

Case Study

A Systematic Approach to Improve Productivity and Increase Regulatory Compliance for a Vaccine

Introduction

Oncolytics Biotech Inc., a Calgary, Canada-based biotechnology company, has developed a novel cancer treatment, REOLYSIN® based on wild-type reovirus expressed in suspension-adapted human embryonic kidney cells (HEK 293). The company has completed Phase II clinical trials with exciting results in the treatment of several different types of cancers using this product alone or in combination with traditional cancer therapies. The clinical trial strategy for Phase II trials required a commercially viable manufacturing process to be in place to allow the production of sufficient clinical inventory for launch.

The Challenge

Reolysin was ready to move into Phase II, but producing sufficient levels of the compound was challenging. Unless Oncolytics could overcome production inconsistencies and limited production capacity, it would be difficult to conduct these critical clinical trials in a timely fashion.

The initial clinical studies were conducted with virus produced in cells grown in a commercially available animal-component free (ACF) cell culture medium cultured in 20 L stirred tank bioreactors. Although producing the product in a non-optimized, commercially available media such as this was capable of supplying sufficient yields for small, local administration studies, it was totally inadequate for the large, system administration studies required for the Phase II trials of Reolysin. Oncolytics identified the following shortcomings with the media used for the initial studies:

- Viral titers in upstream and final product ranged widely in the bioreactor system and it was believed this variability was due to inconsistencies in the feedstock
- Media was developed for suspension culture of HEK 293 cells, not virus production in these cells
- Media contained phenol red which negatively impacted performance of anion exchange columns
- Media could not support cell growth beyond 2E6 cells/mL
- Media contained non-essential components that interfered with downstream processing steps including clarification and UF/DF
- High accumulation of ammonia in the initial media negatively affected production of virus

To address these concerns and to increase the quality of the bulk harvest, and to assist in the development of a scalable and controlled production process, Oncolytics identified the need for a serum-free, ACF cell culture medium for the production of Reolysin.

The Solution

SAFC Biosciences® was given a project to optimize medium formulation with the ability to increase viable cell densities while simultaneously decreasing the ammonia accumulation that had been demonstrated to dramatically reduce reovirus production in tissue culture. SAFC Biosciences worked on optimizing the medium formulation using a Design of Engineering-based approach involving medium screening, medium mixing and factorial-based optimization of specific

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medium components. This initial work resulted in significant improvements in cell growth and viral productivity. However, continued variability in yield during purification in upstream feedstock failed to generate comparable improvements in purified product yield, indicating the need for optimization of the downstream manufacturing process.

Due to the BL2 classification of the agent, SAFC Biosciences was not able to conduct the development work required on the downstream process. Therefore, on Oncolytics' behalf, they selected a third-party CMO. While continuing work on medium development and optimization of upstream production processes, SAFC Biosciences coordinated the transfer of necessary protocols, SOPs and permits to the third-party CMO. The final media selection was concluded, and execution of the first 5 L validation studies was completed within nine months of the start of the project. Validation studies at the 20 L working scale were then completed and SAFC Biosciences conducted the technology transfer of the new upstream and downstream to Oncolytics' cGMP CMO. GMP production with the new media and processes occurred during fourth quarter of 2006.

Results

The developmental work conducted and coordinated by SAFC Biosciences resulted in a new medium, optimization of the upstream cell culture process using new medium and optimization of downstream purification process. Specific benefits included:

- A 2000% increase in the overall productivity of the process. Overall recoveries went from 4% (for a good run) to an average recovery of 26% (in the development runs). The process has been demonstrated to scale linearly to the 40 L scale
- Final medium supports 8 - 9E6/mL viable cell density and a 3 - 4 fold increase in cell density when compared to control formulations
- The combination of improved basal medium and process optimization allows achievement of viral titer greater than 5E10 TCID₅₀/mL, which is a tenfold increase over control medium and process
- The increased productivity yielded by previous studies led to the examination of the downstream purification process for compatibility with the increased level of starting material - a complete optimization of each step of the downstream was implemented to take advantage of the improved upstream product
- Identification of process steps where changes in handling procedure and/or equipment size allowed full benefit of increased productivity in prior steps

SAFC Biosciences work resulted in more reliable and higher level of production of viral material. The new process has received approval from MHRA and has been transferred into cGMP production with multiple lots produced successfully at the 20 L and 40 L scale. Additional development work is underway at the 100 L scale in preparation for transfer to cGMP production with technology transfer to SAFC's cGMP Carlsbad, CA facility in March 2009. SAFC successfully achieved Oncolytics' objective of producing Reolysin at the levels and quality needed for Phase II studies.

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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