From Development to Delivery: How Continuous Manufacturing is Redefining the Commercial Landscape for Biologics

Author: Nick Hutchinson, Head of Market Development, Just – Evotec Biologics

Introduction

In the past twenty years, biologics, such as monoclonal antibodies (mAbs), have become a foundational treatment choice for many autoimmune diseases and cancers. Unfortunately, not all patients who would benefit from being treated with a biologic have access to such therapies. In global markets their use is often restricted due to cost, availability, and manufacturing timelines.

For example, the average price for a daily dose of a biologic can have a price tag of up to 22 times the cost of a small molecule drug (1). This makes small molecule drugs the first and often only option for many patients. One consequence of the high cost of biologics is that they are generally prescribed in regions where patients can afford them, and a recent report estimates only 20% of global sales of mAbs occur in countries outside the USA, Europe or Canada (2). The cost of biologics also has an impact on which conditions they are developed to treat. It is estimated that there are around 7,000 rare disease indications that could be treated using biologics (3) but are currently not, which means this market sector is underserved.

Production timelines also have an impact on access to biologics; for example, during the COVID-19 pandemic, mAb therapies to treat SARS coronavirus 2 (SARS-CoV-2) infections were in short supply because it took 10-months to develop and manufacture the first mAb therapy to treat this virus (4).

Factors Affecting Supply and Access to Commercial Biologics

Lack of agility is a factor that limits the supply of biologics and often access to them. It can be difficult to predict demand in the early years of late-stage/commercial development. This is because many biologics that are developed to treat one condition can be used to treat one or more follow-on indications, but it is difficult to know when initially launching a biologic which conditions it will most successfully treat. This means product demand could be much larger or smaller according to the indication being treated. Lack of agility can also

For more information
info@evotec.com
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be caused during development and manufacturing by inflexible supply chains as these are not able to effectively work with just-in-time principles to address demand fluctuations.

Process risks also affect the development of late-stage/commercial biologics. For example, by avoiding exposure of supply chains to geopolitical risks, biologics manufacturers can operate with greater stability. This stability ensures consistent production and delivery and reduces disruption that could arise from political tensions or conflicts.

As biologics manufacturers go through the clinical phases, they are also concerned about the risks that optimizing their processes could cause due to product comparability. For example, a new optimized process may not deliver the lowest cost of goods manufactured (COGM) compared to a product from previous clinical lots.

Cost is another factor which affects access and availability of commercial biologics. The lifecycle of many biologics is often much shorter than manufacturers would like due to increasing market entry by competing biosimilars which can be marketed at a lower price due to lower development costs.

Finally, manufacturers often want to upgrade their legacy production assets to increase capacity, but do not want to risk investing the capital expenditure (CAPEX) in facilities, technology and equipment without being able to predict if they will achieve a return on investment (ROI). Therefore, the number of biologics they can produce is limited and supply sometimes does not meet global demand.

Production timelines, lack of facility capacity and manufacturing costs can all impact patient access to biologics. In this article, we explain how at Just – Evotec Biologics we have designed and are applying innovative continuous production techniques, which can help address the limiting factors in commercial manufacturing and support expansion of global market access to biologics.

The Continuous Manufacturing Solution

To address agility, risk and cost issues at Just – Evotec Biologics we are leveraging our 10 years' continuous manufacturing and production technique expertise in late phase and commercial manufacturing. Biopharma companies that have developed a fed-batch process and are in the early stages of clinical manufacturing, would benefit from our expertise by transitioning to continuous manufacturing before their Biologics License Applications (BLA) submission to reduce risk and develop an agile, cost-efficient process for commercial manufacturing. This is because we believe addressing these factors are the major drivers behind global accessibility and will have the greatest impact in the shortest timelines.

Advancing Agility

In terms of increasing agility, our continuous manufacturing platform (Figure 1) allows scalable Individualized batch throughput from less than 10 kg to more than 2,000 kg/year of protein-based biologics such as mAbs and biosimilars. We increase production batches by scaling-out our bioreactor numbers and extending our bioreactor run times with steady-state intensified continuous manufacturing technology.

Using the same equipment, we can run our process for 15 days in one bioreactor to produce enough material for early stage and first in human (FIH) clinical trials or we can run up to 6 bioreactors for 25 days to produce biologics at commercial scale (Figure 2). The process can even be run in 6 bioreactors for 40 days if throughput needs to be increased quickly, for example in a pandemic scenario. Using our intensified continuous process means there is no need for risky process transfer. To increase agility, we integrate our platforms into an end-to-end workflow which we house in facilities known as a J.POD®, these can take as little as 18 months to build and become operational. We can construct our J.POD® facilities so rapidly because we can set up our cleanrooms while the rest of the facility is being built in parallel as G-CON POD modules off-site. Our J.POD® facilities can also be flexibly expanded because we can add pre-constructed POD modules as and when we need them. This allows our clients to go from clinical to commercial manufacturing under one roof, which can help them meet fluctuations in market demand.

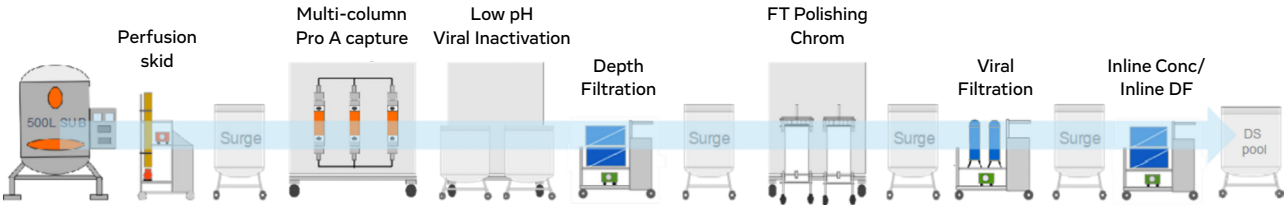

Figure 1: *Typical Just – Evotec Biologics' platform workflow in a J.POD®*

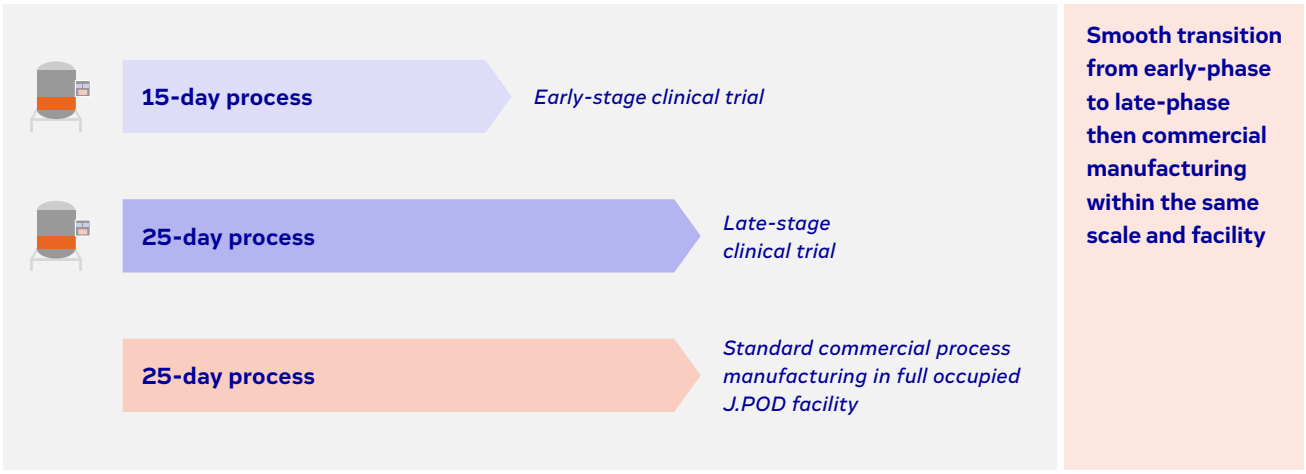

Figure 2: *How Just – Evotec Biologics' platform steady-state intensified continuous manufacturing process can be scaled*

Reducing Risk

Our continuous manufacturing platform lowers risks because it allows tunable product quality (Figure 3) utilizing process levers in the upstream such as media composition, process parameters and bioreactor set-points to make changes to a biologic's product quality attributes (PQAs). Using a design of experiments (DoE) approach we can develop and utilize a comparable continuous manufacturing process even if the previous versions of the process were fed-batch based. This reduces the regulatory risks associated with process transfer and possible time consuming comparability studies that could occur when transferring a biologic from a CDMO or biopharma company with a fed-batch platform.

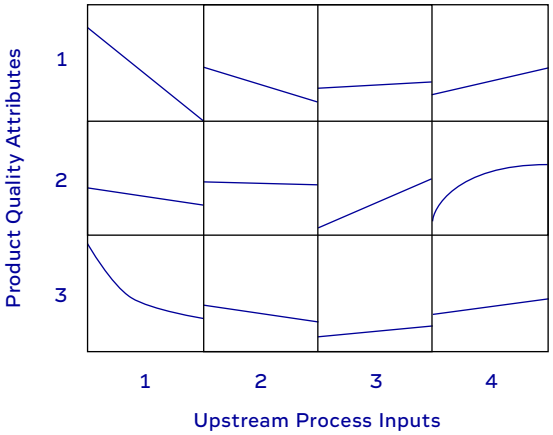

Figure 3: *Example graphs showing the effects of changing upstream process inputs on PQAs*

Additionally, continuous processing in the upstream offers a less aggressive bioreactor environment than fed-batch culture, as cells have shorter bioreactor residence times. This means cells cultured by perfusion are healthier, there is less degradation of the biologics they produce, and they can have a better post-translational modifications profile than biologics manufactured in traditional fed-batch culture. We ensure that our continuous manufacturing process delivers biologics with comparable PQAs to fed-batch cell culture, which means it is straightforward to transition from fed-batch to a continuous process.

We also reduce risk by avoiding commercial manufacturing in areas with geopolitical instability using replicated J.POD® facilities in North America and Europe (Figure 4). These use the same equipment, automation, operating procedures, documentation and quality systems so that, if necessary, a process could be seamlessly transferred between sites. Our clients also have an additional option through a licensing model to integrate a well-characterized process and facility design into their own operations, allowing them to take control of their own production which can again reduce the risks of working with a third party during commercial manufacturing.

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- Phase I – Clinical
- Over 34 runs
- 100% success

J.POD® Redmond, Washington, US
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- 500L & 1,000L SUB
- Phase I – Commercial
- First cGMP run Oct 2021
- Capacity: 2,5 t/yr

J.POD® Toulouse, France, EU
- Process Development
- 500L & 1,000L SUB
- Phase I – Commercial
- Groundbreaking 2022, Expected CQV 2024
- Capacity: 2,5 t/yr

Same J.POD® design
- Equipment
- Automation
- Operating Procedures
- Quality Systems

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Figure 4: *The J.POD® commercial manufacturing network*

Cutting Costs

Compared to the industry standard fed-batch process COGM of $200/gram for biologics, our continuous manufacturing platform routinely enables a 75% reduction in COGM (Figure 5). A standard fed-batch approach is more expensive because it generally needs many operators and time to prepare and run equipment and then dismantle it between each batch. Running a 25-day continuous process requires a higher level of automation, which we have integrated as a proprietary workflow that is unique to Just – Evotec Biologics. Our automated workflow has the additional beneficial effect of significantly reducing the amount of labor time, resources, and costs needed in our process.

For example, in a like for like comparison, with bioreactors of equivalent size (500 L) and 80 % drug substance (DS) recovery , we routinely observe that our intensified continuous manufacturing process after our 7-day initial growth phase produces 3–5 g/L/day which represents up to 10-fold higher productivity (Figure 6) than fed-batch culture. We use proprietary cell lines that express high protein titers and by increasing the number of days we run our process we can significantly increase our mass output to over 50 kg, producing commercial scale DS batches with a lower COGM.

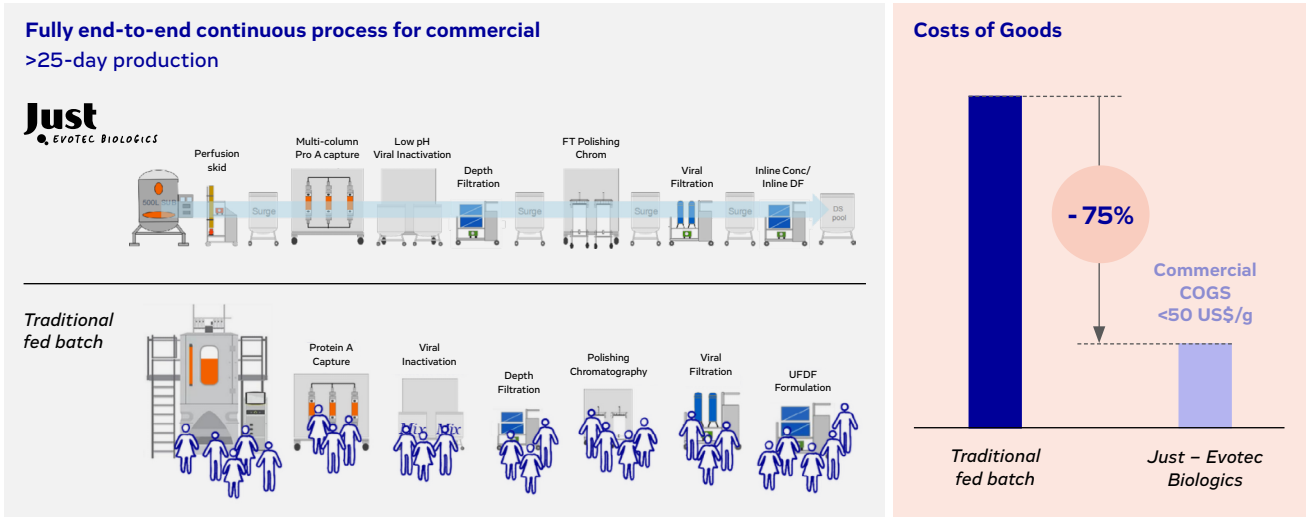
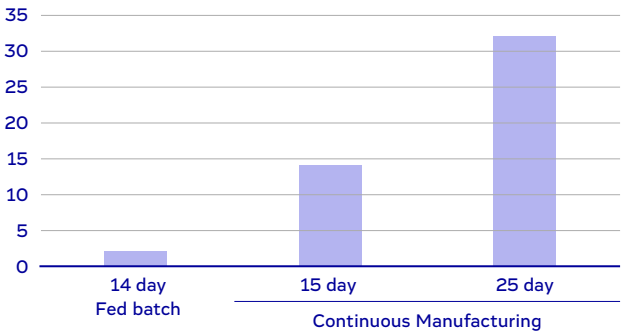
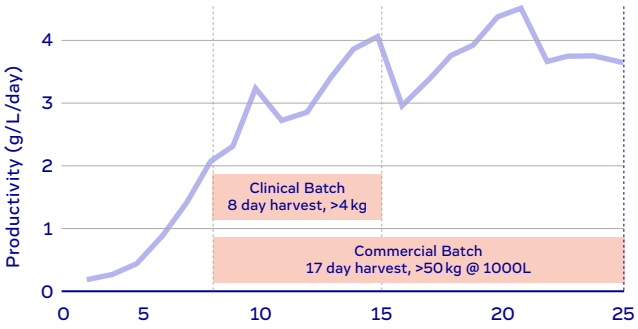


Figure 5: *Unit operations and labor resources needed to run an intensified continuous process compared to traditional fed batch process*

Comparison of 1 × 500L Run
in kg DS per 500L Bioreactor



Productivity vs. Day



→ ***Continuous manufacturing gives >10-fold higher productivity than fed-batch.***

→ ***Extending the culture duration to 25 day increases mass produced still further.***

→ ***High productivity: 3–5 grams product / L / day***

Figure 6: *Productivity of an intensified continuous process*

Our goal is to continuously hone our platform so that our fully-occupied facility, working at capacity will deliver biologics with a COGM of less than $50/g. This will support manufacturers of originator biologics to create value in their drug and compete on price with biosimilars.

Another component of the cost of manufacturing biologics at commercial scale is the amount of capital investment needed to construct and run larger facilities. As well as reducing COGM, our highly intensified continuous manufacturing platform can be operated in smaller J.POD® facilities using more automated equipment in a much smaller area, resulting in 75 % reduction in CAPEX compared to other commercial manufacturing ready facilities (Figure 7).

An additional benefit of our J.POD® facilities having a smaller footprint is that operating costs are lower than traditional fed-batch based manufacturing plants. This is because they use less clean room space, which is a major contributor to energy costs, and require fewer expensive utilities such as steam in place (SIP), cleaning in place (CIP) and water for injection (WFI).

Cost of a J.POD® facility
US$ m

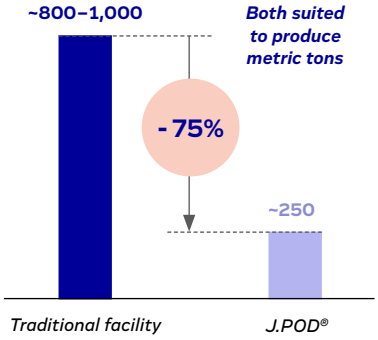


Figure 7: *Investment required to construct a traditional commercial biologics manufacturing suite compared with a J.POD® intensified continuous process facility*

Transitioning to Continuous Manufacturing for Commercial Production

Feasibility Study

When clients decide, they would like to utilize the benefits of continuous manufacturing, before they commit to commercial scale manufacturing, we recommend a low-cost, 3-month feasibility study for proof-of-concept, which includes a cell line evaluation, high-throughput process development and COGM modelling (see Figure 8 for a summary of activities).

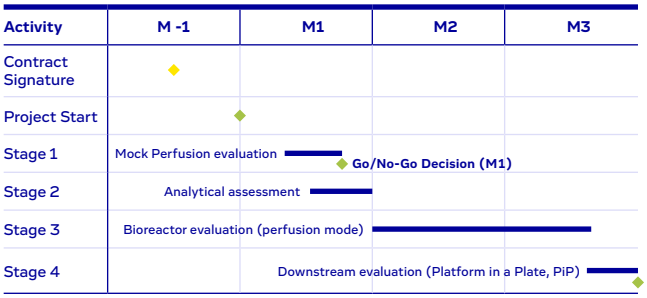


Figure 8: *Timeline of minimally resourced, 3-month feasibility study to demonstrate margin gains, reduce risk and validate ROI assumptions*

The feasibility study helps clients gauge the impact that the process will have on productivity and how it is likely to affect their biologics' product quality. We use this information alongside the data package clients provide for COGM modelling (Figure 9).

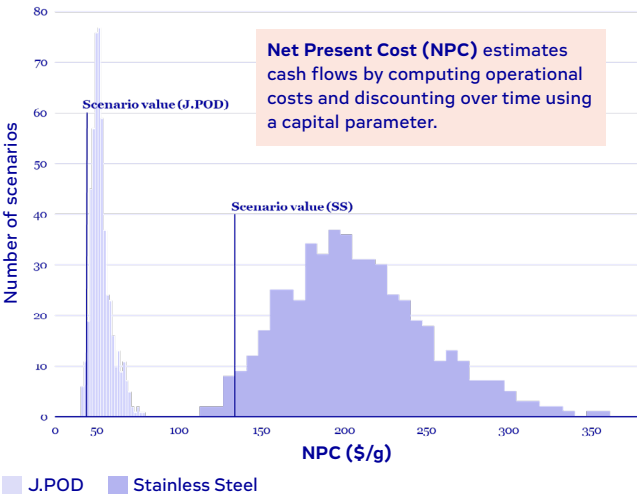


Figure 9: *COGM model comparing an intensified continuous manufacturing facility with a traditional fed-batch process for commercial manufacturing of a biologic*

We have developed COGM models (5) based on Net Present Cost (NPC) which estimates cash flows by calculating operational costs and discounting over time using a capital parameter. Using this model, we can compare COGM for continuous manufacturing to an existing process to predict COGM over a range of post-launch demand scenarios. For example, we can determine if continuous manufacturing will provide lower costs in all demand situations.

Often, over a range of demand scenarios with intensified continuous manufacturing, we see a narrower distribution of NPC irrespective of fluctuations in demand (see figure 9) due to the platform's agility. Clients do not need to invest in as large a facility for commercial production as they would using a fed-batch process. They can start with a small facility that matches their predicted current demand and if a higher one occurs, then they can readily expand the existing J.POD® using parallel construction techniques to meet that new demand in a just in time manner. Since construction times are short, this minimizes expenditure on facilities while maximizing facility usage. With our COGM model, we can therefore demonstrate the opportunity for cost margin-improvement and de-risk commercial process development before clients decide whether they want to transition to continuous manufacturing at commercial scale.

Process Development

When the feasibility study is complete and clients have made the decision to utilize intensified continuous manufacturing for their commercial production, we develop a commercial process. We do this by establishing a full 25-day end-to-end continuous manufacturing process, where we evaluate process robustness, as well as the analytical methods required to assess and maintain the biologic's PQAs at scale. We then carry out a 1000-L engineering run in our cGMP facility to demonstrate the efficacy of the process. When this is successful, we continue to clinical manufacturing runs where we generate and qualify a reference standard and perform stability studies on the DS. We also perform comparability testing using our sophisticated analytical technologies, where for example, we compare particles and physical characteristics in the DS from this run with previous runs.

Process Validation

While establishing the continuous commercial manufacturing process, we also carry out Biologics License Application (BLA)-enabling studies such as process characterization and validation. These include facility risk assessments, DS freeze/thaw studies, as well as shipping validation assessments.

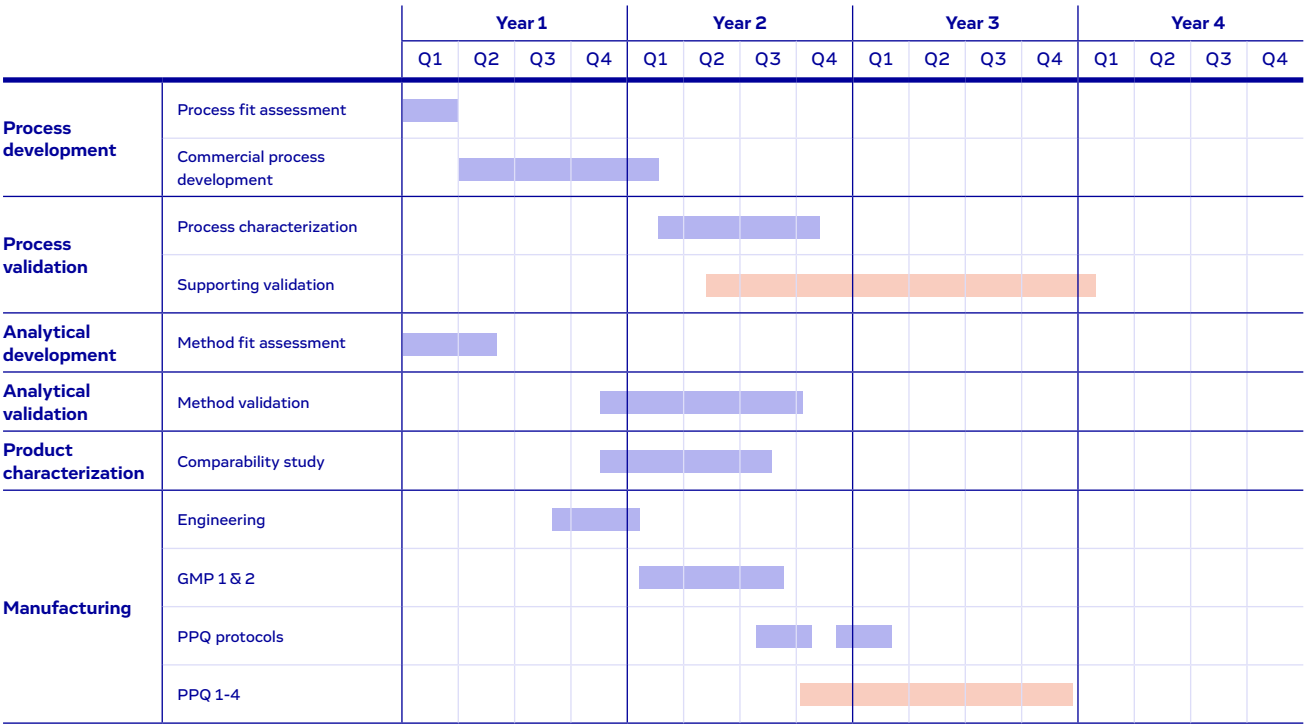


Figure 10: *Timeline from cell line transfer to BLA-enabling studies for developing a continuous process for commercial manufacturing*

We estimate that our timeline for developing a continuous commercial scale manufacturing process going from cell line transfer to BLA-enabling studies is approximately three years (see Figure 10 for an overview of activities). However, there are several validation and Process Performance Qualification (PPQ) activities (shown in pink in Figure 10) that would have to take place if a client were in early-stage clinical trials and was looking to transition to late-stage trials. These would have to occur regardless of the type of process being used for commercial manufacturing. Therefore, from the process assessment through to execution of GMP production runs, we estimate it only takes 18-month to two-years to transition from a fed-batch to a continuous commercial manufacturing process.

Proven Expertise with Commercial Manufacturing

At Just – Evotec Biologics, we are focused on developing and manufacturing antibody and antibody related products, as well as biologic formats expressed in Chinese Hamster Ovary (CHO) cells. We have expertise in producing mAbs, Bi-/multi-specific antibodies and Fc-fusion proteins. We also have experience of working with regulators and by the beginning of 2024 in the US, UK, Canada we have filed 11 Investigational New Drug (IND) applications and have another nine active INDs.

In the past four years, we have demonstrated our cGMP manufacturing success with a 90% success rate, which has risen to 100% in the past three years as our technology has matured. We have achieved several cGMP compliance milestones, including 27 successful client audits. Our team has years of combined bioprocessing and expertise in many global regulatory pathways. They are familiar with developing second generation process BLAs and biosimilar products and can provide support with filing INDs and BLAs.

Conclusions

With a steadfast commitment to innovation and excellence, Just – Evotec Biologics is pioneering a new era in biologics manufacturing. Transitioning to our intensified continuous production before manufacturing at commercial scale can drive value creation in a late-stage manufacturing process. Additionally, because we offer a short feasibility study, this is a low-risk method for evaluating the benefits our workflow can bring, without impeding development timelines. Our proven track record, coupled with unparalleled expertise, and manufacturing ready facilities in the US and Europe positions us as a trusted partner in the journey towards democratizing access to life-saving therapies on a global scale.

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