How an Integrated, Continuous, Intensified Approach for Manufacturing Biologics Provides Productivity and Quality Benefits

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The biopharmaceutical industry continues to need to facilitate faster, lower cost approaches for manufacturing biologics such as monoclonal antibodies (mAbs) for treating chronic and life-threatening conditions, as well as infectious diseases. Unfortunately, many biologics-based treatments are not accessible to patients worldwide due to issues including affordability. Alongside affordability there are also challenges which are hampering the speed of delivery of biologics-based drugs including long lead times for designing and building conventional manufacturing facilities, which can impact manufacturing costs. These drivers are fueling technology innovations to improve facility utilization for multi-product use and provide easy-to-install facilities for domestic manufacturing which could improve efficiency and increase yields. Increasing productivity from each production batch means fewer process runs often at smaller scale, all of which can reduce the cost of goods (CoGs) for producing biologics.

Traditionally, to increase drug substance/ product mass biopharmaceutical companies and CDMOs have produced larger amounts of unpurified product by scaling their fed-batch cell culture processes to 10,000 L, 15,000 L, 20,000 L or 30,000 L stainless steel bioreactors using process transfer into increasingly larger vessels.

Scaling-up a process, for example, from a 2,000L to a 20,000L bioreactor along with the associated downstream processing step involves considerable risks, resources, and costs because not all unit operations scale-up linearly. This often means that multiple engineering runs are performed prior to Performance Qualification (PPQ) to de-risk the PPQ campaign. These engineering runs can be extremely expensive and time consuming.

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Additionally, working at larger scale requires the entire facility to be scaled with larger and often inflexible downstream unit operations to purify a large amount of product mass. This requires different skills sets and can even mean transferring the process to a new, larger facility, as well as training new staff.

In CDMOs or biopharmaceutical firms an alternative approach is to multiplex, or scale-out, the upstream process, with for example a "six pack" strategy using 6 x 2000 L SU bioreactors. Although scale-out has less scale-up risks, managing parallel production bioreactors creates complexity and downstream challenges remain due to the large amount of product mass that needs to be purified. Additionally, even though the capital expenditure might be lower, the high number of SU bioreactors required increases operating costs.

An alternative strategy which is increasingly gaining traction, is to use continuous manufacturing. At Just – Evotec Biologics, we have developed an integrated, continuous bioprocessing platform, based on intensified perfusion cell culture, to provide a highly flexible and economic alternative to the previously described scale-up or scale-out approaches for increasing mass output of drug substance. With continuous processing the duration of the bioreactor perfusion, rather than bioreactor size (scale-up) or number (scale-out), is the principal variable which can be adjusted to increase mass output. Using our continuous processing platform means the mass output can be 'tuned' to precise requirements with only modest increases in bioreactor volume.

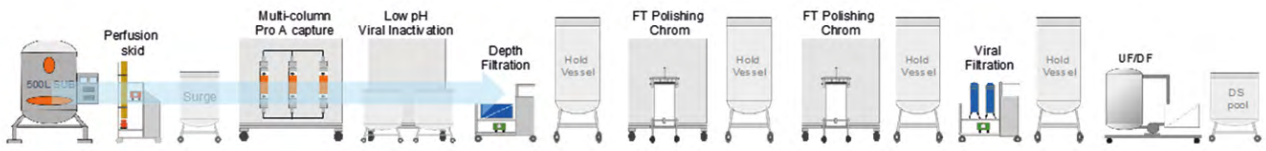
The other major benefit is that the product is purified continuously so that equipment remains compact and flexible and covers a much wider dynamic range than traditional facilities, eliminating the need to scale up the process as the drug advances through clinical development to commercial launch. This approach avoids the traditionally accepted risks, as well as the additional cost and resources associated with, for example, having to scale up and transfer an early phase clinical scale process to a larger scale bioreactor in a different facility to support late phase clinical and commercial needs. This can help reduce the critical path timeline to clinic, as well as de-risk the path to market for biologics.

Integrated Continuous Manufacturing

At Just – Evotec Biologics, we offer hybrid (Figure 1) or fully end-to-end (E2E) continuous platforms (Figure 1) to produce biologics including mAbs, Fc fusion proteins and bispecific antibodies. Both processes utilize intensified upstream cell culture with highly productive cell lines, continuous perfusion of cell culture media to support high cell density, and continuous product passage out of the bioreactor. Concentrated media is used to reduce production and storage costs.

For purification, an intensified downstream process is used where non-continuous steps including virus filtration for virus removal and diafiltration (DF) for product concentration and formulation are converted to continuous ones with high loading to purify the product as it is being expressed.

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



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

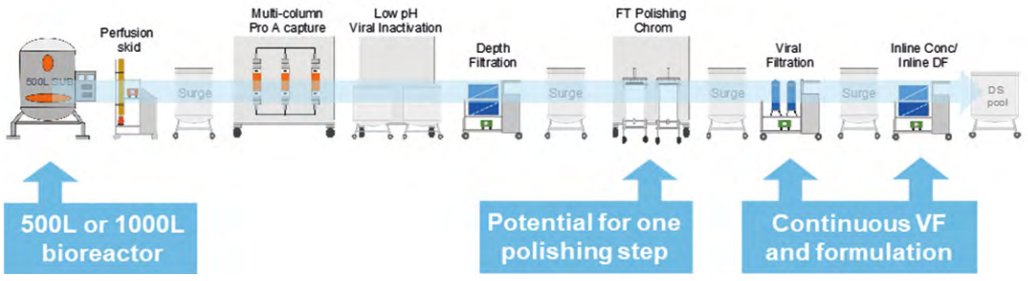
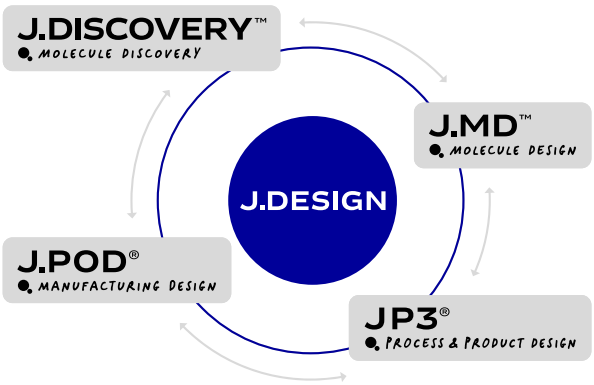


Figure 1: *Hybrid-continuous platform for early-stage products (Phase I/II Clinical trials) (above) and fully end-to-end continuous platform for late-stage products (below).*

We use intensified continuous process technology within our manufacturing facility, called J.POD®, which is part of our integrated J.Design service. J.POD utilizes modular clean room pods, and SU systems where we connect as many steps as possible to shrink the footprint of the unit operations, reduce buffer volumes , as well as limit or eliminate holding tanks. Reducing the process footprint saves the time and costs associated with larger equipment and consumables thus reducing capital expenses and transferring operating costs from fixed to variable. As J.POD provides relatively fast build and fit-out times it could easily be constructed in different regions to support lower manufacturing costs and faster development timelines of quality biologics from DNA sequence to drug substance/product.

Figure 2: *Just – Evotec Biologics' integrated J.DESIGN service*



J.DISCOVERY™ *identifies superior antibody-based therapeutics via two formats: an in vitro platform using the humanoid antibody library (J.HAL ®) and an in vivo hybridoma platform.*

J.MD™ *is a suite of molecular design services which leverages Abacus™ and other predictive computational tools. Parental antibody sequences are humanized and optimized to enhance manufacturability and stability.*

JP3® *is a process development platform leveraging high throughput technology to rapidly deliver intensified, continuous manufacturing processes.*

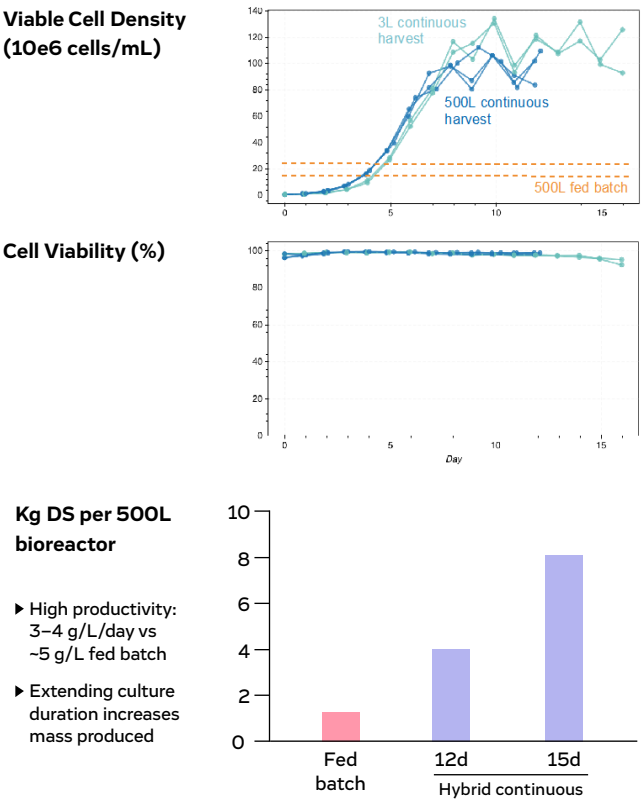
J.POD® *is our manufacturing facility design which uses modular clean rooms, single-use systems, and intensified continuous process technology.*

Productivity Benefits

In our hybrid-continuous platform, by using intensified perfusion culture we have achieved up to 10-fold higher productivity with a continuous harvest bioreactor format compared to traditional fed-batch cell culture (Figure 3).

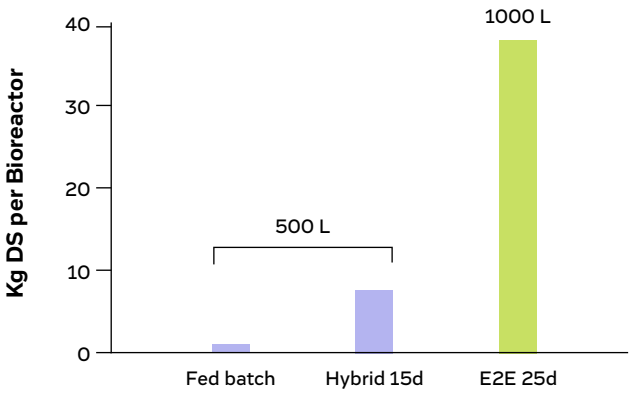
This is because the added nutrients and continuous removal of waste products support significantly higher viable cell densities (80–110 X 106 cells /mL) compared with a fed-batch process which supports lower cell densities that are sustained for a shorter time until the culture viability declines. The higher peak cell density for prolonged periods at high viabilities results in productivity of 3–4 g/L/day which translates into 8 kg batches of mAb drug substance in a 500 L bioreactor in 15-days of production.

Figure 3: *Viable cell density, cell viability and titer from a hybrid continuous process of mAb drug product for First-in-human (FIH) trials.*



Using our intensified, continuous platform, we can achieve 'Industry-Leading' titers and volumetric productivities. The process we develop for FIH drug substance supply at 500 L can remain at that modest scale (500 – 1000 L) for commercialization to supply multi-kilo amounts of material (up to 50 kg of drug substance mAb in a 1000 L bioreactor over a 25-day perfusion run see Figure 4) or annually metric ton scale production for Phase III and commercial supply by simply extending the culture run times. These high productivities, which are possible due to a combination of process intensification and continuous processing, are also achievable for new mAb modalities with more complex structures, such as bispecific antibodies and Fc containing fusion proteins.

Figure 4: *Comparison of Drug Substance Outputs from Fed-Batch versus Hybrid and Fully Continuous (E2E) Processes*



Product Quality Benefits

As well as increasing productivity, our intensified perfusion cell culture process also has product quality benefits. This is because cells maintain high viability in continuous perfusion culture as fresh media is continuously being added, and waste products are constantly being removed. Additionally, the mAb product is being harvested for purification from the bioreactor as it is expressed, which means it is in contact for less time with cells, cell culture components and impurities that could cause product degradation. For example, a mAb drug substance we produced in a hybrid-continuous process showed better quality profiles with lower levels of degradation including, oxidation, deamidation and glycation compared to the mAb produced in fed-batch cell culture (Figure 5), indicating that product quality is improved using this approach.

Figure 5: *Comparison of Product Quality of a Drug Substance mAb from a Fed-Batch versus a Hybrid-Continuous Cell Culture Process*

Location		Residue	Modification	Fed Batch	Hybrid-Continuous
Heavy Chain	Framework Region	Q	PyroGlu	86.4	87.9
		M	Oxidation + PyroGlu	2.9	0.9
		M	Oxidation	1.3	0.5
	Constant Region	K	Glycation	1.0	0.1
		K	Glycation	0.7	0.1
		N	Glycan Occupancy	97.8	99.3
		N	Deamidation	1.3	1.3
		N	Deamidation	2.1	0.5
		N N	Deamidation	1.1	1.2
		M	Oxidation	2.4	0.8
		P	C-term Proline-amidation	5.3	14.2
		G	+ C-term Lysine	9.3	2.5

The Future

It will become increasingly challenging for biopharmaceutical companies addressing niche indications or local markets to deliver cost-effective therapeutic biologics using conventional, batch-based bioprocessing methods. This is why new approaches such as continuous intensified manufacturing processes already established at Just – Evotec Biologics are needed. Furthermore, continuous intensified processes run in smaller facilities that are faster to build and less expensive to operate as demonstrated by our Just – Evotec Biologics' J.POD facility. Using our J.POD facility can increase speed, and reduce cost, as well as improve product quality and has the potential in the future to expand global access to more affordable, high-quality biologics.