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Cell Culture Technologies in Successful Biosimilar Development

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Review Article

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Abstract

The commercial success and expiring patents of biological therapeutics has made biosimilars become attractive to pharmaceutical companies. However, the cost of manufacturing biosimilars has remained a challenge for many companies. Therefore, the ability to mimic the biologically active molecule at the lowest possible cost via cell culture has become the key of successful biosimilar development. Hence, we review current cell culture technologies that are relevant to biosimilar development. The cell line, culture media and bioprocess technology platforms discussed in current review lays a good scientific foundation for the technological competitiveness of biosimilar companies.

Keywords: Biosimilar; Robust; Cell; Biopharmaceutical

Introduction

The commercial success and expiring patents of biological therapeutics has made biosimilars become attractive to pharmaceutical companies [1]. Biosimilars is an attractive mechanism for cost reduction of health care [2,3]. The abbreviated biosimilar approval pathway is often required to ensure the long-term safety and efficacy of a biosimilar. However, the cost of manufacturing and licensing a biosimilar product remains high [4]. Reduction of manufacturing cost has become one of the most important technological advantages for a biosimilar developer. Therefore, the ability to mimic the biologically active molecule at the lowest possible cost via cell culture has become the key of successful biosimilar development [5-9]. The priority of biosimilar companies is to acquire and develop cell culture technology platforms that enable them to manufacture biologics that are similar to reference products; and to produce these products consistently and economically. Hence, we review current cell culture technologies that are relevant to biosimilar development.

Cell Line Engineering

The increasingly competitive biosimilar marketplace requires biosimilar companies to focus on rapid and low cost cell line development with predictable product quality attributes [10-14]. Traditional stable cell line platform involves selection pressure (such as GS, DHFR

system) to enhance and isolate clones with high expression of the protein of the gene of interest (GOI). However, the GOI is usually randomly integrated into the host cell's genome, hence it creates heterogeneity and expression instability. Other factors that contribute to instability of the traditional cell line platform include gene copy number, position effect, insertional mutagenesis, post-transcriptional and post-translational modifications [11,14]. These clonal instabilities can be solved by a combination of host cell clone selection and vector design to generate a stable cell line that is suitable for production [14,15]. Site-specific integration and other new technologies were developed to increase clonal stability while minimizing clonal variation [14,16]. However, such technology might reduce the chance to obtain a "high similarity clone" to the reference product. Nevertheless, a predictable technology will also win out in the risk averse pharmaceutical industry.

Media Development

Media development is one of the keys to biosimilar development. The many components of a typical media provides factors to be adjusted for protein quality optimization [17-19]. Optimization of culture conditions for cell line presents challenges because the diverse nutritional requirements are different clonally. High throughput screening of a library of diverse CHO media formulations with sophisticated Design of Experiment (DOE) experimental design and analysis techniques to develop a new strategic approach to medium development [18]. While formulation of the media is important, a consistent manufacturing process is also necessary to provide a robust production process for biosimilars [20]. However, current cell culture media manufacturing technology still lacks the assurance that the biopharmaceutical companies desire [21]. In recent years, some culture media technologies, such as high throughput technology, multivariate analysis, and study of stability etc., were adapted to improve the media formulation and production of culture media [18,21-25]. It is hopeful that more technologies of cell culture media will be developed and implemented by biopharmaceutical companies for a more robust production process.

Bioprocess Development

The key of bioprocess development is to develop a process that can consistently produce sufficient amounts of the desired protein with a high level of quality. A typical manufacturing process is divided into upstream and downstream processes. The upstream process involves cell culture technologies of cell expansion and expression [26-29]. Control Strategy the cell culture process are developed based upon scientific and risk management principles because it impact the safety and

quality of the therapeutics being produced [26-28]. Regulatory agencies emphasize analysis and characterization of products in relation to the cell culture processes; setting process specifications; and identifying critical quality attributes (CQA) and critical process parameters [26,30,31]. Moreover, process analytical technology(PAT) guidance was issued to help design, develop, and implement analytical tools during manufacturing and quality assurance of biologics [32,33]. The concept of "quality by design" (QbD) was also recommended by regulatory agencies to promote the understanding of the relationship between the product quality and the manufacturing process that enables quality built-in from the beginning of product development to the end of the manufacturing process[32]. The QbD approach in process development usually starts by risk assessment of the process parameter and its impact on CQAs. DOE is then used to screen factors for significant influences on CQAs. The design spaces are then explored in qualified scale down models such as: shake flasks, bench scale bioreactors, pilot scale bioreactors, etc. Building small scale models facilitates the control strategy for the process. When scaling up to production scale, the scaled down models need to be qualified by demonstrating their representation and prediction of large scale production, as well as various scales of operation. The scaled down model can then be used to determine the limits of the design space for the production scale [23,34-38]. The end result of these procedures should be a set of acceptable parameter ranges that conform to the engineering design space for commercial production operations [39,40].

Conclusion Remarks

The European Union (EU) has been the first to establish a regulatory framework for marketing authorization application (MAA) and has labeled copy cat bio therapeutic products "biosimilars", a term also recently adopted by the US FDA [30,41]. Successful biosimilars development strategies rely on platform technology to rapidly develop the cell culture production system that can consistently produce high quality biosimilars at low cost. The know-how of cell culture in biosimilars development along with technical staff trainingis critical for successful implementation [41-60]. The cell culture technology platforms discussed in current review lays a good scientific foundation for the technological competitiveness of biosimilar companies [61-98].

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