Cell Culture Media-Feed Co-Optimization Unlocks Extended Fed-Batch Performance in CHOZN® GS$^{-/-}$ Cells

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Introduction

Despite the substantial success of antibody-based biotherapeutics, which include monoclonal antibody (mAb) products, widespread adoption and patient access of these therapeutics are constrained by high prices[1]. A prominent incentive driving down both the cost of goods (COGs) and overall prices of mAbs is the growing biosimilars market, which is accelerating as originator biologic manufacturing patents expire and competition expands[2]. In addition, upstream cell culture productivity gains have been a major contributor to considerable reductions in COGs in recent decades[3]. Through continued innovation, OPM Biosciences has developed high-performance, chemically defined cell culture media products to improve upstream process efficiency and reduce COGs, thereby enabling greater affordability and accessibility of these life-saving therapeutics. Here, we demonstrate how products in the OPM-CHO media portfolio, tailored for stable Chinese hamster ovary (CHO) cell protein expression, can boost cell proliferation while maintaining high cell viabilities to unlock greater product titers in extended fed-batch processes.

Materials & Methods

CHOZN® GS$^{-/-}$ host cells were obtained from Merck KGaA (Darmstadt, Germany). The CHOZN® GS$^{-/-}$ clone utilized in the following investigation was engineered by the OPM Cell Line Development Department for stable expression of a known immunoglobulin G4 (IgG4) mAb biosimilar. Fed-batch processes were performed in 125 mL Erlenmeyer shake flasks and maintained in an incubator shaker. Cells were inoculated at a density of 1.0×10^6 cells/mL in basal medium, fed with feed medium and feed supplement, and supplemented with glucose to maintain glucose concentrations >1 g/L. Cell densities and viabilities were measured with a Vi-CELL Cell Viability Analyzer (Beckman Coulter), metabolite concentrations were measured with an M-100 Biosensor Analyzer (Shenzhen Sieman Technology), and mAb titers were measured using a Cedex Bio Analyzer (Roche CustomBiotech). Product quality of a selected group was evaluated by the OPM Analytical Department after a one-step purification and compared against the known reference molecule.

Key Takeaways

- Greater viable cell densities (VCDs) and high late-phase cell viabilities enable extended fed-batch processes, **increasing titers by 40+%**
- Process **maintained key quality attributes** to meet reference product critical quality attributes (CQAs)

Results & Discussion

Group	Basal Medium	Feed Medium	Feed Supplement
OPM #1-1	StarCHO™ Medium	StarCHO™ Feed Plus	CDFS12™
OPM #1-2	StarCHO™ Medium	VectorCHO™ Feed	CDFS12™
OPM #2-1	StarCHO™ Plus Medium	StarCHO™ Feed Plus	CDFS12™
OPM #2-2	StarCHO™ Plus Medium	VectorCHO™ Feed	CDFS12™

Table 1. Combinations of OPM basal media, feed media, and feed supplements tested. Performance was benchmarked against two global competitor products following the manufacturers' recommendations.

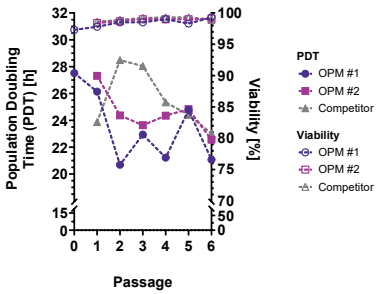

Figure 1. Population doubling time (PDT, closed symbols, left axis) and viability (open symbols, right axis) of cells during passaging and seed train expansion via dilution. Average PDT was lowest in OPM #1 (StarCHO Medium) and highest in the competitor medium. Average cell viabilities were ≥98.0% in all media. Fed-batch shake flasks were inoculated after passage four.

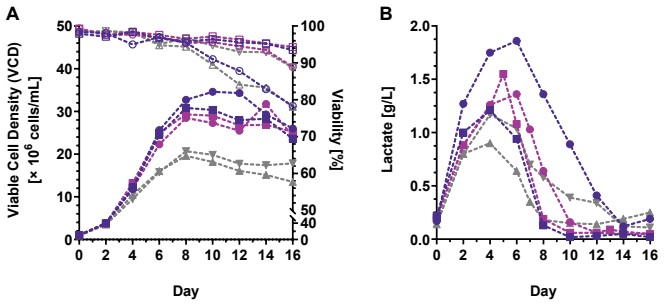

Figure 2. Viable cell density (VCD), cell viability, and lactate profiles during fed-batch processes. **(A)** Viable cell densities (closed symbols, left axis) and cell viabilities (open symbols, right axis). OPM media and feeds supported higher peak VCDs than competitor products while maintaining similar or better cell viabilities. Even with process extension to day 16, viabilities of OPM #1-2, 2-1, and 2-2 remained near or >90%. **(B)** For all groups, lactate concentrations peaked between days 4 and 6 and remained <2 g/L throughout the entire process.

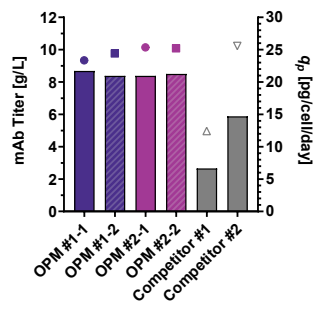

Figure 3. Final volumetric mAb titers (bars, left axis) and cell-specific productivities (q_p, symbols, right axis) after 16-day fed-batch processes. Titer measurements demonstrated considerable titers gains of 40+% with OPM products relative to competitor products and comparable or better cell-specific productivities.

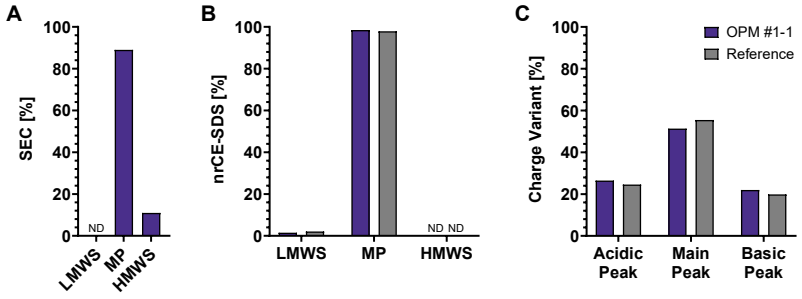

Figure 4. Analytical characterization of product obtained from OPM #1-1 after a 16-day fed-batch process and the reference molecule for comparison. Size variant analysis via **(A)** size-exclusion chromatography (SEC) and **(B)** non-reduced capillary electrophoresis sodium dodecyl sulfate (nrCE-SDS) demonstrated limited product fragmentation or aggregation. LMWS: low molecular-weight species. MP: main peak. HMWS: high molecular-weight species. ND: not detected. **(C)** Charge variant analysis via imaged capillary isoelectric focusing (icIEF) revealed similar charge variant distribution of the product in comparison to the reference molecule.

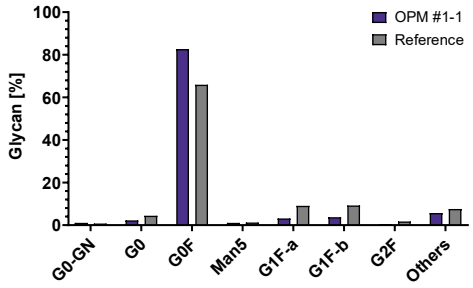

Figure 5. *N*-glycan analysis of product obtained from OPM #1-1 after a 16-day fed-batch process and the reference molecule via ultra-performance liquid chromatography with fluorescence detection (UPLC-FLD). While there is some variation in the glycosylation profile of the product obtained in comparison to the reference molecule, it is important to note that for IgG4 therapeutics, such as the biosimilar here, the glycan profile is not a critical quality attribute (CQA). This is because IgG4 isotype molecules do not rely on fragment crystallizable (Fc) region effector functions such as antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) as part of their mechanism of action[4]; therefore, the therapeutic and clinical efficacy of the molecule is not heavily reliant on its glycosylation profile[5].

Conclusions & Future Work

OPM Biosciences offers a wide range of catalog and custom cell culture media solutions for development and manufacturing of biotherapeutics. These results demonstrate how a few products from the OPM-CHO media portfolio promoted increased VCDs while simultaneously sustaining high late-phase cell viabilities that allowed for extended fed-batch process durations. As a result, OPM media and feeds bolstered final titers, outperforming the leading global competitor products, while maintaining satisfactory quality attributes relative to the reference molecule. Driven by continuous innovation, ongoing future work is focused on advancing an intensified, extended fed-batch strategy enabled by our sustainable media and feed platform. Whether your molecule of interest is an innovator biologic, biosimilar, or biobetter, OPM Biosciences offers solutions to meet your productivity and critical quality attribute requirements.

Acknowledgements

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References

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