ENABLING COMMERCIAL MANUFACTURING FOR HIGHLY COMPLEX SMALL MOLECULE DRUGS THROUGH PROCESS ENGINEERING AND TECHNOLOGICAL INNOVATION

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Much of the innovation occurring in the pharmaceutical industry today is achieved by smaller pharma/biotech firms with limited commercial manufacturing experience. Outsourcing partners with deep process science and process engineering expertise, extensive networks with traditional and nontraditional equipment vendors, and the ability to redesign existing systems and develop new technologies can enable scale-up and commercialization while shortening manufacturing time, simplifying the supply chain, and reducing manufacturing CoGs.

INTRODUCTION

With the pressure to reduce development times and get to the clinic as quickly as possible, many small and medium-sized pharma/biotech companies develop processes with a focus on generating initial material for preclinical and early-phase clinical testing. Often, these processes present challenges with respect to scale-up and commercialization, because they were developed without consideration for the long-term manufacturing plan, from the availability of key raw materials to control of particle size to practical purification at large scale. Complex, "boutique" release testing methods creating major development time and costs are also common. However, experienced CDMOs that have the ability to develop solutions can help these innovators improve their processes and ultimately reduce their costs. This case study presents the collaboration between an early-stage company that was struggling with the development of a realistic and economically viable commercial pathway and BioVectra, a CDMO with 50 years of experience. This collaboration led to the successful commercialization of a product that is now improving the life of millions of patients in the world.

PROCESS SCIENCE AND PROCESS ENGINEERING SOLUTIONS

Like many of today's small molecule drugs, the product presented challenges from synthetic (e.g., chirality, sensitive functionality), efficacy (e.g., solubility, bioavailability, stability) and/or handling (e.g., high potency, controlled substances) perspectives. Therapeutics are often difficult to manufacture. They may require a novel route to circumvent existing patents, and/or may present issues around raw material/building block availability. Safety of both product (i.e., control of impurities) and process (i.e., control of process hazards) is paramount, followed by ensuring that the process design plan is able to meet client economic constraints. An understanding of the behavior of small molecules and the potential problems that could arise enables anticipating roadblocks and rapidly providing solutions, ensuring that even accelerated projects are successfully completed.

For this specific project, where the complex synthetic API product had unique characteristics requiring careful balancing of process conditions, the primary scale-up challenge was filtration of a solid intermediate and final API. Laboratory-scale filtrations for small molecules are typically performed in a funnel using filter paper. The collected filtrate is then washed to provide a pure product. These filtrations can be directly scaled, sometimes resulting in >2-m diameter Nutsche filters, but are simply not practical for commercial API production. Processing time is too long, and large volumes of solvents are required, adding unnecessary cost. Additionally, wet cake quality is hard to control, which creates risk of variability.

Since the customer had limited commercial experience, they requested that BioVectra take control of managing the scale-up implementation challenges. Typical pharma filter units and centrifuge operations were not options due to the need for thin cake filtration, extensive washing, and process constraints for cycle times. The filtration bottleneck created safety issues, supply chain hurdles, and unacceptable CoGs at larger scale.

A personalized, integrated approach was adopted to ensure that development was not performed in isolation, but rather was a joint effort encompassing R&D, manufacturing, quality, and procurement. Process science and process engineering resources were deployed to identify root causes and develop specialized process solutions that would be amenable to implementation at large scale. The result was a reduction in delays between development phases and the identification of optimal manufacturing processes that provided high-quality product with substantially reduced overall CoGs. However, no one knew then that the customer forecasts were vastly underestimated and that technologies that would be needed soon to supply the market did not yet exist.

TECHNOLOGY DEVELOPMENT TO SOLVE PROCESS ROADBLOCKS

Confident of its success in clinical development, the customer entered into agreements with larger partners and quickly saw its commercial forecasts grow beyond prior projections, with approval in several geographies.

Presented with the challenge of scaling up faster and to a much larger capacity than anticipated, the only possible avenue was to align process science, process engineering, and technology innovation capabilities to address the challenges of scaling as the project advanced through its development life cycle. This work included the redesign of certain unit operations and the development of new technology in collaboration with suppliers not typically associated with the pharma industry. Working with a leading vendor in chemical thin-cake filtration to create a novel GMP belt filter unit provided a major breakthrough in the overall process efficiency. Additionally, the redesign of a totally enclosed, solvent-capable filter press emerged, providing a safe, high-yield, and cost-efficient solution.

Planning for rapid scale-up (from 10-kg to >1000-kg batches) required unique interaction with equipment fabricators, while the custom equipment was fabricated with consultation from process engineers.

Lastly, the construction of internal capability also allowed BioVectra to concurrently and proactively plan scaled-up process trains that would accommodate the process conditions and optimal process flow for economic production at scale. The use of multiple processing suites at varying scales aided with acceleration and delivery of the whole project to commercial scale in less than three years, including the build of a new manufacturing area.

SUCCESS, CONTINUITY, AND EXPANSION

For this customer, the deep process science and process engineering expertise, the extensive networks, and the ability to develop new technologies that drive efficiency and value made BioVectra the partner of choice to create a pathway to commercial success. The ability to support projects from R&D to commercial scales, design specific plans, and adapt to the changing needs of the market allows customers to avoid the time and cost associated with technology transfer from one service provider to another during scale-up and after achieving commercial scale. Equally important, a low staff turnover means that a strong contingent of subject matter experts that worked on the project from inception remain employed by the company, which allows for continued oversight and training of a dedicated manufacturing team and for continued success.

In fact, the commercialization of this product was so successful that the construction of a dedicated wing was necessary to increase the annual throughput. This construction (and installation of the specialized equipment) has led to routine metric-ton level production to supply the growing demand of the market.

The flexible technologies utilized can be applied to respond to further increases in demand and to produce other highly complex therapeutic compounds. Our extensive expertise in QA and cleaning validation translates into long experience with multiproduct facilities.

KNOWLEDGE, COLLABORATION, INNOVATION. REPEAT.

In this case, existing technologies were adapted to meet specific process needs. However, in many cases, a CDMO must develop new technologies to solve process scale-up challenges.

Such was the case for a product that formed a solvate with the crystallization solvent. All typical drying techniques and unit operations failed to achieve sufficient reduction of the residual solvent. BioVectra's process development and engineering group developed a temperature and vacuum profile for drying in a mechanically fluidized dryer to produce the API with consistent residual solvent values. A fundamental understanding of physical chemistry led to the solution for this problem, and the process has proven to be scalable from 100-kg to 1300-kg batch sizes.

Having a wide breadth of process knowledge – including process science and process engineering expertise – and available technologies facilitates the development of solutions to complex process challenges. Good predictive knowledge is also a fundamental component of successful process innovation. At BioVectra, close collaboration is not limited to internal process and engineering personnel, but extends to clients, vendors, and the entire partner network who all engage in open and transparent discussions – *for the benefit of patients.* P

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