Biopharmaceutical Production Outsourcing Matures

Greater Percentage of Biomanufacturers Contracting Out for Flexibility

by Eric S. Langer

Biopharmaceutical manufacturers are increasingly outsourcing some of their production. This trend is projected to continue at least through 2011. Based on data from the *Fourth Annual Survey of Biopharmaceutical Manufacturing Capacity,* by that year the percentage of manufacturers producing entirely in-house will have declined to 60% for mammalian cell culture and to 58% for microbial fermentation (**1**).

For comparison, 79% of manufacturers were producing in mammalian systems entirely in-house in 2003. Today the percentage of manufacturers producing entirely in-house has declined to 55.6% for mammalian cell culture and 60.5% for microbial fermentation.

Industry Maturity: Recent trends in outsourcing point to a shift toward a more rational strategic approach across all expression systems. As the industry matures, outsourcing is becoming an integral component to many biomanufacturers' production strategies. Production outsourcing is being used increasingly to maintain flexibility and reduce overhead. Mature biopharmaceutical companies prefer to maintain in-house capacity and use CMOs for "flex capacity," risk avoidance, and technical expertise. According to Geoff Hodge, vice president of process development and technology at Xcellerex, "It makes strategic sense for a biopharm to underbuild capacity because excess capacity can be purchased through CMOs. But excess capacity costs money in depreciation and maintenance."

Useful quantified data on the extent to which drug developers are outsourcing portions of their product development are revealing (**1**). The data show that flex capacity provides more than a temporary fix for capacity shortages. As the industry matures, production data can more accurately project the optimal in-house capacity that will ultimately be needed. Drug developers can then strategically plan for the amount of external capacity required over time. Further, this flex capacity can allow management to keep more resources focused on their core competencies such as drug development and R&D. Outsourcing thus allows for optimal use of existing resources.

With 284 biopharmaceutical products approved for marketing in the United States, 276 products approved in the European Union, and 6,083 products in the biopharmaceutical pipeline (**2**), effective strategic planning for biotherapeutic production is becoming increasingly important.

Biopharmaceutical Outsourcing Today: About 55.6% of all mammalian cell culture production is done "in-house," (Figure 1) whereas only 10.2% of companies outsourced substantial percentages (75–100%) of their production (**1**). This represents a slight drop from 2005 when 58% of companies were performing 100% of their production in-house. Microbial fermentation production is 60.5% "in-house," whereas 16.8% outsource a large percentage (75–100%) of production (**1**). A slight increase in the percentage of companies performing microbial fermentation in-house occurred between 2005 and 2006.

Contract manufacturers such as Lonza offer "flexible" capacity for product companies lacking the facilities to produce biotherapeutics in-house.
LONZA (WWW.LONZA.COM)

Outsourcing in 2011 Projections: Of companies producing in mammalian cell culture, 60% expect that they will outsource at least some of their production by 2011. This

Of companies producing in mammalian cell culture, 60% EXPECT that they will outsource at least some of their production by 2011. This represents a significant increase from the 44% of respondents who are CURRENTLY outsourcing some of their mammalian cell culture.

represents a significant increase from the 44.4% of respondents who are currently outsourcing some mammalian cell culture. For microbial fermentation, 58.2% plan to outsource some production by 2011, compared with 39.5% outsourcing today (**1**). These results reflect the continuing long-term trend toward greater outsourcing for manufacturing of biopharmaceutical products.

Trends Affecting Biopharmaceutical Outsourcing

Cost pressures, globalization, and improved technologies in the biopharmaceutical industry are driving the trend toward greater outsourcing. Growing cost pressures based on reimbursement policies, governmental healthcare policies, and other factors are requiring companies to focus on operational efficiencies, improve cost structures, and develop novel technologies to transform the industry with reduced production costs.

Regionally, qualified service providers and researchers are emerging in new markets. Vietnam, Cuba, Slovakia, and the Czech Republic are a few of the regions increasingly reaching higher levels of manufacturing competence. This global trend is likely to continue as national governments define their biopharmaceutical and healthcare policies. In particular, the opening of Asian and Eastern European markets will be a driver for local biotherapeutics. As industries outside traditional Western biopharmaceutical markets grow, outsourcing activities are likely to follow. A global presence will be important for service providers in emerging markets.

Transformational technologies are new technologies that may dramatically change the way biopharmaceutical manufacturing is done. Addressing the high cost of production and research is critical to expanding availability of biotherapeutics beyond wealthy markets.

"Five of the top 20 pharmaceuticals are biologics, and they address clinical niches and cost a magnitude of order more than other therapeutics," says Bob Adamson, PhD, vice president of global process development at Wyeth. "The average annual cost of a biologic is between $10,000 and $14,000. To address broader healthcare needs, overall cost reductions of up to 10-fold are required." Adamson feels that technology improvements will become a factor to any organization that does not have billions to invest in protein production facilities.

Critical Outsourcing Issues

Industry maturity in terms of client expectations of contract manufacturers is also evident. Important issues concerning outsourcing of biopharmaceutical manufacturing are included in Figure 4. Notably, the first issue, "Be able to stick to a schedule," is common to many manufacturing industries. As a managerial issue, it demonstrates implementation of techniques borrowed from other industries.

Other managerial factors also ranked highly, including "Demonstrate cost effectiveness of services" and "Be able to establish a good working relationship." These needs were indicated by 42% and 40% of respondents, respectively. The first technical factor considered "critical" (by 35.7%) was, "Have production platforms relevant to my product."

Changes Over Time

Contract Manufacturing in 2006 and 2005: In evaluating how outsourcing of biopharmaceutical manufacturing has changed over time, we found that concerns about being on schedule are rapidly increasing. In 2006, nearly 59% of respondents felt that this issue is critical. That is an increase of 12% over 2005, when 47% of respondents indicated the same concern.

Factors that declined in importance over the year include, "Being able to establish a good working relationship," which dropped from 53% to 40% of respondents. It also appears that CMOs are providing the technology platforms required. "Having a relevant production platform" declined significantly from 50% to 36%. This result reflects the increasingly competitive expression technology

Figure 1: Percent of organizations doing 100% of biopharmaceutical production in-house

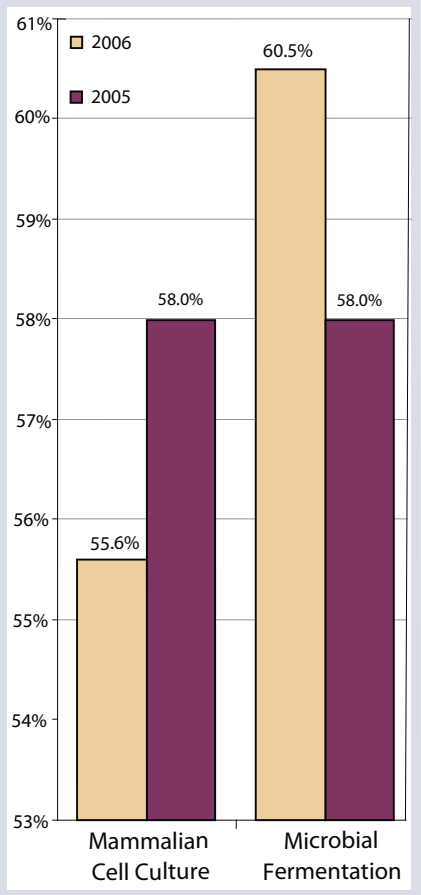


Figure 2: Percentage of biotherapeutic developers planning to outsource at least some production, 2006 compared with 2011, by system

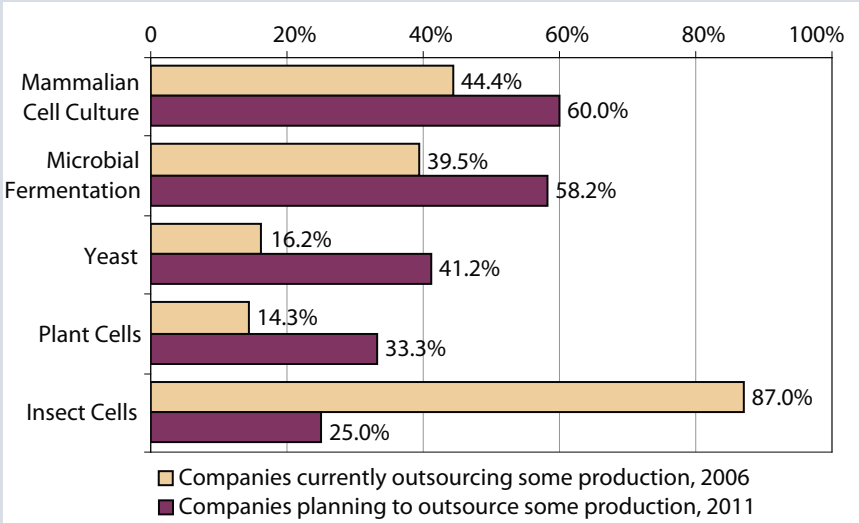
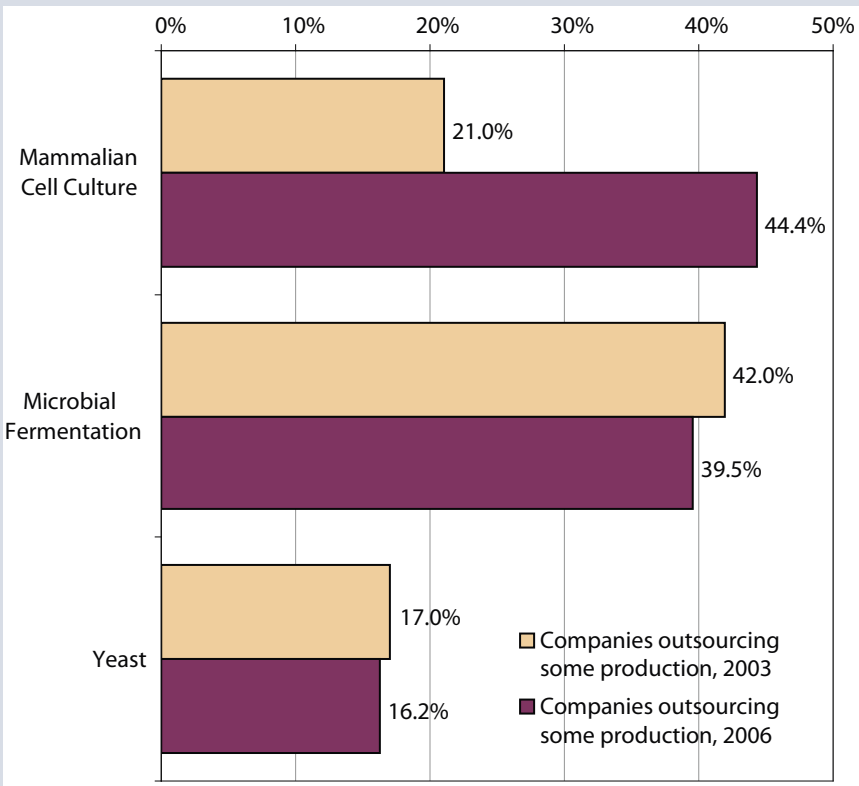


Figure 2: Comparison of outsourcing. In 2003, only 21% of respondents indicated they were outsourcing mammalian cell culture production, compared with 44.4% in 2006. Microbial production has remained relatively flat, with 42% outsourcing some production in 2003 and 39.5% outsourcing in 2006.



area as more expression systems demonstrate technical viability and gain industry acceptance.

Global Production Outsourcing

The global biopharmaceutical outsourcing industry is growing rapidly. The market for biopharmaceutical contract manufacturing is predicted to reach US$2.5 billion in 2006. Most of that will be conducted in the United States and Europe. This regional concentration is expected to shift toward Asia and Eastern Europe over time and as pricing pressures in major biotechnology markets increase. Intellectual property issues are being addressed, and production quality continues to improve. The biopharmaceutical industry spends US$15 billion on outsourcing manufacturing, formulation, and packaging of drugs. Contract manufacturing is expected to grow at an annual rate of 10–15%, with most analysts expecting the biopharmaceutical industry's volume to grow at a rate of 8–10%. Outsourcing by biopharmaceutical companies is expected to grow rapidly given that many of these smaller companies have limited process development or manufacturing capabilities.

Optimizing Production Through Outsourcing

Many larger biopharmaceutical companies recognize that despite the strategic advantages of bringing production capability in-house, over-investment in capacity is costly. In-house production capabilities maximize return on investment in facilities and capital only when they are operating at capacity. Because of the unpredictability of drug development pipelines, sizing a plant to maintain maximum capacity while avoiding idle capacity is very difficult. This is where the "flex capacity" available through contract manufacturers can help larger companies.

Smaller biopharmaceutical developers, typically find that biologics manufacturing and process development are not part of their existing core competencies. Thus, many CMOs find that they are often sent the most challenging projects for process development and production. At some CMOs this has built a unique capability and exposure to different kinds of systems and projects that most drug developers simply do not see.

A trade-off has to be made by mid-tier companies. They recognize the need to create business value by developing production competency and retaining institutional knowledge and control. On the other hand, they must balance that against the interests of their investors, who may be hesitant to accept the costs and potential delays associated with building such internal capabilities. GMP manufacturing and

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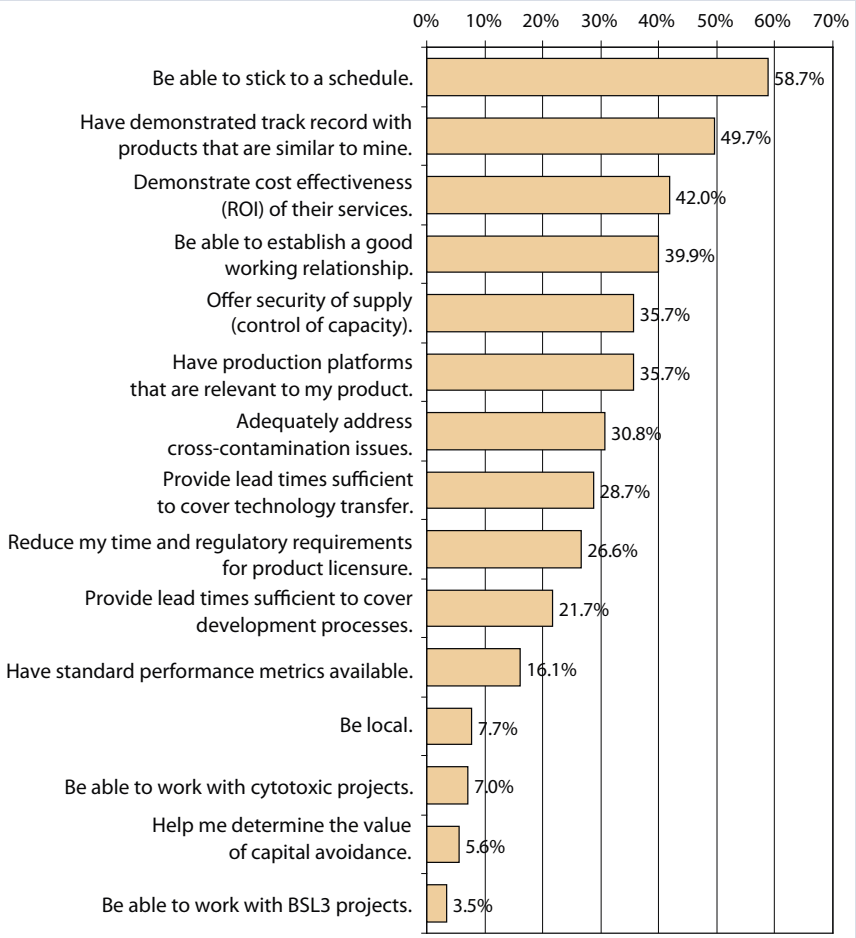
process development require unique skills. Many companies recognize that improving core value may be more valuable in drug discovery. These smaller companies often do not have the resources to invest in manufacturing or process development, and thus they rely on experienced CMOs to perform these tasks.

Outsourcing and virtual manufacturing are sometimes a part of the exit strategy at smaller companies. For them, once a product reaches phase 1 or phase 2 clinical trials, the rights to that product might be sold to a larger biologics developer or biopharmaceutical company. Outsourcing can make sense for smaller companies with thin product development pipelines. Companies that have multiple-product pipelines see greater value in developing an in-house capability. Small companies could see significant capital avoidance through outsourcing to an experienced CMO. Companies with intellectual property or other strategic considerations may also want to keep projects in-house.

Production outsourcing in biopharmaceuticals will continue to mature as it becomes an increasingly important element in the development strategies for most companies. A further indication of continuing maturation of this industry is the consistency of expectations of biopharmaceutical manufacturers toward performance of their CMOs. Such organizations are being asked to keep to schedule, communicate effectively, establish agreements regarding working relationships, ensure capacity when needed, provide appropriate technology access, demonstrate experience and track records, and demonstrate that companies will work together as partners to facilitate their mutual goals.

Figure 4: Critical issues when selecting a CMO. *"For outsourcing biopharmaceutical manufacturing to a contract manufacturing organization, a CMO must . . ."*



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1 BioPlan Associates, Inc. *4th Annual Survey of Biopharmaceutical Manufacturing Capacity.* BioPlan Associates: Rockville, MD, June 2006.

2 BioPlan Associates, Inc. *Biopharmaceutical Products in the US and European Markets, 5th Edition.* BioPlan Associates: Rockville, MD, August 2006.

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The annual study referred to here provides a benchmarking analysis of 337 biopharmaceutical manufacturers and contract manufacturing organizations from 29 countries. In addition to industry data on outsourcing, it presents key quantitative data and analysis regarding outsourcing activities, current capacity, use, bottlenecks, future expansions, disposables, and downstream issues. This year's study benchmarked previous year results and compared aggregated responses of CMOs to biopharmaceutical developers. It also compared regional responses.