SCALABLE DOWNSTREAM PROCESS DEVELOPMENT AND MANUFACTURING IN CGMP FOR HUMAN INDUCED PLURIPOTENT STEM CELL DERIVED PRODUCTS

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Many in vitro culture systems for the differentiation of induced pluripotent stem cells (iPSC) are an extension of the basic laboratory cell culture methods used to pioneer the differentiation of these cells. These T-flask or spinner flask-based cultures and associated open centrifugation operations for downstream processing can be sufficient for initial market penetration – in the case of a research tool product – or pre-clinical and early clinical trials – for cellular therapies. As demand for these products increase, it is necessary to scale up or scale out these operations. Moreover, for clinical application, it is advantageous to use a single-use, closed and controlled system for cell processing. While much attention is often paid to the upstream cell culture operations in cell therapy manufacturing, it is equally important to utilize robust downstream operations including cell washing, concentration, formulation, and cryopreservation.

Toward this end, we have evaluated multiple scale-up and closed system technologies for cell washing and concentration for iPSC and iPSC-derived cell products including high-capacity centrifugation and counter-flow centrifugation. We found that the appropriate downstream technology and its operation scheme varies depending on the volume reduction ratio, shear sensitivity, carryover limitations, and throughput requirements. This presentation will describe applications of these platform technologies to target scale and cell type and their implementation to manufacturing in our current Good Manufacturing Practice (cGMP) clinical manufacturing facility (i-FACT). In one case study, we will describe a closed approach to cell washing of iPSC for passaging from 10L bioreactor culture of iPSC. In another, we will present a closed solution for cell concentration and formulation for cryopreservation.