MODEL-BASED SCALE-UP OF CHO CELL CULTURE PROCESS

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Approximately 70% of the world's biopharmaceutical drugs are produced in suspension culture in bioreactors using Chinese Hamster Ovary (CHO) cells. The high degree of flexibility and short turnaround times required to develop these processes means that most process development facilities have adopted single-use bioreactors (SUBs) for the early phases of a drug candidate, typically operating within the range of 200 to 2000 L. However, when product demand exceeds certain thresholds, it is no longer economically viable to produce biopharmaceuticals in SUBs, and hence, large-scale manufacturing in 10,000-20,000 L stainless-steel bioreactors becomes relevant.

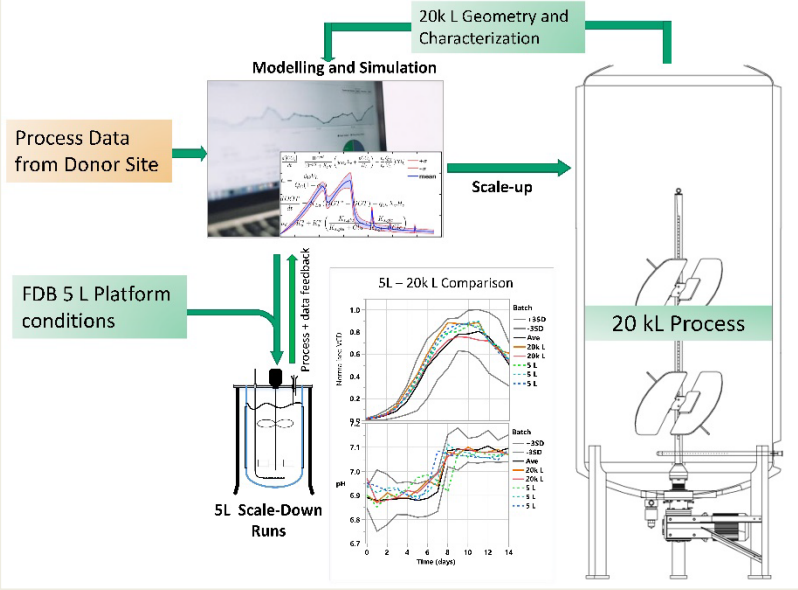

Figure 1 – Model-based scale-up framework with supporting 5 L runs. Insert: comparison between 5 L runs and 20 kL batches.

Given the unique micro-environments required by CHO cells to produce biopharmaceuticals with pre-defined CQAs, the scale-up of these processes from small-scale and SUBs to large-scale stainless-steel bioreactors can be challenging, especially when the bioreactors at the different scales are geometrically dissimilar. The FDB (FUJIFILM Diosynth Biotechnologies) scale-up strategy uses the historical data of the process to derive scale-independent mass transfer, mixing and cellular kinetics that are unique to the cell line and to the process. An intermediate assessment of these metrics is carried out, comparing the mass transfer and mixing requirements of the process to equipment capabilities, site experience and general industry standards. The intermediate assessment is followed by advanced simulation of the process at large-scale, with the objective of matching donor site process profiles in the simulations. The simulations are done with an integrated framework of mechanistic models, where the pre-assessed mass transfer, mixing and cellular kinetics are used as input to the simulations. Concurrently, simulations are also performed for a scale-down version of the process, which is used to run 5 L bioreactors to establish the process at FDB. The results of the 5 L establishment runs and the simulations of the 20 kL process allow a final, holistic strategy to be put in place for runs at the 20 kL scale. The framework is shown in Figure 1. The integrated model ensures that the scale-up of a new process is based on a full assessment of mass transfer, mixing and biological considerations, as opposed to matching a single criterion such as *vvm, P/V* or K_La, which is the novelty of this strategy.

As a large-scale CDMO, FDB receives CHO cell culture processes that are fundamentally variable, with different requirements for each process, such as meeting specific pH, pCO_2, osmolality and metabolite profiles, which all may impact the CQAs of the biological products. As no two donor processes are the same, and likewise rarely no two donor bioreactors are geometrically the same, the scale-up strategy must be versatile enough to accommodate all processes. The integrated, model-based scale-up strategy presented here has proven to be versatile, cost effective, fast and a reliable way to de-risk the scale-up of CHO cell culture processes, irrespective of the donor site bioreactor type and process requirements.