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The use of scale-down models is essential for the development, characterization and continuous improvement of commercial cell culture processes. A model demonstrated to be predictive of large-scale performance is advantageous as small-scale data can be used to support process investigations and changes, reduce costs and consequently accelerate new therapies to market. Aligning geometric aspect ratios and dimensionless engineering parameters improved the overall scale-down model representation for key process outputs such as pCO_2 accumulation and cell viability. Despite these changes, the revised scale-down model did not fully match the large-scale process lactate accumulation. Interestingly, it was demonstrated that pCO_2 accumulation at small-scale reduced net lactate consumption, however pCO_2 accumulation alone was not sufficient to fully match the absence of metabolic shift observed at large-scale. Small-scale pH ranging studies demonstrated that at settings above the large-scale process set point, the scale-down reactors had lactate profiles more closely matching the commercial process. Conversely, a lower pH set point in the commercial-scale reactor combined with an improved sparging strategy to remove CO_2 had a transient increase in net lactate consumption, falling short of a metabolic shift. Combined, these data suggest that physicochemical differences between small and large scale bioreactors are contributing to the differences in metabolic behavior seen in this process. A metabolomic approach was used to elucidate the root cause of metabolic difference between scales. A range of pH settings from 6.8-7.3 were evaluated in the 5L scale down model of the commercial process. Samples from the commercial process operated at different pH set points were also obtained and included in the study. Results of metabolic profiling and hypothesis explaining the metabolic differences observed between scales will be presented.