CHALLENGES AND SOLUTIONS FOR ALLOGENEIC CELL THERAPY MANUFACTURING

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Key Words: allogeneic cell therapies, scalable manufacturing, bioreactor hydrodynamics, oxygenation, medium exchange

Development of a scalable and robust manufacturing process will be critical for successful commercialization of an allogeneic cell therapy product. However, the biological characteristics of anchorage-dependent cells and the process requirements for mass production of living human cells as a final product create different challenges compared to traditional biotech manufacturing. This presentation will discuss some of these challenges and potential solutions, particularly those that relate to manufacturing of allogeneic cell therapy products at larger volumetric scales. Single-use bioreactors have the potential to be the optimal technology for scalable and cost-effective manufacturing of therapeutic cells. However, cell expansion and differentiation processes involving large suspended particles, such as cell aggregates or microcarriers with attached cells, are significantly affected by a bioreactor's hydrodynamic conditions. The intensity and distribution of conditions such as fluid flow, turbulent energy dissipation rate, and shear forces will influence the quality and quantity of cells. A bioreactor that is capable of creating optimal conditions at small scale during process development and then consistently replicating those conditions at larger scales will be a key enabling technology. Maintaining optimal growth parameters for therapeutic cells during scale up in bioreactors is another critical challenge. In particular, providing sufficient dissolved oxygen and maintaining optimal pH for large-scale cell culture processes will be essential to maximizing cell yield and quality. For recombinant protein manufacturing processes, gas is sparged directly into fluid and anti-foaming agents are added, as such chemicals can be removed during extensive downstream purification steps. In contrast, therapeutic cells are the final product and are more susceptible to shear damage from bursting bubbles, and it would be difficult to remove hydrophobic anti-foaming chemicals from cell membranes through simple buffer washes. Any potential solution for large-scale oxygenation and removal of pCO_2 from a bioreactor will likely seek to avoid exposing cells to sparging or foreign chemical contaminants. The process duration and conditions of exchanging spent medium in a bioreactor at larger scales is another potential bottleneck for allogeneic cell therapy manufacturing. Complete and rapid medium exchange is especially crucial for differentiation processes in order to minimize unwanted heterogeneous differentiation of cells. Pausing agitation and allowing cell aggregates or microcarriers to settle in order to remove supernatant and replenish new medium becomes a less desirable option at larger scales due to prolonged processing times and undesirable conditions which can negatively impact cell viability, yield, and quality. The optimal solution will minimize the amount of leftover medium and the time for cells to be transferred into new medium. A final challenge to consider is large scale dissociation of cell aggregates into single cells, or cells from surfaces of microcarriers, for serial passaging or harvesting. Addition of enzymes along with a temporary increase in impeller agitation speed are typically performed to facilitate separation. Depending on a bioreactor's mixing characteristics, the agitation required to efficiently dissociate considerable quantities of cells at larger volumes may also increase the likelihood of damage to cells. A bioreactor and methodology that can minimize potential harm to cells during dissociation processes are desirable solutions. Ultimately, all of these presented manufacturing process challenges will need to be addressed in order to scale up allogeneic cell therapy products from research and development to clinical and commercial production.