_How will biotherapeutics be produced in 2063?

History_

The first regulatory approval for a CHO-produced commercial product (a tissue plasminogen activator) was in 1987. The yield was <50 mg/L.

First recombinant monoclonal antibody (mAB) approved was rituximab, a CHO-produced chimeric mouse antibody, in 1997. At that time, yields for mAB expression of 1g/L were considered excellent.

Progress in CHO_

Thanks to massive and concerted research investments in the past 25 years, there have been huge improvements in CHO-based processes.

Today, 3-8 g/L for mAB production are routinely reported. Improved control of post-translational modifications (PMT) was achieved.

The improvements were across the whole process: better cell line biology but also better media, better construct design, better selection of best producing clones and better bioreactors.

Dominance_

Between 2018-20221, CHO was used to produce 97% of all approved biologics, with CHO-produced mAbs representing 85% of all approved novel biological entities (this number excludes biosimilars). E.coli was used for 20% of new biotherapeutics. Other microbial systems such as the yeasts Pichia pastoris and Saccharamyces cerevisiae were used for 5% of the new biotherapeutics.[1]

CHO and E.coli are certainly dominant. Are they then the BEST? And what do we mean by „Best“?

Fast Adoption_

The COVID pandemic brought bioproduction innovation to the market.

Novel bioproduction systems used for COVID-related products, with Emergency Use Authorization or Market Authorization:

mRNA/LNP— deployed in the BioNTech/Pfizer and Moderna vaccines
PER-C6—AAV-producing cell line for Janssen's COVID vaccine
plant-based VLPs—COVIFENZ vaccine, from Medicago (a former division of Mitsubishi).

Facility trends_

Reactor design and process intensification have also greatly contributed to more efficient CHO-based production.

After two decades of building facilities with 25 000L steel bioreactors for commercial production of mABs, the most recent facilities focus on flexibility, with extensive use of modular design in a „ball-room“ space, smaller single-use bioreactors (SUB) and other SU equipment. SUB are not yet optimized for microbial production, though.

Automation, Process Analytical Technology (PAT), Artificial Intelligence, Digital Twins and Augmented Reality are being extensively used, contributing to safer and more efficient processes.

Ongoing Limitations_

CHO cell lines are not genetically stable. Even after many years of use, full genetic characterization of many producing lines is not widely available, and there are challenges with PTM variation. Some needed recombinant proteins are poorly produced in the expression systems currently most developed.[2]

While E.coli continues to be widely used for plasmid DNA production, needed as starting material in mRNA, viral vector production and in CRISPR-Cas systems, it is far from being an „optimal“ production host.

"If today we asked a graduate student in molecular biology to design a optimized biotherapeutic production system, would they suggest CHO or E.coli? Or would they design a novel system?"

New therapeutic modalities might benefit from totally redesigning the production platforms.

But there never seems to be enough time to try novelties. And despite the recent introductions, the need for novel regulation, perceived as a risk, discourages needed disruptive innovation.[3]

The future_

Market trends are driving the focus on modular and flexible manufacturing, adapted to smaller batches, while at the same time, increased demand for some therapeutics requires production scales and process efficiencies thought to be difficult to reach with mammalian systems.

Novel protein formats, which are challenging for CHO, call for a broader range of expression platforms.

Gene therapy is relying much on HEK-293 lines, which are still poorly characterized. Insect cells are also being used for viral vector production.

Pelican Expression Technology has pioneered the use of P.fluorescens for biotherapeutics production, and is introducing products in the market.

Cell-free prodcution, still in its early stages, is expected to democratize access to biotherapeutics.

Beyond the biology_

Other important challenges related to the global status of biotherapeutics production, which may not be directly solved by biology.

Global access to manufacturing of vital medicines is one such challenge.

The trend for developing and deploying modular and mobile production facilities may enable more equitable share of biotherapeutic manufacturing. Some prodcution systems may be better adapted that others to this end.

Space exploration will also add to the requirement for production systems that can be more easily deployed than existing ones.

[1] https://doi.org/10.1038/s41587-022-01582-x - Nature
[2] https://doi.org/10.1016/j.tibtech.2021.10.003 = Microbial platforms
[3] https://bioprocessintl.com/manufacturing/single-use/embracing-innovation-in-bioprocessing-and-biomanufacturing/

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