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Antibody production☆

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Abstract

The clinical and commercial success of monoclonal antibodies has led to the need for very large-scale production in mammalian cell culture. This has resulted in rapid expansion of global manufacturing capacity [1], an increase in size of reactors (up to 20,000 L) and a greatly increased effort to improve process efficiency with concomitant manufacturing cost reduction. This has been particularly successful in the upstream part of the process where productivity of cell cultures has improved 100 fold in the last 15 years. This success has resulted from improvements in expression technology and from process optimisation, especially the development of fed-batch cultures. In addition to improving process/cost efficiencies, a second key area has been reducing the time taken to develop processes and produce the first material required for clinical testing and proof-of-principle. Cell line creation is often the slowest step in this stage of process development. This article will review the technologies currently used to make monoclonal antibodies with particular emphasis on mammalian cell culture. Likely future trends are also discussed.

Keywords: Fed-batch culture; CHO; NS0; Gene expression systems; Downstream processing; Fermentation; Cell line selection

Contents

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1. Introduction

Currently, there are 18 monoclonal antibodies approved for therapeutic use [2]. The majority (15) of these antibodies are produced by recombinant DNA technology although three are murine antibodies made in hybridomas. The recombinant antibodies are produced in mammalian cell expression systems using Chinese hamster ovary (CHO) or murine lymphoid cell lines (e.g., NS0, Sp2/0-Ag14). Most products in clinical trial are whole antibodies made in mammalian cell systems but some are antibody fragments, which can be made in microorganisms such as *E. coli*. For example, CIMZIA™ [2] is a pegylated Fab′ fragment made in a microbial system and is currently in phase III trials. Reichert et al. [2] report that, of the 15 antibodies they identified in phase III trials, six were single chain or Fab fragments. In this article, we review the technologies used to manufacture antibodies focusing particularly on the current status of mammalian cell culture and approaches taken in process development. There are two crucial issues, which have to be faced in process development. The first is to minimise the time taken to provide material for clinical studies and the second is to develop a process which can deliver sufficient drug substance to meet market demands at an acceptable price per dose.

The industry continues to look at new technologies and process development strategies that will reduce timelines. The resulting processes must be easily scaleable, robust and meet quality and safety criteria. One approach to shortening the timelines is the use of platform technologies for cell culture processes, for example using standard media, feeds and growth conditions. Cell line construction and selection is often a critical path activity and needs to be completed rapidly without compromising quality criteria. Ideally, one would like to rapidly create a highly productive cell line that could be used for long-term manufacture obviating the need to create an improved second generation cell line at a later stage of development.

Productivity of mammalian cell processes has improved dramatically in recent years [3] and modern cell culture processes can achieve antibody concentrations exceeding 5 g/L [4,5]. This has resulted from improvements in expression technology and from process optimisation, particularly of the upstream, cell culture stage. Most current processes are based on fed-batch culture and the development of feeds in particular has made a significant contribution to increased antibody yields. Highly productive cell lines result from using a host cell line that has the desired characteristics, an appropriate expression system, and a good transfection and selection protocol. A number of expression systems with the potential to produce cell lines with high specific production rates (Q_p) are available. The challenge is to create cell lines that not only have high Q_p but also