Chapter 3

LARGE-SCALE PRODUCTION OF THERAPEUTIC ANTIBODIES: CONSIDERATIONS FOR OPTIMIZING PRODUCT CAPTURE AND PURIFICATION

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1. INTRODUCTION

The first therapeutic proteins produced by fermentation of genetically engineered bacteria emerged two decades ago. With the notable exception of insulin, most of the initial wave of biotechnology products launched in the 1980s and 1990s were peptide hormones and enzymes licensed for indications with relatively small patient populations and for short-term rather than chronic use. Consequently, the market requirement for these products was frequently in the low kilogram range.

Products based on monoclonal antibody technology have now reached the market and are creating new pressures for production technology. Two factors combine to increase product requirements significantly – larger patient populations and long term use in chronic indications. There are now several monoclonal therapeutics both on the market and in clinical trials for which the requirements are at or approaching hundreds of kilograms. This has had ramifications across the industry and has impacted all aspects of drug development. Most notably, this demand has spurred drug developers to dramatically expand fermentation capacity, locate capacity at contract manufacturers or explore alternatives such as microbial expression or transgenic technology. Fermentation groups are reporting expression levels into the gram range by different techniques, and drug developers are
exploring ways to boost the potency of antibodies with directed evolution or by coupling with cytotoxins or radiochemicals, indirectly reducing requirements for bulk product. Despite these measures, pressure will continue to be placed on the downstream process to cope with ever-larger amounts of antibody.

The requirement for an ever-increasing mass of antibody is only part of the story. The key driver before product approval is the ‘time to market’. It is critical to get product in time and in sufficient amounts and with high enough purity for clinical trials to take place. Once product approval has been gained, there is usually a fundamental shift in emphasis towards a reduced cost of goods and increased process efficiency, both in terms of yield and reliability. This has occurred in several companies with large scale antibody products on the market and will undoubtedly occur for many more companies when they too reach this stage of growth. One of the key lessons to be learned from this is that the ‘product’ from a pilot scale group should not only be clinical trial material but also a process that is robust, scalable and cost effective. In order to achieve this, process optimization should be considered from the very earliest stages in the pilot plant.

Well designed processes will not only yield sufficiently pure protein but will also maximize throughput and minimize process costs. Efficient processes can decrease the requirement for fermentation capacity significantly, with a direct impact on capital resources for the size of the recovery operations and facilities, and further savings in cost of goods once a plant comes online. There is of course a compromise in terms of time to market, but investment in intensive process development can lead to eventual savings in capital costs and cost of goods sold.

Recent developments in process design and implementation have focused on strategies to improve overall economics. These include: improvements in throughput, which decrease scale of individual process steps, shorten turnaround times and improve utilization of equipment, and process compression to combine one or more steps into a smaller unit area and decrease raw material consumption, hardware requirements and overall footprint. These approaches have been used both in isolation and in combination.

In this chapter we discuss strategies for increasing process throughput and examine how these improvements can be applied to large-scale antibody purification, focusing particular attention on optimizing product capture and trace contaminant removal. We then review a series of new or emerging methodologies being applied to enhance process efficiency and improve economics.