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Adopting a Platform Approach to Upstream Processing Increases the Speed to Clinic of New Biopharmaceuticals

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Abstract

Following the significant expansion of the biopharmaceuticals market over the past few years, around half of the world bestselling drugs are now biologics. Biopharmaceutical product pipelines are burgeoning due to the race to commercialise biosimilar products. With large numbers of projects in their pipelines, biopharmaceutical companies must balance the commercial risks inherent in drug development with their need to control development costs while ensuring final manufacturing processes deliver the lowest Cost of Goods (CoGs). Sartorius has examined various approaches on how companies can best achieve this.

Introduction

The biopharmaceutical market has enjoyed a significant expansion over the past few years. Around half of the world bestselling drugs are biologics and they account for around the same proportion of sales of the world's top one hundred drugs. Biopharmaceutical product pipelines are burgeoning not least because of the race to commercialise biosimilar products. These are products, marketed once patents on originator molecules have expired, that can bring the benefits of biologics to patients at significantly reduced costs (Dorey, 2014).

With large numbers of projects in their pipelines, biopharmaceutical companies must balance the commercial risks inherent in drug development with their need to control development costs while ensuring final manufacturing processes deliver the lowest Cost of Goods (CoGs). In 2004, the success rate for monoclonal antibodies from toxicological assessment through to launch was judged to be around 25% (Reichert & Pavlou, 2004). Our experience is that, a decade later, this success rate has dropped to around 10%. Companies must reach the clinic as quickly as possible to ensure they are not wasting budgets on products that will not succeed in patient trials.

Platform Approaches to Cell Line Development

One of the first steps in the journey of a product to the clinic is the development of a cell line for its expression. Companies can save around 3–6 months of development time by the adoption of a platform approach to cell line development. The Cellca CHO expression platform and development services allow companies to move from DNA to having a research cell bank and cell culture process much more quickly. Cellca adopt a process platform approach to process parameters, media and feeding strategy.

The platform is highly robust and scale-up is straight forward. Among the antibody based biopharmaceuticals expressed by the platform are IgGs, Fc-fusion proteins, FAbs, bispecific-antibodies and biosimilar mAbs. Sartorius has generated extensive data to demonstrate the scalability of the Cellca CHO expression system in our Biostat STR® bioreactor range from 50 L to 1000 L and in stirred-tank and rocking motion formats. Titers typically exceed 3 g/L and our results show protein concentrations as high as 9 g/L can be readily achieved (Figure 1).

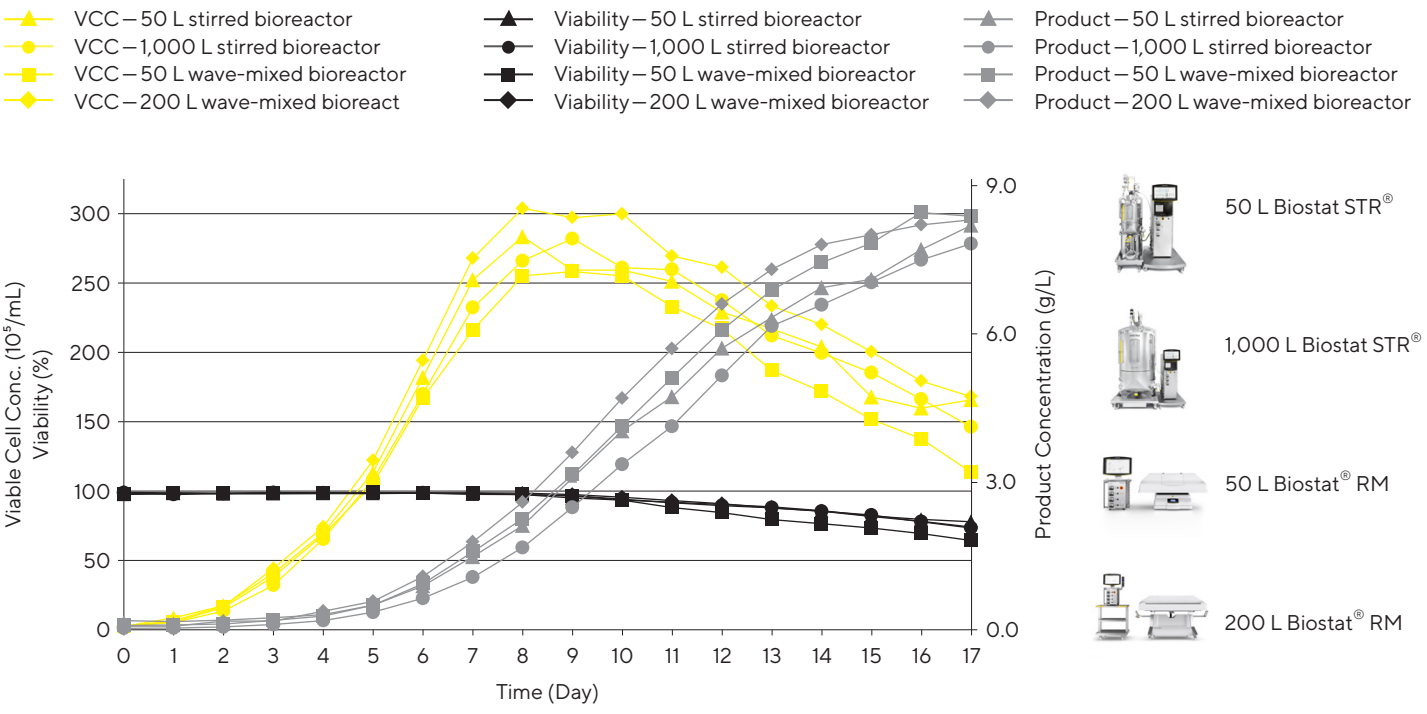

Figure 1: *Scalable, High-Titer mAb Process Using the Cellca CHO Expression System*

Automated High Throughput Cell Culture Development Techniques

Automated high throughput process development will play a significant role in allowing companies to reach the clinic more quickly. Lonza Biologics, UK, showed that the Ambr® 15 cell culture system could effectively rank CHO cell lines according to their specific productivity. The ranking was consistent with results from 10 L bioreactors (see Figure 2) but took much less time to perform.

Cobra Biologics found that the use of the Ambr® 15 to replace 5 L bioreactor experiments could reduce parameter optimization from 22 to 6 weeks. They were able to perform more experiments with the same amount of resources (Lange et al., 2014).

An American biopharmaceutical company we have worked with compared data on viable cell density, product accumulation and offline pH measurements and found good agreement between the Ambr® 15 and the process operated at the 0.5 L, 2 L, 10 L, 100 L and 3,000 L scales. Merck Research Laboratories have compared the Ambr® 250 microbioreactor workstation to 1.5 L bioreactors for the performance of DOE experiments. They found the output to be comparable but the Ambr® 250 to be more efficient at generating the data due to not having to perform certain blocking experiments (Bareither et al., 2015).

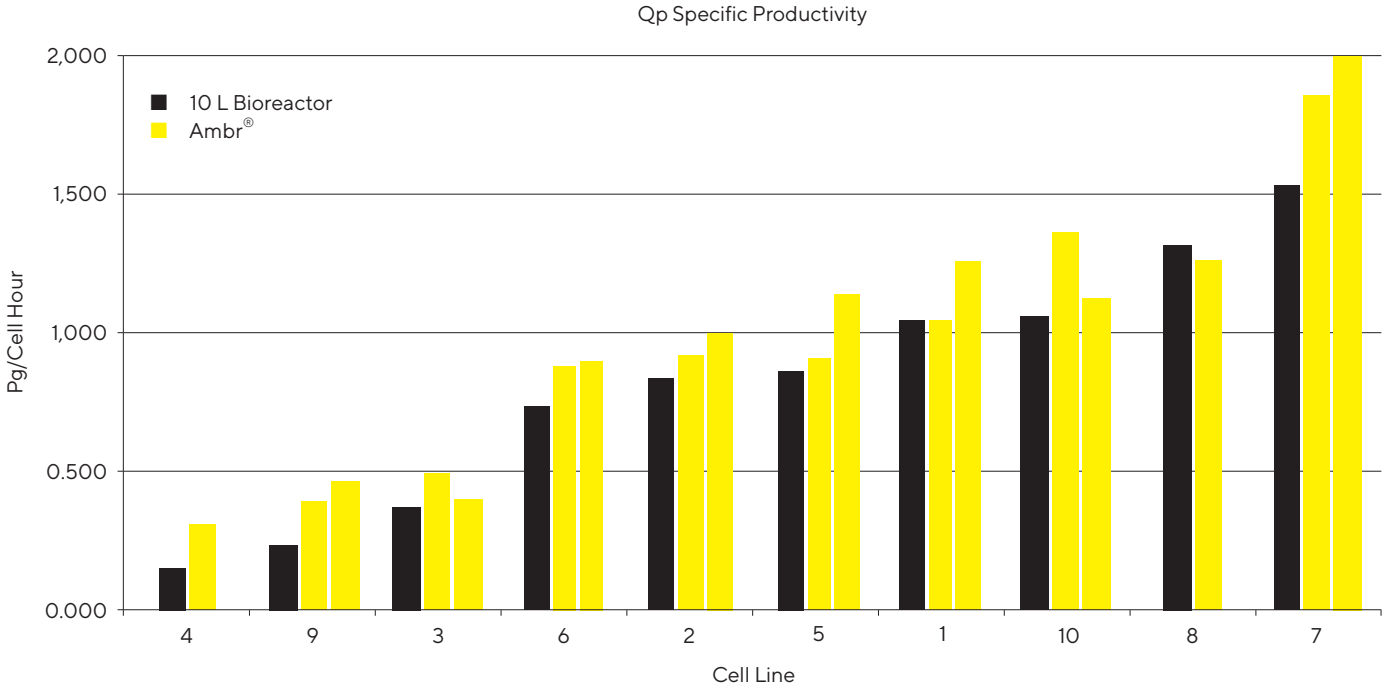

Figure 2: *Ambr® 15 Predicts the Performance of Clones at Scale* (data provided by courtesy of Lonza Biologics, UK)

Rapid Testing of Biosimilar Molecules

Biopharmaceutical companies are reducing the time it takes for products to reach the clinic still further by considering their approach to analytical testing and whether it can be outsourced (Monge & Hutchinson, 2016). By developing a suite of qualified off-the-shelf assays, that are ready for use on drug candidates, BioOutsource is reducing both the time taken and cost of developing biosimilars. Although by no means exhaustive list, Figure 3, indicates the type of characterization and comparability assays available for important innovator molecules biosimilar developers are targeting.

	Humira	Enbrel	Rituxan	Remicade	Herceptin	Avastin	Lucentis
Fcγ-RI by SPR Fcγ-RIIa by SPR Fcγ-RIIb by SPR Fcγ-RIIIa by SPR Fcγ-RIIIb by SPR FcRn by SPR	■	■	■	■	■	■	N/A
C1q by ELISA	■	■	■	■	■	■	N/A
Target binding	■	■	■	■	■	■	■
ADCC	■	■	■	■	■	■	N/A
CDC	■	■	■	■	■	■	N/A
Potency assays	■	■	■	■	(■)	■	■

Figure 3: *Assays for the Biosimilar Characterization and Comparability From BioOutsource*

Increasing Speed to Clinic

Biopharmaceutical companies are reducing the time it takes for their products to reach the clinic by adopting platform processes, using high-throughput process development technologies and outsourcing activities that are not core competencies. In doing so, these organizations increase their competitiveness by ensuring they allocate their resources to those projects in their pipeline that have the greatest chance of reaching the market. Every month that a company can save during development translates to millions of dollars in additional revenues generated by the drug being on the market earlier.

An even bigger challenge, however, is not simply reaching the market more quickly, but doing so with a highly productive upstream process that is robust and delivers product with the required quality attributes. Sartorius is leveraging all of its experience in cell culture and single-use equipment to address this challenge. We have connected our leading upstream technologies and services to create an integrated platform from which the industry can work to deliver safer and cheaper medicines to patients in the shortest possible time.

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