

Outsourcing Biomanufacturing



An increasing number of biopharmaceutical companies are outsourcing biomanufacturing (bio-outsourcing) to bring their products to market in a cost-effective and timely fashion. This article explores the pros and cons of bio-outsourcing and provides some insight into the prospects for future growth of this newly emerging industry.

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During the past 25 years, the biopharmaceutical industry has transformed itself from a research and development enterprise into a robust, product-driven sector of the global economy. Recent reports indicate that worldwide sales of biopharmaceutical products reached \$40 billion in 2004 and are expected to reach \$59 billion by 2010.^{1,2}

Biopharmaceutical new drug approvals have been growing rapidly, rising from seven in 1994 to over 60 by 2004.¹⁻³ At present, there are around 370 biopharmaceutical products in late stage clinical development.¹ Industry analysts project that 125 new biopharmaceutical products should make it to market within the next 10 years.⁴

Unlike the manufacture of small molecule drugs, biopharmaceutical manufacturing (biomanufacturing) is more costly, less efficient and extremely labour-intensive. Consequently, the transition of many biopharmaceutical companies from R&D to manufacturing has placed an enormous strain on existing biomanufacturing expertise

and global production capacity. Historically, biopharmaceutical companies have chosen to bring biomanufacturing 'in-house' to retain control over personnel, production schedules, intellectual property (IP), and regulatory and quality concerns.

Although this strategy has been successful for larger and better established biopharmaceuticals companies, such as Amgen and Genentech, many smaller companies do not possess the internal expertise or the financial resources to manufacture their own products.

Instead, many small biopharmaceutical companies turn to contract biomanufacturing organizations (CBMOs) for clinical or commercial production of their products. This trend has resulted in a rapid proliferation (and a concomitant surge in revenues) of small- to mid-sized CBMOs in recent years.

What is Getting Outsourced?

Biomanufacturing can be subdivided into three distinct activities:

- bioprocess development
- scale-up for manufacture of clinical test materials
- large-scale, commercial manufacturing.

The production systems used by individual companies vary, ranging from microbial fermentations (bacteria and yeast) to mammalian cell culture. The type of production system that is chosen is contingent upon the physical and biological characteristics of the product that is being manufactured.

Recent surveys conducted by the American Society for Microbiology and BioPlan Associates, Inc. indicated that in 2004 approximately 35% of biopharmaceutical companies outsourced some of their biomanufacturing activities (ranging from bioprocess development through commercial manufacturing).⁴ This number is expected to grow to 47–50% by 2008.⁴ The survey data also showed that a higher percentage of companies involved in microbial fermentation outsourced biomanufacturing activities compared with companies that use mammalian cell culture. This is not surprising because manufacturing using microbial fermentations is considered to be a more 'mature' technology than mammalian cell culture. Finally, survey results suggest that smaller companies, with products in scale-up through Phase II clinical production, are more apt to outsource biomanufacturing projects.⁴

To Outsource or Not to Outsource?

Outsourcing of biomanufacturing (bio-outsourcing) grew at annual rate of 20% from 1996–2001, a period in which the biopharmaceutical industry brought an unprecedented number of products to market.⁵ Industry experts expect growth in this sector to increase as many biopharmaceutical companies consider bio-outsourcing as a viable option to in-house manufacturing.

There are several major factors that induce biopharmaceutical companies to consider bio-outsourcing. These include:

- avoidance of capital expenditures and investment in biomanufacturing
- lack of internal biomanufacturing expertise, experience and personnel
- a need to reduce time-to-market for their product(s).

Most industry experts estimate that it costs between \$350 and \$900 million (depending upon the product) to build, equip and validate a biomanufacturing facility. Furthermore, it may take as long as 4 years before a dedicated production facility can be built and made operational. Finally, most regulatory experts agree that the decision to build a commercial manufacturing facility should be made around the time a product is in Phase II clinical testing.

Based on current industry success rates, the probability of approval for a Phase II product is approximately 26%. Therefore, if a company decides to build a manufacturing facility for a Phase II product, it faces a 74% chance that the facility will not be needed upon its completion.⁶

Not surprisingly, the vast majority of biopharmaceutical companies do not want to assume this level of risk, nor can they afford the cost and time required to build their own biomanufacturing facilities.

Instead, many companies choose to outsource manufacturing to CBMOs which, by virtue of their business models, have made large capital investments in infrastructure, personnel and operational capability. Thus, CBMOs provide biopharmaceutical companies with easy, timely and cost-effective access to biomanufacturing.

Another factor driving the bio-outsourcing trend is the realization by many biopharmaceutical executives that biomanufacturing is a complex process and that it is frequently outside of the core competencies of their companies. Further, process development and manufacturing are typically done under current good manufacturing practices (cGMPs); a rigorous set of regulations that requires well-trained and highly skilled personnel. Of interest, the recent cGMP biomanufacturing initiatives mandated by both European and American regulatory agencies has resulted in worldwide shortages of cGMP-trained biomanufacturing personnel.⁷ This shortage, coupled with the unusually high costs of cGMP training, has forced many biopharmaceutical companies to abandon in-house manufacturing in favour of bio-outsourcing. Finally, bio-outsourcing can also mitigate compliance risks for biopharmaceutical companies that generally have little or

no experience with biomanufacturing regulatory requirements.

Time-to-market is another critical factor that is driving biopharmaceutical companies to consider bio-outsourcing. Increasing regulatory complexity is causing dramatic increases in the time required to gain marketing approval for biopharmaceutical drugs.⁷

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CBMOs can help to reduce time-to-market because they understand the nuances of regulatory compliance, employ cGMP-trained personnel and typically work closely with regulatory agencies. Furthermore, in many instances, CBMOs can offer clients access to new, cutting-edge technologies that reduce biomanufacturing time (and costs) by streamlining production processes and enhancing product yields.⁸

Despite its benefits, bio-outsourcing is not without potential drawbacks.⁹ First, many companies feel that they must maintain manufacturing control over a product to ensure regulatory compliance and product quality. A company's reputation is closely tied to the product it manufactures. To that end, any problems with a product will likely have an adverse affect on company's standing in the industry. Many biopharmaceutical executives simply do not think it is worth the risk of entrusting the company's reputation to a third party vendor.

Second, because all CBMOs work with multiple customers, patent and proprietary information concerns can arise.

Third, some companies are not willing to invest the time, effort or costs required to identify, qualify and transfer technology to a CBMO.

The increasing use of disposable, single-use biomanufacturing systems has been a boon to the CBMO industry. These systems offer many advantages over traditional stainless steel biomanufacturing facilities.



Finally, there are considerable tax incentives and benefits for companies that build their own biomanufacturing facilities.

The Future of Bio-outsourcing

By all accounts, the future of bio-outsourcing is extremely bright. All indicators suggest that the biopharmaceutical industry is heading towards an increased reliance on CBMOs. Factors driving this trend include:

- technological advances in optimizing process development and improved product yields
- the advent of disposable, single-use biomanufacturing systems
- the emergence of Asian countries such as China, India and Singapore as low-cost biomanufacturing providers
- the emerging follow-on biologics (biogenerics) industry.

Many CBMOs have made substantial investments into improving biological expression systems and decreasing yield loss during downstream processing of biopharmaceutical products.¹⁰ This has helped CBMOs to reduce manufacturing costs and enhance product yields, which in turn, has increased the willingness of cost-conscious biopharmaceutical companies to outsource some or all of their manufacturing activities.

It is likely that as more technological advances are made, biomanufacturing costs will continue to decline and the number of companies that choose bio-outsourcing will increase.

The increasing use of disposable, single-use biomanufacturing systems has been a boon to the CBMO industry. These systems offer many advantages over traditional stainless steel biomanufacturing facilities.

- They are less capital intensive and provide significant cost savings; for example, at the 20 L bioreactor scale, disposable-bag systems cost approximately \$20000 per year whereas stainless steel vessels are estimated to be about \$40000 per year.¹¹
- These systems can streamline operations and reduce labour costs by eliminating certain manufacturing steps such as the clean in place (CIP) and steam in place (SIP) activities.
- They promote greater regulatory compliance by eliminating many validation requirements, for example, CIP and SIP, and decreasing the volume of in-process documentation typically associated with traditional manufacturing facilities.
- Disposable systems optimize available space and promote faster equipment turn around time.

- They permit CBMOs to manufacture multiple products at a single time and maintain product integrity by eliminating cross contamination that frequently occurs (as a result of equipment cleaning failures) in conventional multiproduct facilities.

The reduced capital expenditure and space optimization offered by disposable systems have allowed many small- to mid-sized CBMOs to enter the bio-outsourcing market. This, along with the inherent cost savings offered by disposable systems, should continue to drive manufacturing costs lower, which in turn, should induce more companies to consider bio-outsourcing.

Over the past few years, countries such as India, China, Korea and Singapore have been quietly building their own biomanufacturing capabilities.

Although Asian biomanufacturing is still in its nascent stages, the endorsement of cGMP initiatives by the Chinese and Indian governments,¹² coupled with recent public statements regarding more stringent enforcement of IP and patent laws, suggest that these countries are gearing up to compete in the bio-outsourcing market.

Given that biogenerics are expected to be sold at reduced prices, it is unlikely that biogenerics companies will be able to invest in building their own costly biomanufacturing facilities.



In support of this, several western companies including GlaxoSmithKline, Bayer, Sanofi-Aventis and Pfizer have already begun to outsource some biomanufacturing work to India.¹³ Nevertheless, the lower costs, quick access to trained and inexpensive labour pools, increased awareness of quality standards and a willingness to work hard suggest that Asian CBMOs ought to be able to compete with more well-established bio-outsourcing companies.

The near patent expiry of many blockbuster biopharmaceuticals has given rise to the follow-on biologics or biogenerics industry. Similar to generic pharmaceuticals, these products are expected to be manufactured and sold more cheaply than their brand name counterparts. Although regulatory pathways for approval pathways of these products does not exist in the US, Europe or Japan, several biogeneric products are already being sold in less-regulated markets throughout the world.¹⁴ Most industry analysts concede that it is only "a matter of time" before approved biogenerics are on the market in Europe and elsewhere.

Given that biogenerics are expected to be sold at reduced prices, it is unlikely that biogenerics companies will be able to invest in building their own costly biomanufacturing facilities. Instead, it is

likely that these companies will choose to out source biomanufacturing to commercial CBMOs.

Alternatively, CBMOs themselves may choose to manufacture and sell their own products and compete for market share with the biogeneric companies. No matter which of these strategies is ultimately adopted, it is likely that continued growth of the biogeneric industry will expand the bio-outsourcing market.

Conclusions

The decision to outsource biomanufacturing is not an easy one. Bio-outsourcing may be the right for some companies, but wrong for others.

Nevertheless, the decision to outsource biomanufacturing should ultimately be made after considering some critical factors: the financial status of a company; stage of product development; philosophy of the management team; and a company's ability to enter into strategic partnerships with its vendors.

It is likely that biopharmaceutical companies will become increasingly reliant on CBMOs as long they can continue to manufacture quality products in a timely and cost-effective fashion.

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