Journal of Biotechnology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Biotechnology

journal homepage: www.elsevier.com/locate/jbiotec

The business impact of an integrated continuous biomanufacturing platform for recombinant protein production

Jason Walthe[a,1], Rahul Godawat[a,*,1], Chris Hwang[a], Yuki Abe[b], Andrew Sinclair[b], Konstantin Konstantinov[a]

[a] Late Stage Process Development, Biologics R&D, Sanofi, Framingham, MA 01701, USA
[b] Biopharm Services, Chesham, HP51SD, UK

ARTICLE INFO

Article history:
Received 6 March 2015
Received in revised form 11 May 2015
Accepted 12 May 2015
Available online xxx

Keywords:
Continuous bioprocessing
Perfusion cell culture
Continuous capture
Biosolve
Cost of goods
Net present value

ABSTRACT

The biotechnology industry primarily uses batch technologies to manufacture recombinant proteins. The natural evolution of other industries has shown that transitioning from batch to continuous processing can yield significant benefits. A quantitative understanding of these benefits is critical to guide the implementation of continuous processing. In this manuscript, we use process economic modeling and Monte Carlo simulations to evaluate an integrated continuous biomanufacturing (ICB) platform and conduct risk-based valuation to generate a probabilistic range of net-present values (NPVs). For a specific ten-year product portfolio, the ICB platform reduces average cost by 55% compared to conventional batch processing, considering both capital and operating expenses. The model predicts that these savings can further increase by an additional 25% in situations with higher than expected product demand showing the upward potential of the ICB platform. The ICB platform achieves these savings and corresponding flexibility mainly due to process intensification in both upstream and downstream unit operations. This study demonstrates the promise of continuous bioprocessing while also establishing a novel framework to quantify financial benefits of other platform process technologies.

1. Introduction

The biotechnology industry is relatively young, beginning with the commercial launch of recombinant insulin and monoclonal antibodies in the 1980s. Over the next twenty years, the industry grew rapidly and focused on bringing innovative products to the market. This era of product innovation led to high revenues and large profit margins, resulting in the establishment of a manufacturing technology base with little regard for cost and effectiveness of manufacturing assets.

As the industry has matured, it has increasingly recognized that there are major issues with the structure and cost of these manufacturing approaches (Farid, 2007). Extensive research has improved understanding around the costs of goods (COGs) for recombinant protein production, leading to large reductions (as much as 100-fold) in operating expenses via process improvements and operational efficiencies (Sinclair and Monge, 2002; Rathore et al., 2004; Werner, 2004; Rajapakse et al., 2005; Farid, 2013). Key examples of process improvements include cell culture titer increases (Croughan, 2008) and improved downstream yields (Gronemeyer et al., 2014). Examples of operational efficiencies include template platform processes (Kelley, 2007; Shukla and Thömmes, 2010) and operational improvement programs (Han et al., 2010) allowing better utilization of existing infrastructure. Collectively, this work has been a celebrated success for cost engineers, development scientists and operations groups in the industry.

However, biotechnology companies are now facing a new set of business realities and uncertainties that include adapting to potential competition after patent expiry, supplying complex and rapidly evolving biologics portfolios and driving growth through patient access beyond current mature markets (Gottschalk et al., 2013; Love et al., 2013; Ernst and Young, 2014). (For clarity, in this manuscript, we focus only on bioprocess development and specifically omit challenges in discovery and clinical research.) In the face of this changing landscape, two common needs for future biomanufacturing are emerging: increased flexibility and reduced cost of goods. Manufacturing flexibility allows companies to manage a complex and evolving portfolio where product numbers, volumes and types are always in flux due to scientific and market uncertainties, and mergers and acquisitions. Although operating expenses for

* Corresponding author.
E-mail address: rahul.godawat@sanofi.com (R. Godawat).
[1] Contributed equally to the work in this manuscript.

http://dx.doi.org/10.1016/j.jbiotec.2015.05.010
0168-1656/

Table 1
Hypothetical product launch scenario.

Product type	Launch date	Annual demand (kg/yr)
mAb	2025	200
Non-mAb	2026	20
mAb	2027	200
Non-mAb	2029	20
mAb	2029	200
mAb	2031	200
Non-mAb	2031	20
mAb	2033	200
Non-mAb	2034	20
mAb	2035	200

some biologics products have decreased considerably, manufacturing facility construction requires significant time and capital, and operating expenses remain high for many non-standard products. If additional manufacturing must be co-localized with new patient markets, simplified facility design and reduced capital investments become even more critical.

These challenges may appear unique to the biologics business but, in our view, are integral to the business lifecycle of many industries and offer similar opportunities to spur innovations in process development. Many industries successfully transition from batch processing to continuous processing to maximize flexibility and minimize cost of goods while still maintaining operational excellence (Tanner, 1998; Thomas, 2008; Reay et al., 2013). Other benefits that typically accompany this transition include standardization, simplified scale-up, and more consistent product quality (Anderson, 2001). Recently, several of these benefits have been qualitatively described and explored for the biotechnology industry (Baker, 2013; Weintraub, 2013; Whitford and Sargent, 2013; Konstantinov and Cooney, 2014). A quantitative understanding of these benefits is critical to drive process and technology development and organizational decision-making. In this manuscript, we describe an integrated continuous biomanufacturing (ICB) platform for the production of drug substance with robust product quality and propose a novel methodology to quantify its benefits and develop a business case via comparison to conventional batch processing. Previous research has focused on continuous upstream (Pollock et al., 2012), continuous downstream (Pollock et al., 2013) and continuous processing for monoclonal antibodies (Biopharm Services, 2014). Because evaluation of individual unit operations or individual products can lead to biased technology selection that may result in a suboptimal biomanufacturing strategy, we holistically compare entire platforms (comprising all unit operations) together with a complex product portfolio. We also probe the relative flexibility of the ICB platform by evaluating the impact of several business and technical uncertainties, including product type, product approval, product demand and technology transfer delays. Overall, our work establishes a new way to build a business case for bioprocess platform technology selection and reveals the potential of continuous bioprocessing.

2. Methods

2.1. Product launch scenario

In this study, we assume a hypothetical, mature product portfolio of ten products transitioning into phase III over ten years (Table 1). Because current protein therapeutics have varying degrees of stability and demand, we assume two different product types: a more stable, high-demand product (such as a monoclonal antibody) and a less stable, low-demand product (such as enzymes, growth factors or fusion proteins). In the product launch scenario, we generically use the terms mAb and non-mAb to refer to these stable and less stable product types, respectively. Annual demands of 200 kg for mAb products and 20 kg for non-mAb products were based on industry averages (Kelley, 2009; Aggarwal, 2014).

2.2. Platforms and processes

In this study, we evaluate a novel ICB platform that couples 500-L single-use reactors to a continuous capture operation. We chose a 500-L working volume because this volume is well positioned to serve both low- and high-demand products. For mAb production, the entire process is fully continuous from production bioreactor to drug substance, including intermediate and polishing purification steps, and filtration. Because non-mAb purification cannot necessarily rely on affinity chromatography and typically has a more complicated downstream process architecture, we designed the non-mAb facility such that the continuous capture step is followed by batch intermediate and polishing purification and filtration. (Hereafter, we refer to this combination of continuous and batch operations as hybrid purification.)

Table 2
Bioprocessing facility descriptions.

Platform	Producttype	Bioreactorvolume (L)	Upstreammode	Upstream material	Downstreammode
Continuous	mAb	500	Suspended perfusion	Single-use	Continuous
	Non-mAb	500	Suspended perfusion	Single-use	Hybrid
Conventional	mAb	10,000	Fed-batch	Stainless steel	Batch
	Non-mAb	2,000	Microcarrier perfusion	Stainless steel	Batch

Table 3
High-level process assumptions for both conventional and continuous platforms.

Parameter	mAb	Non-mAb		
	10,000 Lstainless	500 Lcontinuous	2000 L stainless	500 L continuous
Avg. viable cell density (Mcell/mL)	12	120	5	60
Specific productivity (pg/cell/d)	35	35	10	10
Product titer (g/L)	5	2.1	0.05	0.6
Perfusion rate (RV/d)	–	2	1	1
Growth phase duration (d)	–	5	5	5
Production phase duration (d)	12	60	60	60
Reactor turnaround time (d)	2	1	2	1
Downstream capture	Batch	Continuous	Batch	Continuous
Downstream post-capture	Batch	Continuous	Batch	Batch
Product yield (%)	70	70	50	50

Please cite this article in press as: Walthe, J., et al., The business impact of an integrated continuous biomanufacturing platform for recombinant protein production. J. Biotechnol. (2015), http://dx.doi.org/10.1016/j.jbiotec.2015.05.010