Key Challenges Facing Biomanufacturing

a report by
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Robert J Broeze is the President and Chief Executive Officer of Laureate Pharma. He has over 20 years of experience in the biopharmaceutical industry, with technical expertise spanning research, development, characterisation, validation and current Good Manufacturing Process (cGMP) manufacture of biopharmaceutical products, from pilot to phase III clinical and commercial scale with a strong emphasis on monoclonal antibody products for parenteral use. Prior to joining Laureate, Dr Broeze held positions as Vice President, Biologics Research at Purdue BioPharma L.P. and Vice President, Operations at Bard BioPharma L.P, where he was responsible for the development and manufacture of the company's proprietary monoclonal antibody and biopharmaceutical products. Prior to this, he held positions of increasing responsibility at Cytogen Corporation and ultimately held the position of Vice President, Operations, with overall responsibility for development and cGMP manufacture of Cytogen's products. Dr Broeze served on the Board of Directors of the Council of Radionuclides and Radiopharmaceuticals, Inc. (CORAR) (1998-1999) and currently serves as a Director on Laureate Pharma's Board. Dr Broeze was a Postdoctoral Fellow in the Department of Molecular Biophysics & Biochemistry at Yale University, where he studied the molecular biology of the interferon system. He is a graduate of Rensselaer Polytechnic Institute, where he earned both his BS and PhD in biology.

There are a number of challenges facing the biomanufacturing industry, from both the contract manufacturing organisation (CMO) and industry perspectives. Biomanufacturing is a complex, labour-intensive and expensive process and therefore it is extremely important to understand and balance capacity versus demand and staffing level. Identifying, hiring, training and retaining properly qualified personnel are very critical to the successful operation of a facility, since biomanufacturing requires a very specialised and experienced workforce. Staff must have technical expertise in specific areas including upstream or downstream current Good Manufacturing Practice (cGMP) manufacturing operations, process development, project management, process engineering, quality assurance, analytical development, quality control, regulatory compliance, and many other highly specialised functions. Once on board, new employees must be trained on facility, process and testing standard operating procedures (SOPs) in order to be qualified to perform their job functions. Training and qualification in some aseptic operations can be quite complex, taking several months to complete, and can involve on-the-job training and, in some cases, qualification testing using established procedures such as media fills.

Key Industry Drivers

Global manufacturing of biopharmaceuticals has increased significantly over the last decade due to several factors. A major industry driver has been the expansion of the market for biopharmaceutical products. Biopharmaceuticals can be highly effective and potent, can have fewer side effects and can cure diseases rather than merely treat the symptoms. These advantages, combined with the increasing number of new diseases treatable with biopharmaceuticals, are driving demand for these drugs worldwide. In 2005, biotechnology revenues worldwide were forecast to reach more than US$45 billion, or almost 10% of total global drug sales. The therapeutic antibody market represents over US$8 billion. More than 100 biotechnology drugs have been approved since 1997 and, today, at least seven of the top biotechnology drugs bring in more than US$1 billion annually. It is estimated that 300 biopharmaceutical products are in clinical trials, with another 600–700 in pre-clinical or early clinical development. Large pharmaceutical companies continue to outsource manufacturing and filling of selected products, but the real growth is from the many biotechnology companies that elect to outsource pre-clinical to commercial development to avoid the cost and risk of establishing in-house manufacturing.

Outsourcing Biomanufacturing

Certainly a key advantage of outsourcing biomanufacturing pertains to capital utilisation requirements. Not all companies have the capital, internal expertise or time to invest in constructing a cGMP-complaint facility for manufacture of their biopharmaceutical product. Outsourcing to an experienced CMO can lower production costs, improve manufacturing efficiency and have a positive impact on the balance sheet. Companies can buy and make capacity at the same time, accessing external technology and expertise early in the clinical development of the drug and maintaining flexibility until internal manufacturing capability becomes strategically important. Companies are finding that certain operations, such as lyophilisation and aseptic processing, that are not core competencies are not economical to run in-house. They are looking to outsource more of these activities. Outsourcing biomanufacturing also reduces time-to-market as constructing a new, fully validated facility takes several years. Outsourcing manufacturing gives companies an opportunity to place greater focus on their own core competencies.

When selecting a contract manufacturer, a company needs to evaluate the contractor's capacity, capability and track record. The two businesses should also be aligned behind common scientific standards.A CMO's ability to take over the manufacturing process and its experience making similar products with similar production processes

needs to be considered. The CMO's capacity and flexibility to handle current volumes and its ability to expand operations if needed down the line is another critical factor. The company also needs to assess the CMO's 'corporate culture' – that is, how well the contractor's management team will work with the sponsor and how smoothly the project is likely to go. Other factors that could affect the outsourcing decision are the goals and scope of the outsourcing initiative: which products will be manufactured in what volumes and on what timeline? Which functions will be handed over to the contractor and which will be retained by the sponsor or outsourced to another third party service provider? Careful planning and well thought-out execution can eliminate any obstacles to successful technology transfer.

Issues in Technology Transfer

Technology transfer is critical to the success of any project that is outsourced and is typically a long, tedious and labour-intensive process. Many times, sponsors underestimate the time required for successful transfer. Due to 'time to market' pressures, they will push contractors to move as quickly as possible. It is important to assign project team managers who have technical expertise with several years of experience in manufacturing or quality control. Successful technology transfer requires specific documentation of all product stability data; completed product batch records; properly qualified equipment; analytical methods; specifications for raw materials and excipients; assay validation; any manufacturing or process experience that the sponsor has with the product; and cell line stability data, product purification data and any undocumented verbal information about the product. The challenge of technology transfer is to determine how a process can be completed using the facilities, equipment and space available to the contractor without compromising the quality and specifications of the process or product. Once the information transfer is completed, a well designed plan to duplicate the process at the contractor's facility and a production plan or method by which a product will be manufactured during an actual production campaign need to be developed. Technology transfer can be considered to be complete only when several consistent production batches are completed and the resultant product meets specifications.

Current Capacity

There is a lot of speculation about the demand and supply equation for biomanufacturing capacities. The prevailing wisdom is that the sector has been suffering from undercapacity and a number of

sources suggest that a capacity gap exists. In a survey conducted by BioPlan Associates in 2005, over 34% of respondents agreed that their organisation is currently experiencing significant capacity constraints. Over 42% of respondents believe they will experience constraints in five years. The survey also found that overall worldwide biopharmaceutical manufacturing is perceived to be 70% of capacity with mammalian cell culture production being currently at 74% capacity, compared with microbial fermentation, which is at 68% capacity.

However, Frost & Sullivan suggest that the global manufacturing capacity of biopharmaceuticals was around 2.27 million litres in 2004 and is expected to increase to 3.69 million litres in 2011, at a compound annual growth rate (CAGR) of 7.2%, and will exceed demand through to 2011. Currently, global demand stands at 1.37 million litres and is likely to increase to 3.13 million litres in 2011. Companies are now achieving improvements in productivity from 1g/litre to 2–3g/litre and above. Bioreactor and purification capacity requirements are very sensitive to these improvements.

Smaller Companies and Outsourcing at an Earlier Stage in the Drug Development Cycle

Contract manufacturing is very well suited for small and emerging companies and can serve as the basis of a company's product development strategy. They can gain access to external technologies and expertise early in the clinical development of their drug through outsourcing and can utilise these resources until an internal manufacturing capability becomes strategically important. Contract manufacturing companies provide a high-quality and economical alternative for small and medium sized biotech and diagnostic companies. By handing over the responsibility and complexity of daily production to CMOs, these companies can significantly minimise their risk and decrease their development timelines. Their time and resources can be better spent in drug discovery and lead optimisation.

Services Offered by CMOs

CMOs can offer services ranging from cell line development, cell banking, bioreactor production, process development, protein purification, scale-up, pilot scale production, cGMP production, analytical and testing services, validation, quality control testing, protein conjugation, modification, radiolabelling, to final formulation, lyophilisation, fill and finish. This essentially covers the entire drug development and manufacturing process.

Future of the Industry

The future for CMOs is very bright. The market is growing for the foreseeable future at double-digit rates. There is a steady stream of biopharmaceutical products in clinical trials and approved biotechnology drugs are generating high levels of revenue. Outsourcing is key not only for small to medium biotechnology companies that do not have the resources or have decided not to build their own manufacturing facility, but also can be beneficial for large pharma and biotech companies. A survey recently conducted by BioPlan Associates found that, by 2008, nearly half of all biopharmaceutical manufacturers might contract out production of biologics. Currently, 35% of biomanufacturers outsource at least some of their biologics production in mammalian, microbial, yeast, plant, or insect systems. These manufacturers project that, by 2008, this number will increase by over 30%. The fact that the contract manufacturing industry is projected to grow at these multiples suggests that it is delivering value to its customers.

Protecting Jobs and Leadership

Globalisation could effectively move manufacturing jobs overseas, so companies will need strategies to protect jobs and leadership. The best way to do this in contract manufacturing is to offer customers the best value. Time and language differences, long travel distances, variations in experience level, conflicts regarding intellectual property and process compatibility issues are major barriers to overcome before manufacturing jobs move overseas. In the pre-clinical and early clinical areas it is believed that companies will be reluctant to move overseas due to the evolving nature of the manufacturing process, and the benefits of being closer to where the development is occurring. Commercial production of less complex and well-characterised processes is more likely to go overseas in the medium- to long-term.

In time, companies wishing to produce biogeneric products may base their production operations overseas, to achieve production economies. In a biogenerics market, US companies need to differentiate themselves by successfully adding value to existing products. For example, companies can formulate proteins with novel delivery systems or generate products in a more cost-efficient manner. Companies need to balance the increased costs of novel formulations made in the US with lower production costs of bulk material manufactured overseas. ■

This article is continued, with graphics, in the Reference Section on the website supporting this briefing (www.touchbriefings.com).

bioProcessUK

Knowledge Transfer Network

www.bioprocessuk.org

The UK has the second highest number of biopharmaceuticals in development worldwide, with 70 products in clinical trials and over 50 companies developing these innovative medicines. Their activities are supported by a strong contract manufacturing specialist supplier base providing an integrated biopharmaceutical development and manufacturing infrastructure.

Moving a biopharmaceutical from early discovery through to the end of clinical trials is a long, complex and expensive business. Manufacturing even the least sophisticated biological medicine is fundamentally different, and far more complicated, than manufacturing small molecule pharmaceuticals. Bioprocessing involves turning living cells into manufacturing units to produce biological medicines.

bioProcessUK is responsible for supporting the growth of the biopharmaceutical development and processing sector in the UK. This will be achieved by:

- Building powerful networks of academics and industrialists
- Benchmarking, developing and promoting UK bioprocessing capability
- Investing in the UK bioprocessing research and education infrastructure
- Providing an attractive investment environment

bioProcessUK is a Knowledge Transfer Network dedicated to advancing the UK biopharmaceutical bioprocessing sector. Knowledge Transfer Networks are a DTI business support product delivered through the Technology Programme, whose purpose is to facilitate further investment in science, engineering and technology with the active participation of business and industry.[1] bioProcessUK is managed by the BioIndustry Association (BIA).

For further information about bioProcessUK visit us at www.bioprocessuk.org

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[1]To find out more about Knowledge Transfer Networks visit **www.dti.gov.uk/ktn**