

Case Study

Custom Optimization of Cell Culture Media for Production of Viral Vaccines

Introduction

Vivalis, a Nantes, France-based biotechnology company, has developed EB66®, a novel cell line derived from duck embryonic stem cells for the cell culture production of viral vaccines. The cell line circumvents the quality and quantity control issues associated with traditional chicken egg and primary chicken embryo fibroblasts, while eliminating the risk of contamination and the costs associated with serum for growing the fibroblasts. As a result, EB66 cells have become a superior industry alternative for the safe, cost effective manufacturing of viral vaccines. Vivalis offers research and commercial licenses for this cell line to pharmaceutical and biotechnology companies for the production of prophylactic and therapeutic vaccines.

The Challenge

Earlier in development, while Vivalis was rapidly moving forward to register EB66, several pharmaceutical and biotech customers had expressed interest in this cell line for production of viral vaccines. However, preliminary testing by Vivalis of available media formulations from several companies had not identified media meeting the required cell growth and virus production parameters. Vivalis needed acceptable media formulations in time for customers' evaluation of the cell line prior to their commitment.

Several issues and challenges posed a significant threat to Vivalis' ability to position EB66 as a competitive cell line for next-generation cell culture produced vaccines:

- An aggressive timeline was required to meet customer needs to generate master cell banks in the chosen media.
- The media had to support robust growth of cells in bioreactors and high titers of virus production for several different virus types.
- The cells were prone to aggregation, which was undesirable during the growth phase and for production of lytic viruses, but was necessary for production of cell-associated viruses.

- The identified media must be superior to all known competitor media for cell growth and production of secreted virus, such as influenza A and B strains and of intracellular virus such as vaccinia virus.
- Multiple strains of viruses needed to be tested for this project.
- The final process needed to be competitive with the current egg-based vaccine production process.

The Solution

Vivalis entered into collaboration with SAFC Biosciences® to develop serum-free, animal-component free (ACF) media for the robust, large-scale growth of EB66 duck cells in bioreactors and the subsequent infection and production of virus in those cells for vaccines.

Initial studies focused on media screening and component optimization for growth of EB66 cells, since changes in the growth media could affect optimization of the production media. SAFC Biosciences identified promising growth media formulations for evaluation by both companies. Two formulations that exceeded target parameters were identified for growth of EB66 cells. Separate formulations were developed for the production phases of secreted viruses (such as influenza, measles, etc.) and intracellular viruses such as influenza and MVA because of the different requirements for lytic and cell-associated viruses.

Media screening and optimization for the production phase was initiated after the two growth media were identified. Using media prepared by SAFC Biosciences, Vivalis performed most of the initial virus infectivity and productivity studies because they already had in place all required SOPs, reagents and assays. This approach minimized lost time while SAFC Biosciences developed this capability. One media was chosen for production of lytic viruses (eg. influenza, measles, NDV); a second media was chosen for production of cell-associated viruses (eg. MVA).

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Results

In eight months, a multi-disciplinary team from SAFC Biosciences in Lenexa, Kan., working in conjunction with Vivalis scientists, optimized media meeting target criteria for both growth of EB66 cells and production of virus. Final products and availability of cGMP media were launched within one year of project initiation, meeting timelines for Vivalis customers. In addition, several potential customers were involved in external beta-site testing and evaluation of the chosen media.

Peak viable cell densities achieved with media during growth phase exceeded 10^7 cells/mL. Virus production media achieved high levels of performance, with MVA titers of approximately $10^{8.5}$ TCID₅₀/mL. These virus titers are highly competitive with other cell culture systems for vaccine production.

The Next Steps

This project demonstrates SAFC Biosciences potential for custom optimization of media to meet specific customer applications related to virus production. In Vivalis' collaboration with SAFC Biosciences, there is potential for further optimization to create second generation media and feeds.

SAFC Biosciences project management, under the guidelines of Design Control, has coordinated all development activities necessary to launch these four media as cGMP catalog products:

EX-CELL™ EBx® GRO-I (Catalog No. 14530C) and EX-CELL™ EBx® GRO-II (Catalog No. 14532C) are serum-free, animal-component free liquid media developed for the growth of EB66 cells.

EX-CELL™ EBx® PRO-I (Catalog No. 14531C) and EX-CELL™ EBx® PRO-II (Catalog No. 14533C) are serum-free, animal-component free liquid media developed for virus propagation in EB66 cells.

For all information about the EB66 cell line and licensing conditions, contact Vivalis (www.vivalis.com) via phone at +33 228 073710, fax at +33 228 073711 or e-mail pierreminiou@vivalis.com.

About SAFC Biosciences: SAFC Biosciences is a leading provider of cell culture materials and development services for upstream and downstream processes in the biopharmaceutical industry. Providing an integrated services package in mammalian cell culture media development, along with analytical and regulatory support, SAFC Biosciences employs a wealth of industry experience and scientific know-how to deliver reliable, consistent solutions that accelerate customer success – from development through to commercialization. The unit has a 35-year history as a manufacturing partner providing leading biopharmaceutical companies with the broadest range of highly customized products and services possible.

About SAFC: SAFC is the custom manufacturing and services group within Sigma-Aldrich that focuses on high-purity inorganics for high technology applications, cell culture products and services for biopharmaceutical manufacturing, biochemical production and the manufacturing of complex, multi-step organic synthesis of APIs and key intermediates. SAFC has manufacturing facilities around the world dedicated to providing manufacturing services for companies requiring a reliable partner to produce their custom manufactured materials. SAFC has four focus areas – SAFC Pharma®, SAFC Supply Solutions®, SAFC Biosciences®, and SAFC Hitech® – and had annual sales of \$624 million in 2008. SAFC is one of the world's 10 largest fine chemical businesses. For more information about SAFC, visit www.safcbiosciences.com.

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