Genetic Engineering News
January 2004

Big Shifts in Outsourcing of Biopharmaceutical Manufacturing—
Half of Manufacturers to Outsource Production by 2008

Eric S. Langer, MSB

By 2008, nearly half of all biopharmaceutical manufacturers may 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, and 47% will outsource at least some production.

These data, from the *Second Annual Survey of Biopharmaceutical Manufacturing Capacity,* by BioPlan Associates, Inc., are part of a major study on biopharmaceutical large-scale production for the American Society for Microbiology. The study quantitatively assesses industry capacity and evaluates potential industry bottlenecks that may develop over the next five years. The survey of 100 international biopharmaceutical manufacturers and contract manufacturing organizations provides information and insights on current capacity, utilization, projected future capacity needs, and reasons for production bottlenecks.

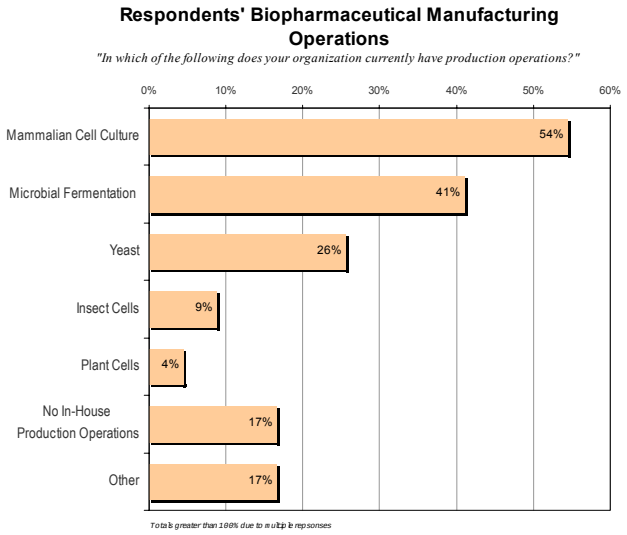
With as many as 125 new drugs reaching the market over the next five to seven years and more than 370 biotech therapeutics currently in clinical trials, the shift toward outsourcing certain projects may come as a boon to contract manufacturing organizations.

Outsourcing to Maximize Internal Capacity

Many larger biopharmaceutical companies are convinced that, despite the strategic advantages of bringing production capability in-house, over-investment in capacity can be highly risky. Those that invest in in-house production capabilities do so primarily to maximize their return on investment in facilities and capital by operating at near full capacity. However, because of the unpredictability of the drug development pipeline, sizing a plant to maintain maximum capacity, and avoid idle capacity is challenging. To reduce risks, some drug developers plan to divert some of their capacity to contract manufacturing services to handle their excess internal demand.

Another factor in the shift toward contract manufacturing is that smaller biopharmaceutical developers in particular are finding that biologics manufacturing and process development is not part of their core competency.

"One factor driving the upward trend in the number of projects being outsourced is the recognition that biologics process development and manufacturing is often not part of the core competency within smaller companies. Manufacturing and process development in a GMP environment requires complex sets of skills. A number of companies are increasingly recognizing that their time and resources may be better spent in drug discovery and lead optimization," believes Geoff Hodge, Vice President, Technology at Xcellerex, a process development and contract manufacturer.



Hodge, however, is hesitant to generalize, or categorize companies. In his experience, the determination to outsource is dependent upon multiple variables. Smaller companies often do not have the resources or capital to invest in process development and manufacturing facilities. But even among the larger pharmaceutical companies, there are some that are more amenable to outsourcing, while others are more inclined to keep as much as possible in-house.

"Ultimately, it may be a function of a company's personal experience with outsourcing, control issues, or intellectual property concerns," says Hodge.

What's Getting Outsourced, and What's Not?

Most biopharmaceutical developers would prefer to manufacture biopharmaceuticals in-house in order to build institutional knowledge and retain control over resources, time and production schedules, intellectual property, and quality issues. Such control issues are central to many of the common arguments for and against outsourcing.

On the other hand, smaller, less mature companies may do the opposite, and send their more challenging projects out-of-house. Smaller companies often do not have the internal expertise to tackle the more challenging problems. As an example, a smaller biotechnology company considering in-licensing a project with a poorly designed, commercially infeasible process, with a questionable regulatory perspective, and challenging scalability factors, may likely consider bringing in

outside expertise to manage the overall process.

Smaller companies without a staff experienced in working in a regulated GMP environment often find it challenging to acquire the needed expertise. Such companies may be able to produce quality materials and cell lines at the research level, but once they enter a GMP environment and are required to perform regulated process validation, viral clearance studies, and many other activities they have not had experience with, they may turn to outside expertise.

Moreover, the decision to outsource may be part of a smaller company's exit strategy. For these companies, once a product reaches Phase I or Phase II clinical trials, the product will be sold to a larger biologics developer or biopharmaceutical company. Once acquired, the products are brought in-house for process development or commercial manufacturing.

"Outsourcing makes sense for smaller companies, especially those with products in scale-up production, through Phase II, and companies with thin product development pipelines," says David Williams, Senior VP Operations at Chlorogen, an early-stage developer of plant-based therapeutics. "Companies that have multiple products in their pipeline staggered out chronologically are the ones that see the value of developing an in-house competency. Small companies typically don't have this luxury and could see significant capital avoidance and greater ROI through outsourcing to a more experienced CMO."

Williams goes on to say that mature companies that keep their challenging projects in-house also tend to keep their early-stage projects requiring further process development in-house. This is especially true when the company has invested in, and developed the competency for process development, or in-house manufacturing. Companies with intellectual property considerations, or other strategic issues may also be more likely to keep projects in-house.

R&D Investment Driving Capacity and Outsourcing

Strategically and narrowly focused investments and recent capacity expansions by large manufacturers will result in increased volumes for CMOs who will at the same time experience a marked drop in their market share of overall manufacturing over the next few years.

"The majority of the smaller companies' Phase I and Phase II projects will be outsourced. Their dynamic is driven by the investment cycle," according to Andrew Sinclair, Managing Director Biopharma Services, Chesham, UK. "The recent lack of investment in biological R&D projects has had a direct impact on small-scale contract manufacturing."

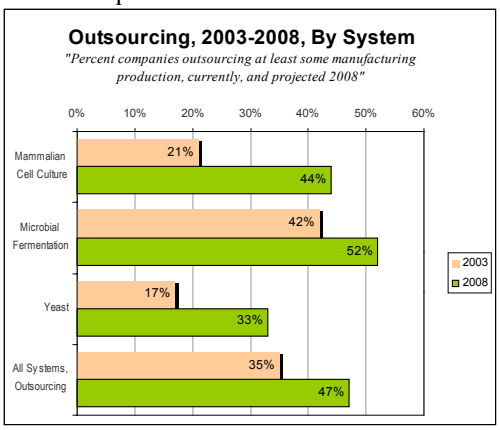
Sinclair has done modeling in this area, and believes that the level of investment, in mammalian cell culture especially, appears to have been declining as a result of the financial doldrums in biotech over the past 3-4 years. "As investments dried up, the small- and medium-scale biotech companies slowed their R&D programs, and focused on their drug candidates of greatest opportunity. As a result, the number of drug candidates going into clinical trials has not kept up with recent historical trends."

Suppliers of small-scale contract manufacturing have not seen the level of contract work that had been expected. This has led to excess capacity, which has been compounded by the fact that a number of CMOs had expanded their smaller scale capabilities.

The recent dip in capacity utilization has hit both the larger scale producers and the early clinical stage producers. At the larger scale, many of the larger pharmaceutical companies have made substantial investments in production capacity. Sinclair notes that the majority of capacity (70% or more) is held by the big companies such as Genentech, Biogen/IDEC, Wyeth and others. As a result, it is the larger biopharmaceutical companies that ultimately determine whether there will be a capacity shortage, at least at the large scale. Sinclair estimates that, based on overall volume and liter capacity, the CMO's share of the market will decline, even as their total liter capacity increases. This, because the CMO's relative proportion will continue to decline as larger biopharmaceutical manufacturers continue to build their in-house capacity.

Production Systems Play a Role Today

The companies contacted for the survey indicated that the percentage outsourcing manufacturing and production ranges from 42% for microbial fermentation, to 0% for insect cell production. Of respondents producing in mammalian cell culture, 79% performed all their production in-house, while 13% of these respondents outsourced the great majority (80%-100%) of their production. In comparison, of respondents producing in microbial fermentation, 58% performed all their production in-house, and 21% outsourced between 80-100% of their production. For all systems, 35% of respondents outsourced some production, and 8% outsourced between 80 – 100 % of their production.



The survey data show that a higher percentage of companies involved with microbial fermentation outsource projects, compared to mammalian cell culture. Manufacturing using microbial fermentation is seen by many as a more mature technology. As technologies become more standardized and commoditized, biopharmaceutical companies developing drugs in these systems are more likely to consider outsourcing. This is partly because there are fewer business advantages to keeping commoditized technologies in-house.

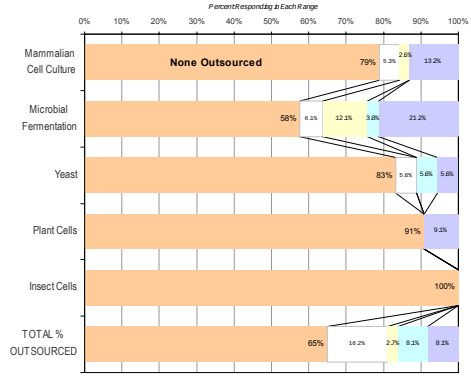
On the other hand, there remains a significant level of sophistication and "art" involved in mammalian cell culture manufacturing today. Because of this many manufacturers prefer to keep production in-house where they can oversee it. However, as with other production systems, this will change as processes become more streamlined and predictable. According to Gordon Pugh, VP Operations, at Alkermes, "As mammalian cell culture manufacturing matures over time, companies will become more comfortable with outsourcing. Many will decide that bearing the overhead costs associated with production will not outweigh the advantages of keeping production in-house."

Contract Manufacturing Shifts by 2008

According to survey respondents, more manufacturing projects will be outsourced over the next five years. Respondents were asked to project the percentage of their overall production they expected to outsource by 2008. Of respondents producing in mammalian cell culture, 44% indicated they would outsource at least some of their production in 2008. This represents an increase from 21% of companies currently outsourcing mammalian cell culture today. The percentage of companies outsourcing the majority (80-100%) of their production will not change significantly (8% today, vs 11% in 2008). This suggests that companies may be planning to outsource specific projects. For all production systems, the percentage of companies outsourcing at least some production will increase from 35% currently, to 47% in 2008.

Current Percent Outsourced Manufacturing, by Type

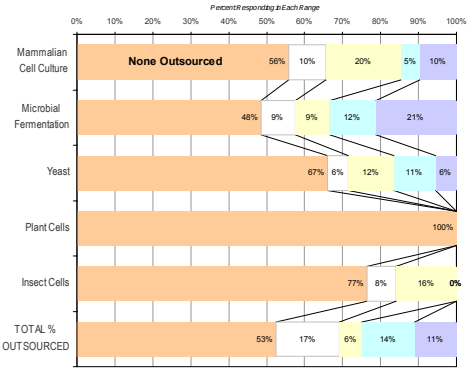
What % of your organization's production is currently outsourced for each of the following?



	TOTAL % OUTSOURCED	Insect Cells	Plant Cells	Yeast	Microbial Fermentation	Mammalian Cell Culture
80% - 100%	8.1%	0.0%	9.1%	5.6%	21.2%	13.2%
50% - 79%	8.1%	0.0%	0.0%	5.6%	3.8%	0.0%
10% - 49%	2.7%	0.0%	0.0%	0.0%	12.1%	2.6%
<10%	16.2%	0.0%	0.0%	5.6%	6.1%	5.3%
None Outsourced-bio	64.9%	100.0%	90.9%	83.3%	57.6%	78.9%

Respondents' Projected Outsourcing in 2008, by Type

"My organization probably be outsourcing around _____ % of our production in each of the following by 2008:"



	TOTAL % OUTSOURCED	Insect Cells	Plant Cells	Yeast	Microbial Fermentation	Mammalian Cell Culture
80% - 100%	11%	0%	0%	6%	21%	10%
50% - 79%	14%	0%	0%	11%	12%	5%
10% - 49%	6%	16%	0%	12%	9%	20%
<10%	17%	8%	0%	6%	9%	10%
None Outsourced	53%	77%	100%	67%	48%	56%

Factors to Take into Account

Even though the industry may be heading toward increased reliance on CMOs changes in productivity, and improvements in potency and dosing may reduce some of the need for additional capacity, even as total therapeutic production increases. Also, bioreactor yields and improvements in drug dosing and potency will have a direct impact on the need for capacity. "Purification yields are currently around 50-70%, so the best a manufacturer could ever achieve is a 2-fold yield improvement in terms of capacity utilization," says Xcellerex's Geoff Hodge,

However, Hodge indicates that improvements in cell culture yields can more than double or triple the output of a plant, and drug potency could impact capacity utilization by log orders. For example, conjugated antibodies are much more potent than naked antibodies. As such, a much smaller reactor to produce a commercial supply is required. Which means companies may be able to produce economically in-house, or may be able to do it more efficiently at a contract manufacturer. As production becomes more economical, determining factors as to whether companies produce in-house, or with a CMO, may be based as much on company philosophy, and breadth of development pipeline, as on economics

The impact on outsourcing from titer and yield improvement programs will be significant as we approach 2008. As titers improve, the absolute liter capacity requirements will decline. According to Biopharma Services Sinclair, "Companies are now quoting significant increases in titer and production, and some are achieving improvements from 1 gram/liter to 2-3 grams/liter and above. Capacity requirements are very sensitive to these improvements. This will, of course, have no impact on downstream purification costs, which will remain the same."

Outsourcing Strategies for Success

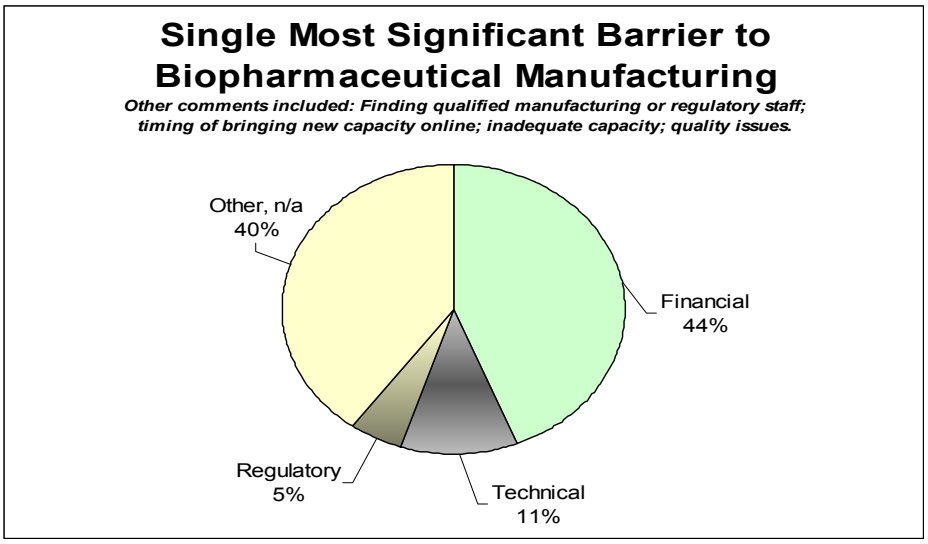
As previously indicated, CMOs will increase their total installed capacities over the next five years while loosing market share. as the larger biopharmaceutical manufacturers continue to build in-house capacity. Successful CMOs are likely to continue moving their focus away from straight capacity, and toward supporting moving therapeutics to the clinic faster, and less expensively.

"Every CMO will be working toward faster, more efficient ways to get products to the clinic, but the larger ones will be integrating technology processes and leveraging their capacity and infrastructure," predicts Alkermes' Gordon Pugh. "The smaller ones will be focused on developing efficient expression systems, disposable processes, and niche technologies. They may also consider partnering with larger organizations to resolve potential scale-up and capacity problems."

Of respondents producing in mammalian cell culture, 44% indicated they would outsource at least some of their production in 2008. *Second Annual Survey of Biopharmaceutical Manufacturing Capacity, November 2003, BioPlan Associates, Inc.*

Barriers to Production Success

The single most significant barrier to biopharmaceutical production is *financial* and not technical according to 44% of respondents. The number of manufacturers seeing financial factors as the primary barrier suggests that the costs associated with building, validating, and operating a biopharmaceutical manufacturing facility are a primary concern, especially as costs increase due to complexities associated with the regulatory environment, and requirements for sophisticated processes and controls.



Among survey respondent's common concerns with outsourcing was, predictably, the client's loss of control over operations. Issues regarding control of capacity were also critical factors. The degree of control a company can exert over a CMO's capacity may determine business strategy for companies seeking additional capacity. Companies increasingly asking for clear cost justifications and ROI calculations to rationalize and defend outsourcing versus the construction of new facilities. In addition, factors such as lead times need to be clearly established to ensure technology transfer and development processes are addressed prior to manufacture. Outsourcing remains an important element in the development of plans for clinical phase projects. According to survey respondents, areas of importance for effective outsourcing included:

- Security of supply, and capacity availability
- Relationship management—establishing mutually beneficial relationships
- Establishing and maintaining a schedule
- Effective handling of technology transfer issues
- Establishing standard performance metrics
- Handling cross contamination issues
- Dealing with general quality concerns
- Time and regulatory requirements for product licensure

Net Yield

The results of the *Second Annual Survey of Biopharmaceutical Manufacturing Capacity* clearly indicate that large and small biopharmaceutical manufacturers will increasingly consider CMOs as part of their production repertoire when it comes to handling parts or all of their manufacturing. However, the playing field has changed and those CMOs expecting to get the lion's share of outsourcing contracts may likely be those who have specialized and have proven records of consistently mastering challenging processes. On the other hand, as much as things have changed there is one element that will remain a critical factor in a biopharmaceutical manufacturer's decision to outsource and that is return on investment. It will be up to the CMO to help their clients understand their true ROI potential through improved yields, reduced capital expenditures, and the incremental savings realized by not having to develop niche expertise in-house. The CMOs that can deliver in these key areas are likely to be the leaders come 2008.

Eric S. Langer is President of BioPlan Associates, Inc. a life sciences business information company providing analysis of biotechnology markets since 1989. In addition to providing marketing analysis and management services, principals at BioPlan develop and teach biotechnology graduate courses, including Biotechnology Marketing, Services Marketing, Pricing, Advertising Strategy, and other programs at Johns Hopkins University, and elsewhere. elanger@bioplanassociates.com, 15200 Shady Grove Road, Suite 202, Rockville, MD 20850, 301-921-9074, www.bioplanassociates.com

Top Things Clients Expect of Their CMO:
According to biopharmaceutical developers, CMO's should:

- Establish clear agreements that cover working relationships, trade secrets, and regulatory issues associated with outsourced operations
- Communicate more regularly and effectively with clients
- Work more effectively with clients to optimize systems and improve productivity
- Have capacity available, technology access (proprietary technologies), fully validated facilities, and demonstrated regulatory expertise
- Demonstrate their experience and track record
- Avoid exaggerated claims regarding performance
- Manage 'non-harmonized' global regulatory issues effectively
- Provide specialized contract manufacturing capabilities, such as live/attenuated vaccines, BSL-3 facilities.

Top Things CMO's Expect As Part of Good Client Relationship:
According to CMO's, biopharmaceutical clients should:

- Understand and give credit for competency—CMO's typically take on difficult, problem processes
- Recognize that CMO's help the biopharmaceutical industry make optimal use of available internal and external capacity and capabilities
- Work as partners to facilitate resolution of IP and licenses/royalty issues to reduce the up-front problems associated with development
- Recognize CMO's efforts in ensuring a flexible mix of technical and regulatory competence
- Recognize the challenges of timing of bringing new, efficient capacity on-line and keeping it filled with client projects
- Understand that the delays experienced by drug discovery companies might lead to poor capacity utilization across the industry over the next 3-5 years.

Average biopharmaceutical industry capacity utilization for biopharmaceutical manufacturing in 2003 was estimated to be 79%.
Second Annual Survey of Biopharmaceutical Manufacturing Capacity, November 2003, BioPlan Associates, Inc.