UNDERSTANDING ELEVATED LACTATE LEVEL IN A LARGE-SCALE PERFUSION PROCESS TO IMPROVE PERFORMANCE

Peter Amaya, MedImmune, LLC., One MedImmune Way, Gaithersburg, MD, 20878
amayap@medimmune.com
Brena Williams, MedImmune, LLC.
Chris Klaver, MedImmune, LLC.
Jeong Lee, MedImmune, LLC.

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Operational differences between the development lab and the GMP manufacturing facility can present challenges when developing a scalable process that conforms to the intended facility. Differences in the media storage conditions and metabolite sampling method between the bench scale and manufacturing scale perfusion processes were found to contribute to discrepancies in process parameters and ultimately lower productivity during scale-up runs.

Unlike the bench scale runs, perfusion media was prepared and stored in an air-sparged vessel prior to being fed into a 500L bioreactor. Media air sparging resulted in elevated media pH, which consequently altered the dissolved amino acid and metal ion levels in the media prior to being fed into the reactor. During a subsequent run, the pH level was controlled during air-sparging. Productivity from the 500L process with pH-controlled media storage was higher than the 500L process with uncontrolled pH during media storage. Additionally, lactate levels were lower for the 500L scale process when pH was controlled during media storage.

Comparing the 500L scale process to the 3L scale process used in development, measured lactate concentration levels during all 500L scale runs were elevated relative to the lactate concentrations measured during the 3L development runs. A key difference between development and 500L runs was the procedure used to measure lactate, specifically the difference in timing between drawing the sample and measurement. This difference combined with the fact that the 500L runs were performed in pressurized vessels led to the discrepancy in measured lactate levels during the process. The mechanism involved is likely related to CHO cell regulatory volume decrease (RVD).[1] When CHO cells are withdrawn from a pressurized reactor, they undergo osmotic swelling followed by efflux of ions such as potassium and chloride as well as organic osmolytes such as amino acids, glucose and lactate. This efflux is known to occur over only a few minutes; therefore, a delay of such time in metabolite measurements can lead to a discrepancy between scale-up and development data.

Careful consideration must be given to differences not only in the process (e.g. media storage), but also in the methods utilized to gather process parameter data. Because adjustments to the cell culture conditions affecting cell productivity are made based on measurements of process parameters (e.g. pH level), discrepancies in the data acquisition methods for these parameters can indirectly affect cell productivity if not carefully evaluated.

[1] Sarkadi, B., Attisan, L., Grinstein, S., Buchwald, M., Rothstein, A., “Volume Regulation of Chinese Hamster Ovary Cells in Aniisoosmotic Media”, Biochimica et Biophysica Acta, 774 (1984) 159-168.