Adopting Continuous Biomanufacturing Workflows Slashes Production Costs By 75%

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Valued at $326.01 billion in 2022, the global biotherapeutics market remains buoyant and with a forecast Compound Annual Growth Rate (CAGR) of 9.40%, this market is projected to reach $668.92 billion by 2030 (1). However, the cost of these therapies is high. For example, the US list price of popular rheumatoid arthritis monoclonal antibody (mAb) treatment, Humira® was quoted at $6,922 per month in 2023 (2). Additionally, with the average daily dose of these types of therapies costing over 20 times more than that of a small molecule drug (3), an estimated 80% of the world's population cannot get access to or afford treatment with biotherapeutic drugs (4).

Part of the reason biotherapeutics have a high price tag is that manufacturing is costly, running at US$ >200 per gram. This is because these therapies are large molecules which require complex processing. Most are protein based and use cells to express them. The cells require specific culture conditions, with expensive media and feeds to produce safe and effective therapeutic molecules. These molecules also need to be purified and concentrated using a range of chromatography and filtration steps. In contrast, small molecule drugs are synthesized with fewer ingredients using chemical processes that are often more straightforward and cost-effective, which means average production costs are over 12-fold lower (3) than for biotherapeutics.

Since the cost of biotherapeutics is one of the biggest constraints facing the biopharmaceutical industry, this could restrict their growth and use especially in emerging markets or large-scale emergency situations such as pandemics. Therefore, to contribute towards making these types of therapeutics more affordable, the industry needs to find methods of reducing the cost of goods manufactured (COGM) to be able to offer patients the choice of access to biotherapeutics.

At Just – Evotec Biologics, a strategy being implemented for producing more affordable biotherapeutics is to reduce COGM by implementing

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three major principles. These are to (10 intensify, (2) minimize and (3) simplify the manufacturing process in both the upstream and downstream unit operations.

Process Intensification for Lower COGM

Intensifying manufacturing processes is a key factor for reducing the COGM of biotherapeutics. To intensify the upstream process, an integrated, continuous perfusion cell culture can be used, and mAb production using this method has been shown to significantly lower COGM compared to batch and fed batch culture (5).

At Just – Evotec Biologics, we offer hybrid (Figure 1) or fully end-to-end (E2E) intensified upstream processing (Figure 1) to produce biotherapeutics. Both processes use intensified continuous perfusion culture with highly productive cell lines and expression vectors, in cell culture media which supports high cell density, and continuous expression of high protein titers.

Hybrid continuous process for early-stage products (12–15 day production)

Fully E2E continuous process for late-stage products (25–30 day production)

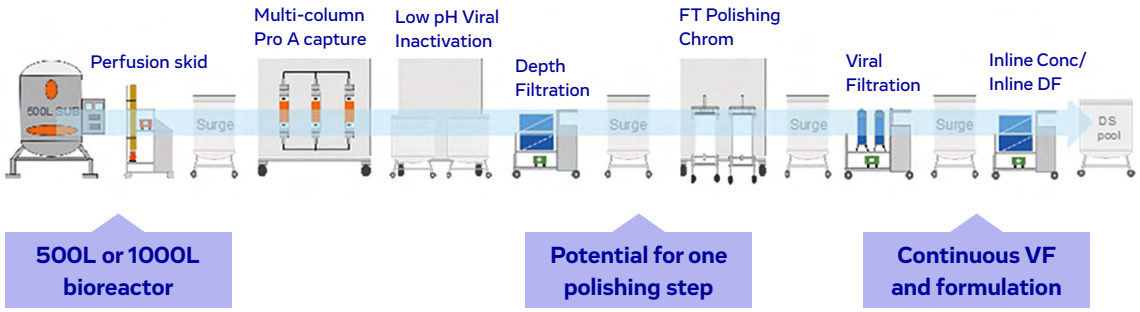

Figure 1: *Hybrid-Continuous Platform for Early-Stage Products (Phase I/II Clinical Trials) (above) And Fully End-To-End Continuous Platform for Late-Stage Products (below).*

To ensure optimal performance of our intensified cell culture process, we have engineered our own Chinese hamster ovary (CHO)-based glutamine synthetase knock-out (GS KO) host cell line, the J.CHO™ High Expression System. We use this cell line to select clones for maximum mass output and high protein titer in continuous perfusion culture. This is important as we have observed that not all clones that perform well in fed-batch culture conditions show equivalent performance in continuous perfusion culture.

Using J.CHO™ High Expression System, we have shown that by choosing the right clones and optimizing their culture conditions, cells can produce higher titers (almost double) that compared to an industry standard CHO cell line in continuous perfusion culture (Figure 2).

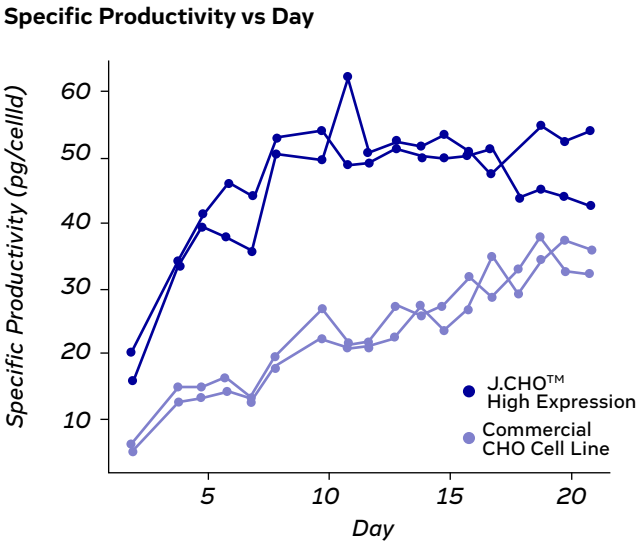

Figure 2: *mAb Yield in A 20 Day Continuous Perfusion Culture Using an Industry Standard CHO Cell Line Compared with J.CHO™ Cell Line.*

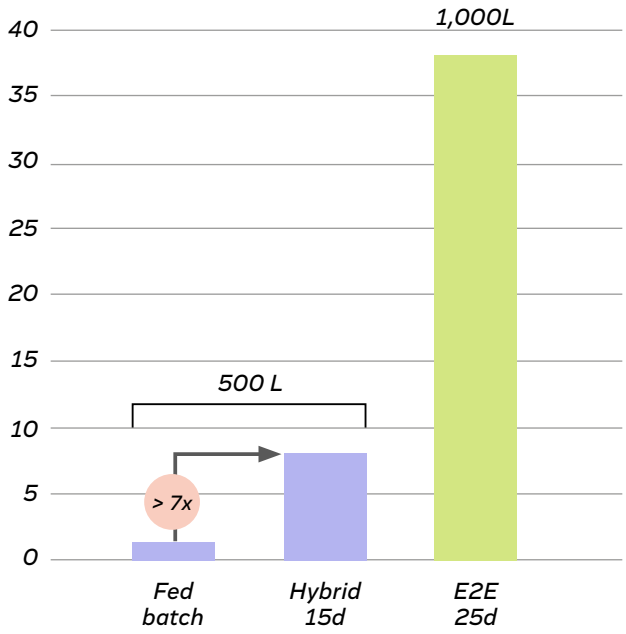

Figure 3: *Comparison of Drug Substance Outputs from Fed-Batch versus Hybrid and Fully Continuous (E2E) Processes*

To reduce COGM, we can intensify our continuous upstream process further to increase mass output, by simply adjusting the run time of the bioreactor perfusion culture (scale-on), rather than bioreactor size (scale-up) or number (scale-out). Using our continuous processing platform means our mass output can be 'tuned' to precise requirements with only modest increases in bioreactor volume.

With our intensified, continuous process, we have achieved 'Industry-leading' titers of 4g/L/day in a 25-day run (Figure 3) of a mAb drug substance (DS) for use in First-in-human (FIH) trials. This means we can reduce our COGM compared to traditional scale-up or scale-out approaches by increasing mass output of a biotherapeutic drug substance without significantly increasing labor, equipment, or consumables costs.

Using our 25-day intensified process at the 500L–1000 L scale, we can supply multi-kilo amounts of material (up to 50 kg of DS). If this process is used on an annual basis, we could supply metric ton scale amounts for Phase III and commercial production (see Figure 4). We estimate that utilizing our intensified upstream process for commercial scale running 6 x 1000L bioreactors within our J.POD® manufacturing facility, to produce 4g/L/day we could by 2025 reduce our COGM to $50/g which is 75 % less than a traditional CDMO producing a biotherapeutic at a today's typical COGM of $ 200/g.

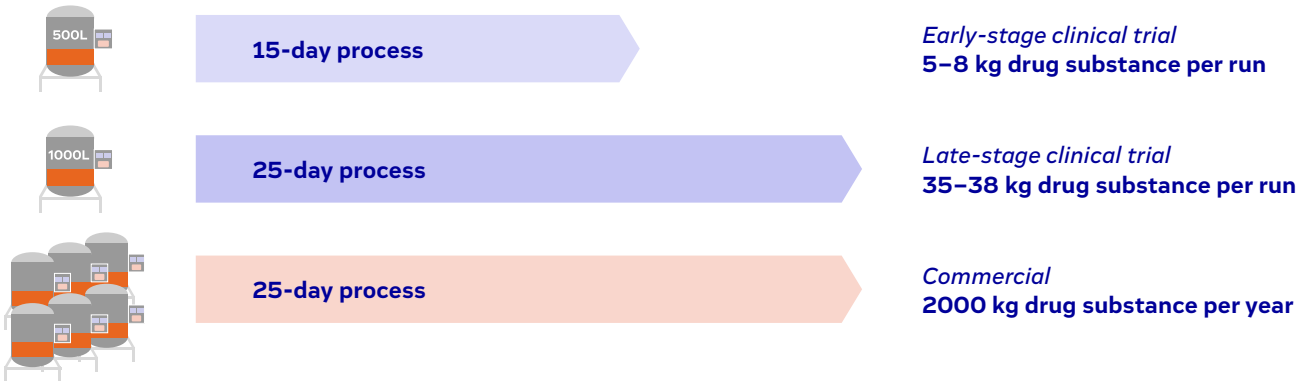

Figure 4: *Just–Evotec Biologics Scale-On Intensified Continuous Perfusion Process for Early FIH Trials Through to Commercial Manufacturing*

COGM Benefits of Minimization

Since the continuous intensified process, we typically run within our J.POD manufacturing units produce higher mass output and titer than traditional bioprocessing facilities this enables us to run a more efficient and streamlined process. The higher productivity allows us to shrink our operational workflow. We can utilize lower volume single-use (SU) bioreactors (typically 500L–1000L), and because we are using continuous downstream purification of healthier cell permeates, we use fewer or smaller chromatography columns and filters. This means we can reduce buffer volumes, as well as limit or eliminate buffer holding tanks and reduce the costs and footprint associated with buffer usage.

Reducing the operational footprint allows us to better utilize space and enables us to run smaller J.POD units, leading to cost reductions with for example Heating, Ventilation and Air Conditioning (HVAC). Utilizing SU systems also means we have no steam-in-place or clean-in-place utilities. We estimate this reduces our water usage by more than 50 % compared to a traditional bioprocessing facility. We also produce our water for injection by reverse osmosis (RO) instead of distillation which, in addition to saving energy in WFI production, reduces our HVAC usage because it uses less does not require having to heat water to boiling point or need to power air circulation utilities for removing steam. Minimizing our process footprint, we estimate provides us with cost savings of up to 90 % (currently between $0.7–$2.1 m per year). Requiring fewer supporting utilities, such as water, steam, and cleaning agents, lowers our environmental impact, as well as our operational expenses and as a result reduces the COGM of biotherapeutic products.

As the footprint of our J.POD units is smaller and requires less equipment, these facilities have fast build and fit-out times (around 18-months to two years). We currently have two operational units in the US in Washington and will have another in Europe by 2024 (see Figure 5). At a total capital expenditure (CAPEX) of around $270 m per J.POD site these costs are around half that of a typical commercial bioprocessing unit. Therefore, if manufacturing COGM calculations include a CAPEX element, then utilizing a J.POD facility will be more cost-effective for biotherapeutic production than a new commercial traditional bioprocessing facility.

Figure 5: *J.POD Facilities in the US and Europe*

Why Simplifying Bioprocessing Workflow Impacts CoGs

We use a perfusion continuous intensified process in 3L bioreactors and then transfer the process directly to 500L or 1000L bioreactors. We have shown that growth and viability performance in our 3L bioreactor models is comparable with that at 500L scale (Figure 6), which provides confidence that this a valid transfer strategy. Our approach avoids the risks, as well as the additional costs associated with, for example, having to transfer an early phase clinical scale process to a larger scale, potentially different type of bioreactor, in another facility (which could even be in a different country) that can support commercial scale production. In short, our clinical scale is our commercial scale, no need for scale-up.

Technology transfer can be expensive, with one study estimating that for a biotherapeutics with $1 billion annual sales, every month lost during transfer costs around $80 million in lost revenue (6). Simplifying the process to avoid as many transfer steps as possible eliminates the need for idle periods between transfer from one vessel (or even site/country) to another, as well as reduces cleaning and set-up times, ensuring that bioreactor utilization is more efficient. This in turn increases resource utilization which in combination with fewer transfer steps can significantly reduce manufacturing costs (COGM).

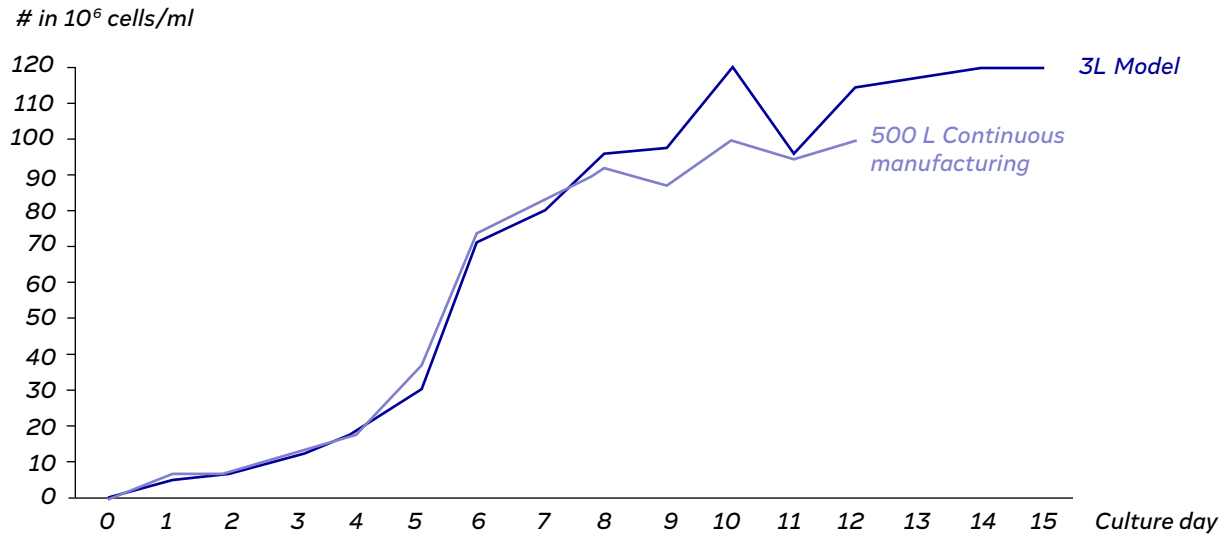

Figure 6: Comparison of VCD In 3L Model Versus 500L Scale Continuous Manufacturing SU Bioreactor

Additionally at each step in a traditional scale-up, scientists often perform multiple engineering runs and one lock-down run to achieve optimum process performance (7). At the 2000L commercial manufacturing scale media, reagents, and staff resources costing are extremely expensive (7). By eliminating the need for engineering runs, we both achieve speed to the clinic, as well as minimizing the cost of manufacturing at this phase of development.

Conclusions

By leveraging intensification, minimization, and simplification in bioprocessing workflows, CDMOs such as Just – Evotec Biologics can achieve higher productivity, better resource utilization and lower facility costs. Collectively, these benefits contribute to reducing the COGM of biotherapeutics, making them more economically viable and accessible for underserved patient populations, as well as supporting their use as a rapid response in global health emergencies and pandemic situations.

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