

BIOMANUFACTURING

Commercial small scale manufacturing

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➤ The increasing maturity of the biopharmaceuticals market - together with a rising number of biosimilar developments and market applications - is leading to a sharper focus on the cost of goods (COG) for biomanufacturing. Discussions about COG generally lead to reflections on the economy of scale, i.e. decreasing costs by manufacturing more of a given product. However, there are several other factors that can lead to decreasing volume demands for biomanufacturing processes, and these can counteract the economy of scale argument. Examples for these parameters include: higher manufacturing yields, lower dosages in therapy, and the development of projects for smaller niche markets. Any or all of these can go hand-in-hand with decreased demand for a product. This article gives a short overview on the trends leading to smaller fermentation scales, particularly in microbial manufacturing processes.

In recent years, improved process technologies have significantly increased production efficiency. The most obvious improvement is the use of optimised expression systems combined with optimised fermentation characteristics. Together, these aspects can lead to fermentation titres exceeding 20g/L, as was recently reported by Richter-Helm BioLogics for an *E. coli* inclusion body process (Fig. 1)^[1]. A thorough process optimisation program starting with a basic fermentation scheme in 1L reactors, yielding a recombinant protein titre of 1.8g/L, led to a more than 10-fold increase through parameter optimisation and up-scaling. The initial fermentation harvest titre of 1.8g/L was already well in the range of actual commercial manufacturing processes (half of these yielding <1g/L with an overall average of approximately 2.2g/L)^[2]. However, for the subsequent transfer to a commercial manufacturing facility, this would mean a possible reduction in scale by the opti-

misation factor, assuming all subsequent step yields remained the same.

Increasing yields ...

The increase in yields in upstream processing has changed the focus in today's process development programmes. Existing purification schemes based on large-scale columns that employ expensive resins are no longer matching these yields. There is thus a need to develop and establish new solutions for the purification of biologicals. Several technologies are available today, some of which - like membrane chromatography - are employing analogous purification functions for a lower price^[3]. Others are reducing costs by applying purification steps that combine several classical purification steps. An example for this approach is the implementation of expanded bed adsorption (EBA) chromatography, which combines cell debris separation and capture chromatography in a single step.

The implementation of EBA technology with "Streamline SP" resin in a project for the manufacturing of a chimeric molecule (Fab + effector molecule) at Richter-Helm BioLogics led to a significant improvement by reducing process and CIP times without a negative impact on yield. As a direct result, the utilisation rate for the project at the multipurpose facility was reduced, freeing up the resource pool to handle more customer projects per year in that facility. And as the number of necessary process steps dropped, efforts for additional activities - including QC testing and QA record review - fell as well, along with the consumption of process media such as WFI, steam, buffers, etc. (Fig. 2). In a collaborative effort, Richter-Helm BioLogics and Upfront Chromatography A/S were able to improve these initial results even further. The final process yield in total, purified product per fermenter volume was increased 1.8-fold, thus significantly reducing the COG per final purified product^[4] and making smaller scale manufacturing feasible.

... are driving trends to reduce manufacturing scales

On the same process technology note, another issue driving the trend to reduce manufacturing scales is the move towards disposable equipment for bio-

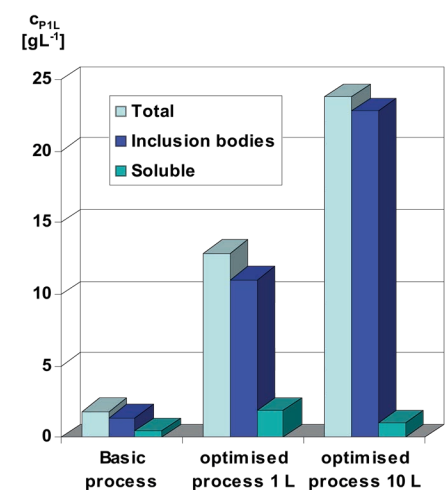


Fig. 1: Recombinant protein yield (cP1L) after *E. coli* fermentation at several stages in an optimisation process

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Fig. 2: Improvement in processing and cleaning cycle times driven by the introduction of EBA technology to the manufacturing process for a chimeric protein (Fab + effector molecule)

pharmaceutical manufacturing. Disposable equipment offers the benefit of reduced effort for cleaning and – even more important in some cases – reduced workload when it comes to cleaning validation. However, using disposables also often limits scale. This is most critical in microbial fermentation, where to date no bioreactor is available in several litres scale which can generate the mass and energy transfer rates required for the cultivation of bacteria and yeast. Even disposable bags to hold buffer and media in biomanufacturing are limited to approximately 2,000L.

Technology improvements and increased process yields in upstream and downstream processing, however, are not the only factors contributing to lower

manufacturing scales. The trend is also being driven by a decrease in demand for state-of-the-art biologic therapeutics. As biopharmaceuticals are often developed for rare or previously untreatable diseases, the total number of patients – and thus the total amount of active substance that must be produced – is often relatively low^[5]. In addition, the product amount per dosage remains low, as the potency of biotech products is generally relatively high. Some good examples for microbial-derived products with low product amount per dose are Interferon alfa-2a (each dose contains 11.1µg of recombinant protein, leading to a yearly administration of only 1.7mg per patient), Interferon beta-1b (each dose contains 0.25mg of protein, leading

to a yearly administration of just 46mg per patient) and Somatropin (just 0.2mg of protein in one dose, leading to a maximum yearly administration of 70mg)^[6].

Taking into account the average yield mentioned above of 2.2g/L after fermentation and a reasonable total process yield of 25%, the resulting total fermentation volume required per year could easily be met by a facility having no more than 1m³ of fermentation volume. Thus a multipurpose facility like that shown in Fig. 3 today provides sufficient capacity to supply the demand for several commercialised products.

References

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Fig. 3: Upstream processing equipment with a 1.5m³ fermenter (left) and support tanks at Richter-Helm BioLogics in Bovenau, Germany