Improved and consistent cell culture performance of CHO-K1 fed-batch culture and cost savings achieved through Recombinant Insulin supplementation

Background

Biomanufacturing of therapeutic proteins, especially monoclonal antibodies (mAbs), relies typically on CHO cells, due to their adaptability, infection resistance, and ability to create high-quality post-translational modifications. While convenient ready-to-use cell culture media for CHO cells are widely available, they cannot perfectly suit every cell line and monoclonal antibody production process. Therefore, customizing media formulations to address specific process requirements and cell line needs remains essential for optimal results. In this optimization of the biomanufacturing process, insulin is crucial to enhance cell growth and productivity. The use of high-quality raw materials plays a key role in ensuring the efficiency of these processes. Particularly, consistency in the quality of the raw materials used, like insulin, is crucial to ensure reproducible performance, leading to reliable results across various production batches. In efforts to reduce manufacturing costs, some bio-pharma manufacturers have attempted to remove insulin from the process. However, this has frequently led to counterproductive outcomes, ultimately prompting a return to the use of insulin, driven by its overall convenience.

Aim of the study

In this study, we explored the effects of insulin supplementation on two different catalog chemically defined media, measuring changes in cell proliferation and mAb production in CHO-K1, cultured in a fed-batch system. Additionally, we assessed the consistency of different insulin batches in stimulating mAb production. Lastly, we conducted an economic impact assessment of insulin supplementation in biomanufacturing processes for mAb production, calculating how the cost per gram of mAb can change in response to insulin supplementation.

Study description

Cell culture conditions: To assess how insulin supplementation enhances cell proliferation and mAb production, varying concentrations of Recombinant Insulin were added to fed-batch cultures of mAb-producing CHO-K1 cells. Specifically, CHO-K1 cells were grown in 125 ml shake flasks (120 rpm, 37°C, 5% CO2) using two different commercially available chemically defined media (Media 1 and Media 2). Recombinant Insulin was added to both basal media and feed every 2 days at three different final concentrations (2, 5, and 10 mg/L), and cells received feed supplementation either daily or every three days according to media manufacturer instructions. Cell proliferation was monitored daily throughout the 14-day period, while mAb production was measured at day 14. Three separate batches of Recombinant Insulin were evaluated and compared for their capacity to promote mAb production.

Results

Supplementation of Recombinant Insulin to two chemically-defined media enhances CHO-K1 cell growth and increases mAb yield

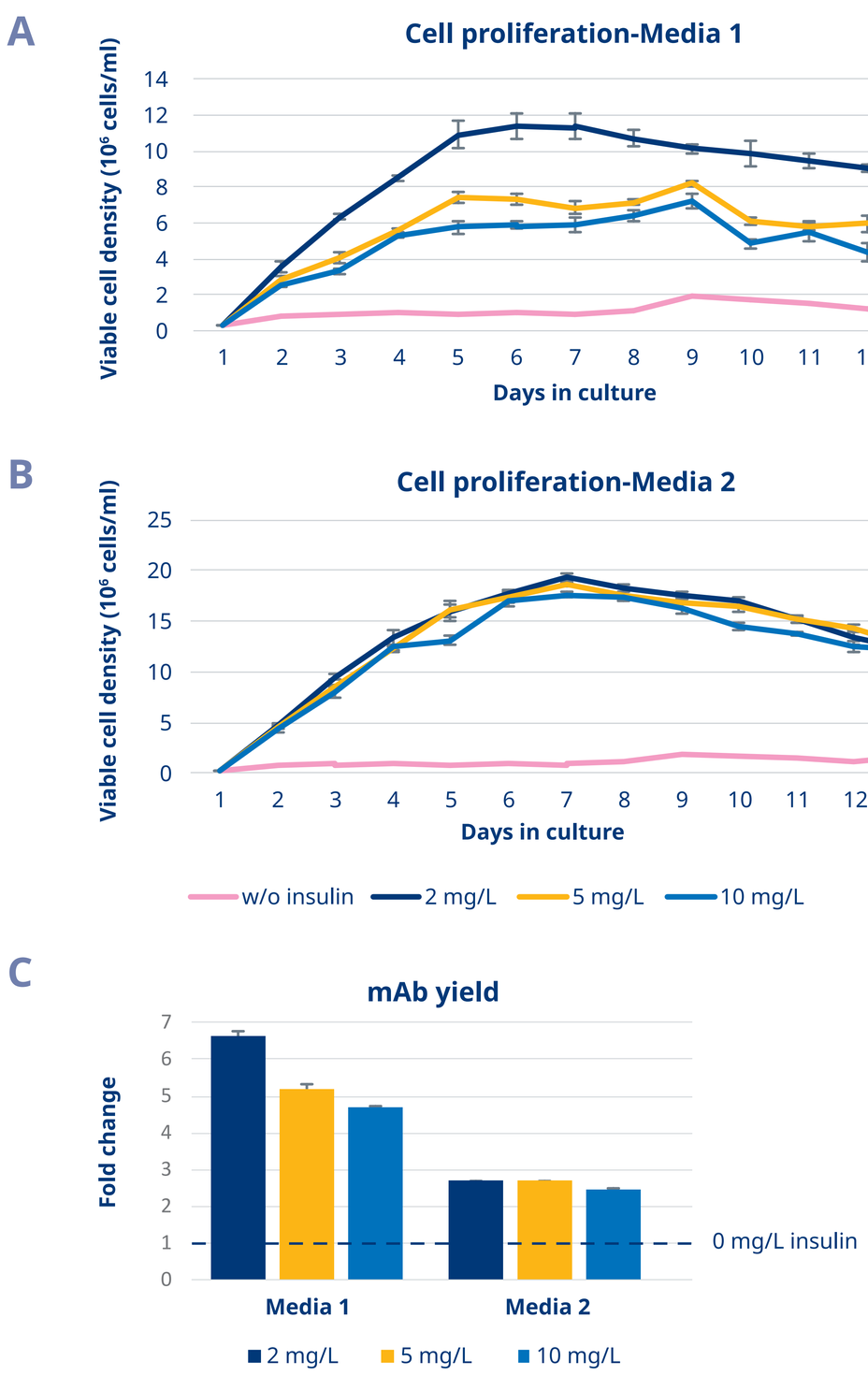

Figure 1. Although cell proliferation varied between different media types, adding Recombinant Insulin at three different concentrations (2, 5, and 10 mg/L) consistently enhanced CHO-K1 cell growth in both chemically defined media tested (A, B). The CHO-K1 cell line produced significantly higher mAb yields with all insulin concentrations, regardless of which media was used. Notably, the lowest insulin concentration tested (2 mg/L) produced effects that were either superior to or comparable with those achieved at higher insulin concentrations (C).

High-quality Recombinant Insulin exhibits batch-to-batch consistency in enhancing mAb production

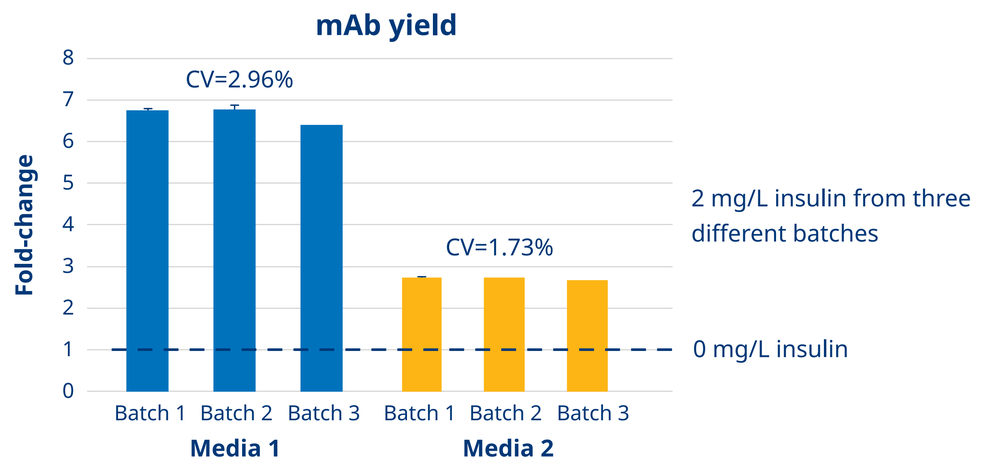

Figure 2. Recombinant Insulin from different manufacturing batches shows consistent performance when supplemented to a chemically defined media. The variation in mAb yield between three different insulin batches was minimal, ranging only from 1.5 to 3.3%. This coefficient of variation (CV) was calculated using the average yields from three technical replicates for each of the three insulin batches.

Recombinant Insulin supplementation reduces mAb production costs

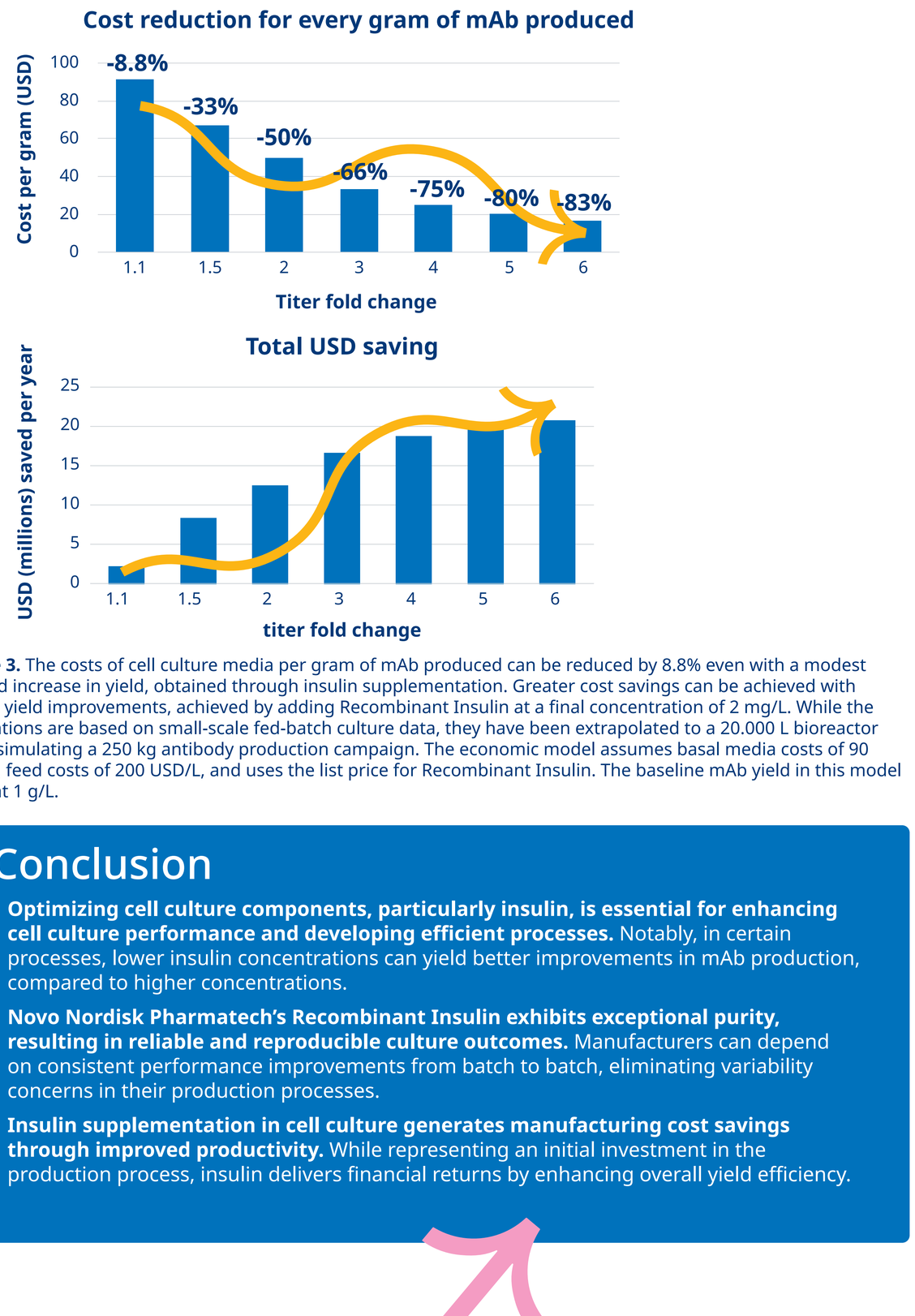

Figure 3. The costs of cell culture media per gram of mAb produced can be reduced by 8.8% even with a modest 1.1-fold increase in yield, obtained through insulin supplementation. Greater cost savings can be achieved with higher yield improvements, achieved by adding Recombinant Insulin at a final concentration of 2 mg/L. While the calculations are based on small-scale fed-batch culture data, they have been extrapolated to a 20.000 L bioreactor scale, simulating a 250 kg antibody production campaign. The economic model assumes basal media costs of 90 USD/L, feed costs of 200 USD/L, and uses the list price for Recombinant Insulin. The baseline mAb yield in this model is set at 1 g/L.

Conclusion

- **Optimizing cell culture components, particularly insulin, is essential for enhancing cell culture performance and developing efficient processes.** Notably, in certain processes, lower insulin concentrations can yield better improvements in mAb production, compared to higher concentrations.
- **Novo Nordisk Pharmatech's Recombinant Insulin exhibits exceptional purity, resulting in reliable and reproducible culture outcomes.** Manufacturers can depend on consistent performance improvements from batch to batch, eliminating variability concerns in their production processes.
- **Insulin supplementation in cell culture generates manufacturing cost savings through improved productivity.** While representing an initial investment in the production process, insulin delivers financial returns by enhancing overall yield efficiency.

Recombinant Insulin: the ally for efficient biomanufacturing

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