GenScript PROBIO

White Paper

Late-stage Process Development and Cost of Good Reduction Strategies for Biologics

Costly medicines are a burden for both individual patients and national budgets. The Prescription Drug Law within the Inflation Reduction Act (IRA) exemplifies efforts to make medicines more affordable. The production of biologics requires intricate manufacturing processes within a highly regulated environment, leading to high production expenses. Greater control over the production costs of biologics has emerged as a pivotal factor for drug manufacturers to uphold competitiveness in the biopharmaceutical industry.

After drug candidates enter clinical trials, the focus of Chemistry, Manufacturing, and Controls (CMC) often shifts towards developing late-stage processes with the objectives of enhancing process stability and reducing production costs per unit of drug substance (DS).

Taking monoclonal antibody products as an example, this article focuses on reducing the commercial production costs of biopharmaceuticals. It explores two aspects: the timeline of late-stage processes development and factors in the reduction of cost of goods (COGs) per unit of DS.

The timeline of late-stage process development

Late-stage process development can begin when the project enters Phase II clinical trials (Figure 1). From the overall project lifecycle perspective, this smart strategy prevents wasting resources on projects that perform poorly in Phase I clinical trials, while ensuring sufficient time for process development and subsequent clinical sample production before the project enters Phase III trial. Once the project enters Phase III clinical trial, it's not recommended to do any significant process changes. Table 1 illustrates data published by Paul et al. on clinical success rates. This information provides a basis for our strategic timing of late-stage process development, which demonstrates both cost and time efficiency.

Table 1 Biologic product success rates at different stages

Stage	Pre-clinical	Phase I	Phase II	Phase III	Regulatory review	Overall successful rate
Average successful rate	69%	54%	34%	70%	91%	11.7%

The late-stage process development typically requires 6 to 8 months, with additional time allocated for stability data collection and process change filling. Late-stage process development includes upstream process development, downstream process development, formulation stability validation, and other tasks.

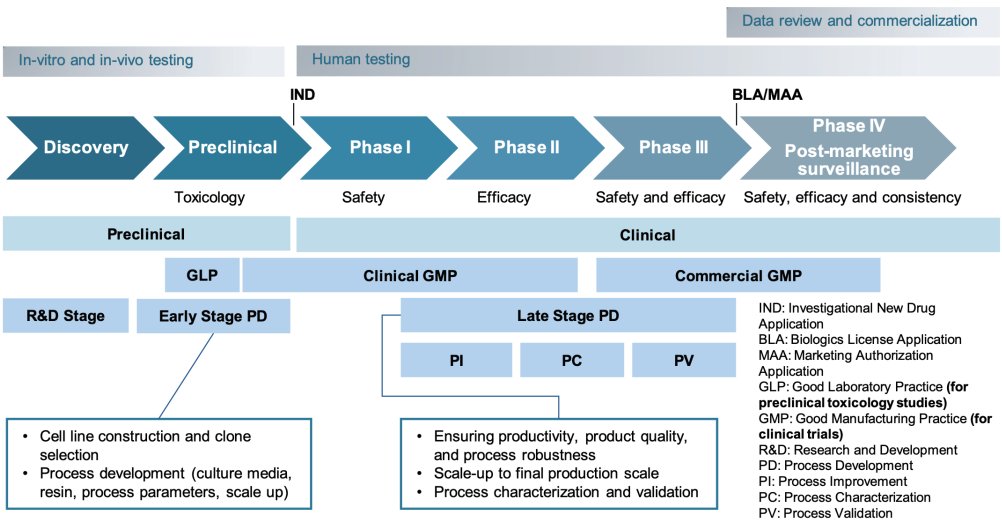

Fig 1 The development cycle of biopharmaceuticals and the content of early/late-stage process development

Factors that reduce production cost

The CoGs mainly includes fixed assets, operating expenses, raw materials, and consumables. Based on the actual production model analysis, GenScript ProBio has established a comprehensive cost estimation system. The model encompasses various production costs such as raw materials (media, substrates, and consumables), equipment and facilities, quality control, labor, and energy/environmental costs. According to the model, the primary ways to reduce production costs are ranked by effectiveness as follows: increasing upstream production yields, expanding the production scale, and substituting costly media and materials with more economical alternatives.

a.Increasing upstream production yields

Increasing production yield is the most efficient way to reduce CoGs. As production yield increases, fixed costs are spread across a greater number units of DS, reducing the cost on a per-unit. As shown in Figure 2, increasing production yield can rapidly decrease the production CoGs per unit of DS. It's worth noting that there is an exponential relationship between product yield and CoGs per unit of DS. When product yield doubles, CoGs per unit of DS can decrease by up to 40%. In late-stage process development, GenScript ProBio aims to increase production yield while ensuring the product quality remains comparable. This is achieved by methods such as optimizing bioreactor process parameters, optimizing feeding strategy, and implementing intensified fed-batch processes to rapidly increase upstream process yields.

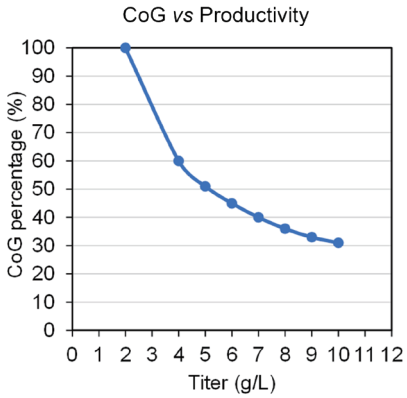

Fig 2 Upstream yield and production costs (The data is generated from GenScript ProBio's internal cost model).

In Figure 2, the x-axis represents titer of upstream process. Y-axis represents the CoGs per unit of drug substance with different upstream titer. The CoGs per unit of drug substance at an upstream process titer of 2 g/L is set as 100% for baseline

The easiest way to increase production yield is to perform process parameter optimization. Parameters like pH, temperature, culture duration, feeding volume, and feed composition should be optimized to ensure the cells are cultured under proper physical parameters with sufficient nutrient supply. Table 2 shows the outcomes of the upstream development of a late-stage clinical project transferred to GenScript ProBio. The process development team made significant yield increases through optimizing feeding strategies (including feed composition and feeding volume). The yield increased by 95% compared to the early-stage process. Under the same conditions, CoGs per unit DS decreased by nearly 40%, while the quality parameters remained comparable to the Phase I process.

Table 2 Phase I process and optimized process comparison

Content	Phase I process	Optimized process
Titer (g/L)	3.9	7.6
Harvest Viability (%)	81	79
CEX Main Peak (%)	64.3	64.5
CE-SDS-NR Main Peak (%)	96.3	97.3

In addition to process parameter optimization, GenScript ProBio introduced the Intensified Fed-Batch (IFB) technology in 2021. Unlike conventional fed-batch (FB) processes, IFB utilizes perfusion technology to significantly increase the N-1 cell density, thereby enhancing the inoculation cell density in the production phase. This technology enables rapid yield improvement. As shown in Figure 3A-B, in the application across 14 projects, IFB doubled the yield in the majority of projects. According to Figure 2, these yield improvements are leading to significant reductions in CoGs per unit of DS. Figures 3C-E demonstrate stable scale-up cases of IFB technology. In these cases, IFB processes were effectively scaled up to 500 L, achieving approximately 60% increase in yield compared to the original process, while maintaining consistent product quality.

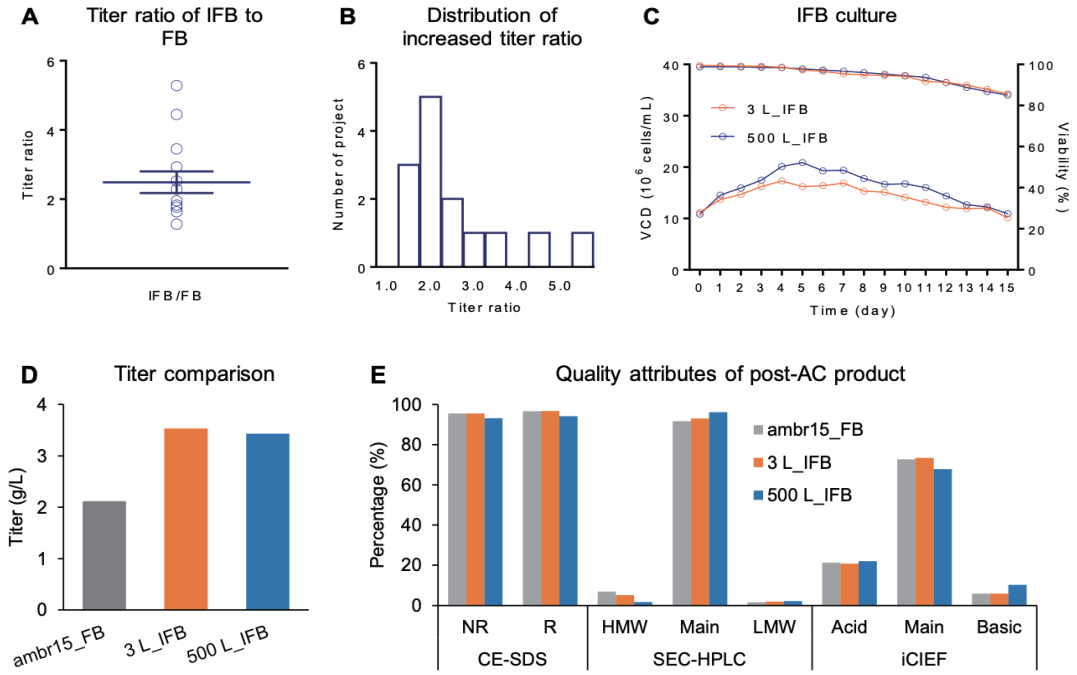

Fig 3 IFB Increase upstream yield

A-B. Summary of IFB Project Applications. N=14 projects, data sourced from the maximum scale production yield of each project. A. Titer comparison between Intensified Fed-Batch (IFB) and conventional fed-batch (FB). B. Distribution of Titer increase ratio between IFB and FB. C-E. IFB Project Applications at 500 L Scale. C. Viable cell density profile at 3 L and 500 L scales. D. Titer comparison between original FB process, IFB at 3 L scale, and IFB at 500 L scale. E. Comparison of product quality after one-step affinity purification between original FB process, IFB at 3 L scale, and IFB at 500 L scale.

b.Expanding the production scale

Scaling up production is another important approach when reducing production costs. Figure 4 shows a CDMO (Contract development manufacturing organization)-based cost model which excludes factors such as facility depreciation and labor costs. As shown in Figure 4, when the production scale increases from 500 L to 2000 L, the CoGs per unit of DS reduces around 50%. When the scale is up to 4000 L, the CoGs per unit of DS is approximately 30% of the CoGs per unit of DS at the 500 L scale. GenScript ProBio's 8 × 2000 L disposable cell culture system, scheduled to be operational in April 2024, will allow for a maximum production volume of 6000 L in scale-out mode, effectively reducing production costs.

When considering production scale, it's also crucial to take into account the production frequency which is typically controlled within the range of 3 to 10 batches per year. Producing fewer than 3 batches per year can result in higher costs for failed batches. On the other hand, when annual production exceeds 10 batches per year, increasing the production scale may be considered. The best scenario varies depending on the project and requires a specific project-based assessment.

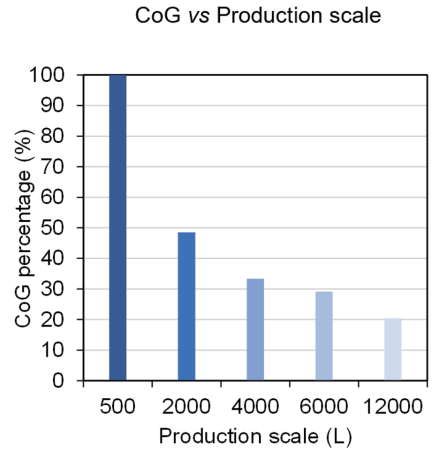

Fig 4 The relationship between production costs and production scale.
(The data is generated from GenScript ProBio's internal cost model)

X-axis represents the upstream production scale. Y-axis represents the CoGs per unit of DS. The CoGs per unit of DS at 500L scale is set as 100% for baseline.

c.Replacing expensive raw materials

The cost of raw materials for biologic products accounts for 30 – 40% of the total production costs. Since 2019, GenScript ProBio has actively promoted lower-priced alternatives, such as media, shake flasks, deep-well plates, resins, and vials. Using alternative sourced raw materials can reduce the cost of raw materials by up to 50% in multiple projects without compromising product yield and quality. The common high-value raw materials that could be exchanged to lower-priced alternatives include cell culture media, resins, and fill/finish vials. Table 2 uses data from GenScript ProBio's CoGs model to summarize the cost reduction when exchanging high-value raw materials with lower-priced alternatives.

Table 2 Use of lower-priced raw materials

Raw material	Proportion of raw material cost at different process sections	Price comparison (Lower-priced raw material/early-stage raw material)	The proportion of raw material cost in total production cost before raw material swap	The proportion of raw material cost in total production cost after raw material swap
Cell culture media	50 – 65% (Upstream)	30%	30 – 40%	11 – 20%
Resin	50 – 77% (Downstream)	35%		
Vials	50 – 70% (Fill/finish)	6%*		

** 6% In addition to lower-priced alternatives, significant cost reductions are achieved through automated bottle washing and sterilization processes*

Process modification at the clinical stage

Process changes at the clinical stage can necessitate filing supplemental applications which are part of clinical-stage development. When implementing process changes before Phase III clinical trials, it's crucial to conduct comparability studies between the products before and after the process change. These studies aim to demonstrate that the process change does not affect the safety or efficacy of the product, thereby avoiding the need for additional clinical trials. Comparability studies typically focus on physicochemical properties, activity assays, and pharmacokinetic studies of the product. If the results of these three aspects are comparable, process changes generally proceed smoothly. However, if there are differences in quality attributes, additional evaluations such as risk assessment, animal models, or even clinical trials may be required, depending on the specific circumstances.

Summary

The market environment for biologics products is impacted both by the pressure of national budgets and the low drug costs desired by patients. In this environment, precise control of biopharmaceutical production costs is a key factor for companies to maintain competitiveness. GenScript ProBio is committed to the field of biopharmaceuticals and has accumulated deep expertise in process optimization and process changes. By increasing process yield, using lower-priced raw materials, and leveraging the upcoming commercial production center in Zhenjiang, GenScript ProBio aims to provide customers with one-stop services from IND to BLA, empowering partners to better serve patients around the world.

Reference

Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos Lindborg SR, Schacht AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010;9:203–11. doi:https://-doi.org/10.1038/nrd3078.

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