MANUFACTURING HUMAN MESENCHYMAL STEM CELLS AT CLINICAL SCALE: PROCESS AND REGULATORY CHALLENGES

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There is an obvious increasing interest in human mesenchymal stem cell (hMSC)-based therapies for regenerative medicine (e.g. neurology, cardiology, immunology, orthopaedics). At the beginning of May 2018, there were 253 registered clinical trials using hMSCs (www.clinicaltrials.gov). Despite the large number of current clinical studies, only 13 hMSC-based products have received regulatory approval. In order to efficiently manufacture hMSC-based products, not only must the targeted cell quantity and quality be taken into account, but the production costs must also be considered. In general, autologous and allogeneic stem cell products are characterized by similar upstream processing (USP), downstream processing (DSP), formulation, and fill & finish operations. Typical USP operations are manufacturing of the Master Cell Bank (MCB) and the Working Cell Bank (WCB), seed cell production, and subsequent cell expansion. The DSP steps include cell harvesting, cell detachment, cell separation, washing and concentration procedures, and medium exchange. However, before hMSCs can be administered as an Advanced Therapeutic Medicinal Product (ATMP), additional formulation, and fill and finish steps have to be carried out. The main differences between allogeneic and autologous manufacturing approaches are the number of therapeutic doses generated in each batch and the number of patients treated. Therefore, it is unsurprising that allogeneic therapies are the more cost-effective method in terms of hMSC production. Furthermore, various economic studies have demonstrated that USP and in particular, hMSC expansion, represent the main cost drivers when examining the entire manufacturing process. In order to achieve the high cell numbers of up to 10^{13} cells per batch needed in allogeneic hMSC manufacturing processes, manufacturers have to move away from traditional planar cultivation systems. Many reports over the last years have shown that instrumented, single-use bioreactors in combination with microcarriers are promising systems for this task.

Even though different procedures and equipment for USP and DSP are already available and established for allogeneic production of hMSCs, various challenges still exist. Therefore, the authors intend to highlight the current state of the art of allogeneic hMSC manufacturing and show the current main process and regulatory challenges for USP and DSP operations.