required for cell access to nutrients, DO, and maintenance of pH. Moreover, suboptimal agitation rates may impact cell-to-microcarrier attachment and transfer. Here, we summarize a stepwise approach to optimizing pH, DO and agitation set-points in the Mobius® 3L single-use bioreactor for mesenchymal stem/stromal cells (MSCs). The theoretical agitation operating range best suited for microcarrier cultures was calculated based on the Zwietering equation for suspension of solids in stirred tanks, and verified experimentally with human bone marrow-derived MSCs. Upper agitation limits were defined by Kolmogorov's theory of turbulent eddy lengths, and were substantially higher than the agitation rates required to keep microcarriers suspended. Identifying optimal pH, DO and agitation rates for microcarrier-based bioreactor expansion of adherent cells is paramount to developing a robust platform for use in a controlled manufacturing environment.