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A new, integrated, continuous purification process template for monoclonal antibodies: Process modeling and cost of goods studies

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ABSTRACT

An evolving biopharmaceutical industry requires advancements in biomanufacturing that offer increased productivity and improved economics without sacrificing process robustness. Accordingly, we have developed a new monoclonal antibody purification template comprised of flocculation-based clarification, capture by continuous multi-column protein A chromatography and flow-through polishing. The new process offers a robust, single-use manufacturing solution while significantly reducing overall cost of goods. Modeling studies verify that the individual clarification, capture and polishing solutions offer significant advantages as stand-alone unit operations. These technologies were also designed to be integrated into a continuous purification template.

Process modeling studies have been used to highlight both cost and operational advantages of the new process template. Depending on scale, savings of more than 20% and 60% were seen for commercial and clinical operation, respectively. Integrating the technologies into a continuous process consistently offered additional cost advantages. During template development, process modeling was instrumental in highlighting the importance of identifying technologies that provided high product yield and purification factors. Additionally, high product concentration and eliminating the need for intermediate product dilution emerged as important considerations for newly developed unit operations. Combining experimental work with insights from modeling can significantly improve the outcome of product and process development.

1. Introduction

Monoclonal antibodies (mAbs) are typically produced and purified with highly templated methods that allow for a relatively quick process development and scale-up phase. As a result of their therapeutic importance, mAbs are currently being produced at a very large scale, with multi-kilogram amounts per molecule needed yearly. In 2011, sales of mAbs constituted about 36% of all biotherapeutics and the market was projected to exhibit significant future increase, as a large proportion of molecules in the clinical pipeline was also mAbs (Aggarwal, 2011). This duality, large-scale processes practiced by large biotechnology companies and significant preclinical discovery of mAbs that are not yet being manufactured, offers the opportunity for innovation, both in terms of incremental improvements in existing facilities and of radically different processes that address mAb production and purification in novel ways.

Templated processes are most frequently used for the production and purification of mAbs. On the production side, CHO cells provide the glycosylation pattern necessary for proper functionality while fed-batch processes allow titers to approach 10 g/L. On the purification side, the unique affinity of protein A toward the constant Fc portion of mAbs has made protein A chromatography the centerpiece of most downstream purification (DSP) processes. Protein A typically provides multi-log clearance of impurities along with significant product concentration. Additional unit operations are usually built around the use of protein A and are designed to remove residual impurities. Most biopharmaceutical companies employ process templates that are broadly similar in their components. There are differences in terms of the type or order of these unit operations, but a typical current template can be defined without much controversy. Such a template offers robustness and relatively straight-forward process development for newly developed antibodies. A strong argument has been made that the current template is fully capable of fulfilling our needs for antibody production for the foreseeable future (Kelley, 2008).

A schematic of the current template is given in Fig. 1. Key aspects are the use of centrifugation for cell removal, followed by depth filtration for removal of cell debris. Clarification is followed by three chromatographic resin column steps, with virus inactivation performed in a vessel after protein A. Virus filtration in normal flow

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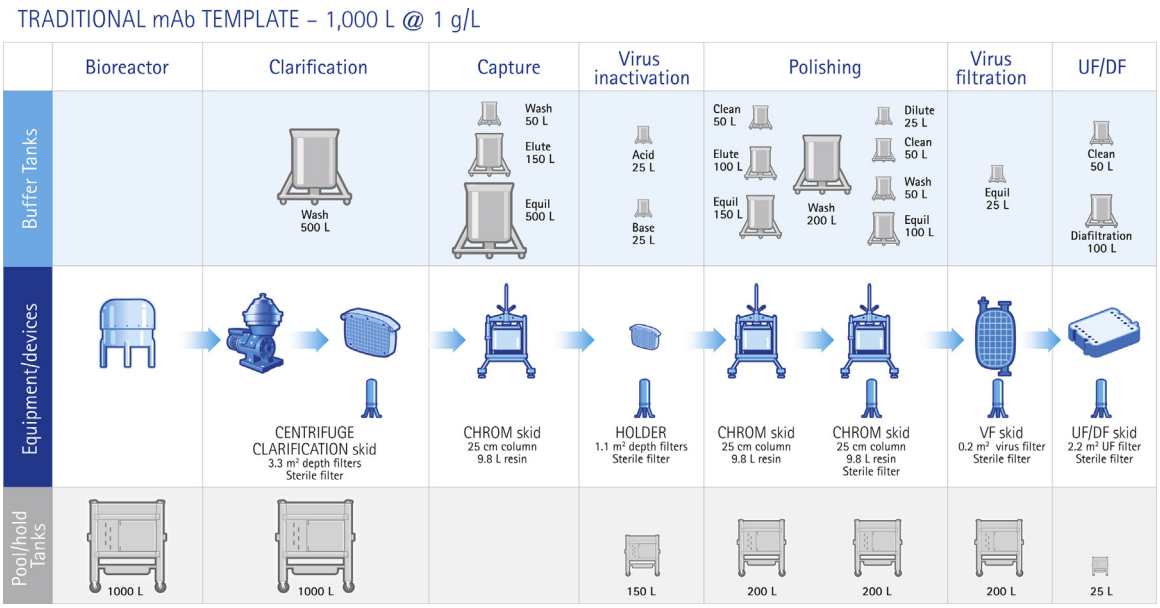

Fig. 1. Process schematic of traditional mAb production template.

filtration mode and ultrafiltration/diafiltration in tangential flow filtration mode complete the template. The effluent of the filtration operations and the eluate of the chromatographic operations are collected in intermediate pool tanks and stored – typically overnight – until the next unit operation. With each unit operation shown in Fig. 1 usually scheduled to last one daily shift, the time needed to complete downstream purification ranges between 6 and 8 days. There have been several reviews of the current process (Shukla et al., 2007; Shukla and Thömmes, 2010). In spite of its ubiquity, shortcomings in terms of cost, facility fit and process throughput have been identified by practitioners. While several alternative solutions have been proposed and explored (Thömmes and Etzel, 2008), minimal commercial implementation is known.

The advent of biosimilars and the opening of the developing world to new therapeutics is starting to put pressure on the cost of antibodies and process economics of both current and alternative templates have received increased interest (Farid, 2007). Two software packages commercially available at the time of publication, Aspen (AspenTech, USA) and SuperPro (Intelligen, USA), were compared for the analysis of a vaccine antigen and broadly similar results were obtained (Shanklin et al., 2001). SuperPro was combined with SchedulePro®, a scheduling software package by the same company, and used to model a real antibody facility (Toumi et al., 2010), with the focus and strength of the work being on sizing shared resources and evaluating capacity scenarios. A sophisticated research tool was introduced early on from the laboratory at University College London, UCL (Farid et al., 2000) and was subsequently used extensively to generate both upstream (Lim et al., 2005) and downstream (Mustafa et al., 2004) case studies. A distinguishing attribute of the evolving UCL tool is its ability to introduce uncertainty in the simulations through stochastic Monte Carlo algorithms that address both business and process aspects of facility operation. For example, intangible factors, such as contamination failures and titer fluctuations, can be included in the analysis. The UCL package was used most recently to model a semi-continuous antibody process where periodic counter current (PCC) chromatography was compared to batch chromatography (Pollock et al., 2013). The goal was to provide a useful and industrially relevant decision tool by combining modeling with experimental data. The authors concluded that PCC offers most cost benefits for clinical production while facility fit issues arise during implementation for commercial manufacturing, resulting in similar costs with batch.

Biosolve software (Biopharm Services Ltd, UK) was used to study the economics of a novel antibody purification process based on precipitation steps replacing all clarification and chromatographic unit operations (Hammerschmidt et al., 2014). The authors found cost reductions for the disposable precipitation-based process due to reduced capital expenses, elimination of clean- and steam-in-place activities and lower labor requirements for both production and QA/QC testing. Savings were higher for clinical compared to commercial production because of the omission of expensive chromatographic resins. Savings were most pronounced for the case of continuous precipitation-based purification with batch upstream production compared to a fully continuous process matched to perfusion production.

We recently proposed a novel antibody purification process that offers significant operational advantages to traditional processes (Gillespie et al., 2015; Xenopoulos et al., 2014). In the work presented here, extensive process modeling studies of the new template were performed to understand whether it also offers cost benefits and indeed it was found that it does. Several of our conclusions were in line with analyses published in the literature, yet new insights were obtained on the newly proposed unit operations and on their integration. It was possible to delineate the specific contributions to cost savings of individual unit operations, of interfaces between process steps and of continuous operation, while highlighting the importance of holistic process development.

The structure of the paper is as follows. Section 2.1 (Experimental background) describes the process as practiced in the laboratory and summarizes the experimental results that form the basis of the modeling exercise. Section 2.2 (Modeling background) presents the assumptions used for the modeling scenarios and case studies presented. Section 3 contains results of process modeling, supported by extensive tables. The results are analyzed and placed in context in Section 4, followed by conclusions in Section 5.

2. Background

2.1. Experimental background

Fig. 2 presents the schematic of the novel process. Key aspects are the use of flocculation-assisted clarification, continuous multi-column chromatography and flow-through polishing,

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