

Manufacturing Capacity Put on Simmer

Yield Improvements and Market Factors on Front Burner

by Eric S. Langer

Biopharmaceutical developers and contract manufacturing organizations do not plan to add substantially to their existing manufacturing capacity. This news comes at a crucial time of unprecedented industry growth in which as many as 125 new drugs may reach the market during the next five to seven years and more than 370 biotech therapeutics are in clinical trials. And most manufacturers agree those numbers are likely to grow. How manufacturers plan to deal with the potential opportunities, bottlenecks, and production requirements was the subject of a recent survey of 100 international biopharmaceutical manufacturers and contract manufacturing organizations.

As part of a major study on biopharmaceutical large-scale production for the American Society for Microbiology, BioPlan Associates undertook its second annual survey of biopharmaceutical manufacturers to quantitatively assess industry capacity and evaluate potential industry bottlenecks that may develop over the next five years. The results provide information and insights on current capacity, capacity availability, projected future capacity needs, reasons for

production bottlenecks, and ideas for how those bottlenecks might be eliminated.

THE STATE OF THE INDUSTRY

Current capacity and capacity availability for recombinant proteins appears to be generally satisfactory for existing products. Over the next five years new products will move through the biopharmaceutical pipeline at an increasing rate. But manufacturers, in general, do not plan significant increases in physical capacity.

Why, with so many recombinant therapeutics in the pipeline, are both biopharmaceutical manufacturers and contract manufacturing organizations planning only modest growth of their total production capacity over the next five years?

According to Dr. Vince Narbut, vice president of operations at Biogen/IDEC Pharmaceuticals, "Biopharmaceutical capacity needs today are becoming more company-specific, rather than an industrywide issue." Therefore, as the industry matures, biopharmaceutical capacity bottlenecks are going to be based on organizational and market factors rather than operational ones. That means a major planning issue for companies is projecting market demand for specific classes of therapeutics in development.

Companies developing products with a large market need are more likely to face capacity issues. Accurately projecting the level of consumer demand, then, becomes important strategically and becomes a major risk factor to producers.

Narbut says, "Oncology-related antibodies are hot at the moment. So are rheumatoid arthritis products and those in immunology areas, anti-inflammatories, and immune modulators."

The ability to meet the demand for biopharmaceutical production capacity, whether through in-house manufacturing or outsourced contract manufacturing, carries long-term cost implications. Building production facilities, bringing capacity on-line, and establishing the necessary support services requires accurate market knowledge and lead-time. A facility can cost upwards of \$250 million and require three to five years to bring on-line. Errors in judgment can be costly. Companies tend to be cautious and do not commit to building a facility until the product outlook appears certain, thus reducing the financial risks. But the timing can be tricky.

"There will be a lot of successful biopharmaceutical products being approved in 2004 that are now in the later phase III development. These will eat up much of the existing capacity by 2005," says Dr. Hugo de Witt, manager, operations implementation at Lonza. "If one or two blockbuster drugs are approved and begin to take up manufacturing capacity, there will be very little capacity available. So capacity is dependent on the approval of these blockbuster therapeutics. For smaller projects, as products are approved, contract manufacturers will be contacted. For blockbuster drugs, the larger manufacturers will be building out for themselves. Companies like Biogen-IDEC and others that may have current excess or idle capacity will begin to move into the contract production business."

Conversely, for projects in the scale-up manufacturing stage, there

Figure 1: Planned production increase by 2008. "To what extent do you believe your organization is planning to increase production capacity over the next five years (2008) in each of the following?" Average industry percent capacity increase for each area.

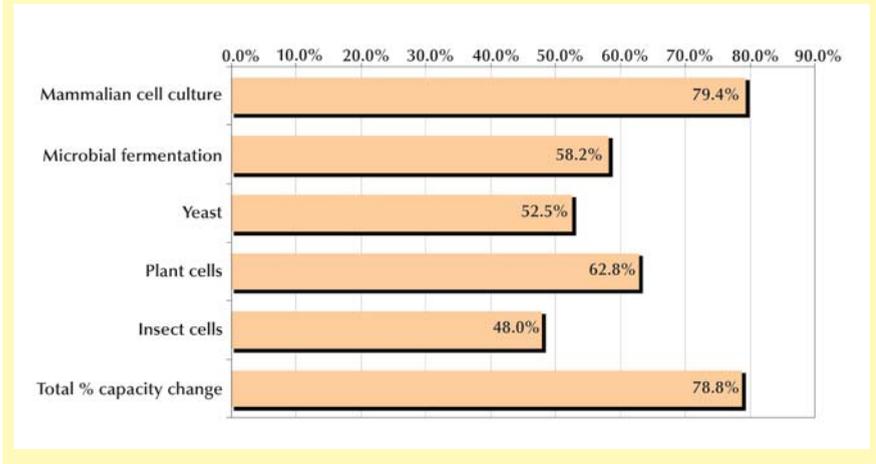
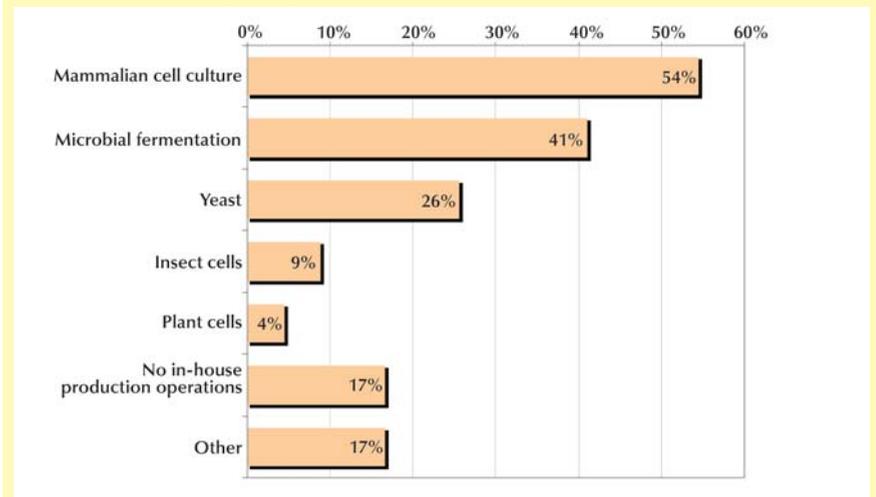


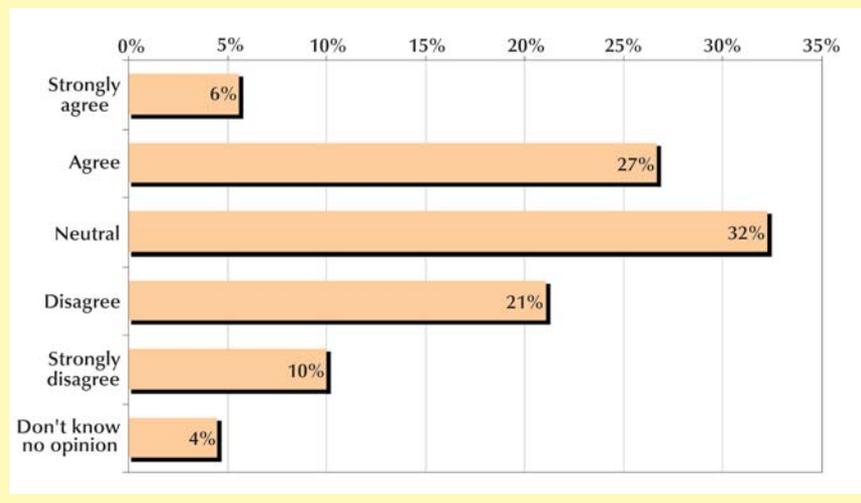
Figure 2: Respondents' biopharmaceutical manufacturing operations. "In which of the following does your organization currently have production operations?" Totals greater than 100% because of multiple responses.



may continue to be demand for additional small-scale capacity. Ray Watkins, vice president of operations at Vaccinex says, "For small-scale clinical supply, where margins are thinner, we need more capacity in terms of the number of projects, not necessarily in terms of the liter capacity available. The increasing number of biotherapeutic products in clinical trials will need to be made somewhere."

Watkins believes that many smaller manufacturers are building in-house capacity now. He says that companies able to manufacture in-house are creating unique value in their assets and increasing their share value. The value to these smaller companies is not only in the

Figure 3: Perception of capacity constraints on respondents' organizations. "I believe that our organization is experiencing significant capacity constraint issues today."



assets associated with biomanufacturing capacity, facilities, and equipment but also in the fact that they can demonstrate organizational competence and value in the company's intellectual property.

According to Biogen's Narbut, "It is no longer that difficult to bring a new facility on-line. The engineering firms, equipment manufacturers, the consultants, and the technology are all there. It's now more a matter of financing."

THE NUMBERS EXPLAINED

Biomanufacturers Project Modest Growth Through 2008: The BioPlan survey captured the expressed opinions of 100 decision-makers from biopharmaceutical manufacturers around the world. The results of the survey show the perceived reasons for projected bottlenecks and ideas for how those bottlenecks might be eliminated.

Participants indicated that plans for capacity increases are modest over the next five years. On average, respondents indicated that they would increase their internal capacity by 79% in mammalian cell culture by 2008. That corresponds to an annual capacity growth rate of 12.3%. For microbial fermentation, the five-year growth is projected to be 58%, a 9.6% annual growth rate (Figure 1).

Biopharmaceutical Manufacturing Operations: More than half of the

Table 1: Capacity use by production system

Production system	% capacity used
Mammalian	76.4%
Microbial	71.0%
Insect	70.4%
Yeast	63.8%
Plant	59.0%

survey respondents (54%) had production operations involving mammalian cell culture. Forty-one percent had production operations involving microbial fermentation. Seventeen percent had no in-house production operations (Figure 2).

Capacity Constraints: A relatively small number of respondents, six percent, felt strongly that their organizations are experiencing significant capacity constraints today. In contrast, 63% were either neutral or disagreed that they were experiencing capacity constraints today (Figure 3).

Contract Manufacturers Have Plenty of Capacity Through 2008: According to the survey, only five percent of contract manufacturers felt strongly that they will experience significant capacity constraints by 2008. Biopharmaceutical producers were slightly less optimistic: 15% felt they would experience significant capacity constraints by 2008.

Avoiding Capacity Constraints: Despite the relative optimism regarding capacity availability, respondents indicated areas that must be addressed if the industry is to avoid capacity constraints: optimizing cell culture systems (indicated by 60% of respondents) and improving downstream purification technologies (indicated by 57% of respondents). In addition, more than half of all manufacturers surveyed believed that more training and education in production areas is needed to ensure adequate production capacity. When asked about the factors that may be responsible for creating capacity constraints by 2008, only 26% felt that physical capacity of fermentation equipment would be a factor.

Show Me the Money: The single

most significant barrier to biopharmaceutical production is not technical but financial, according to 44% of respondents. In fact, only 11% of respondents felt that technical factors were affecting their production capabilities. The number of manufacturers who see financial factors as the primary barrier to production suggests that the costs associated with building, validating, and operating a biopharmaceutical manufacturing facility are a primary concern. That concern is likely to grow as costs increase because of complexities in the regulatory environment and requirements for sophisticated processes and controls.

CAPACITY USE AND AVAILABILITY

Current capacity availability in the industry appears to be reasonably healthy compared with other industries. Respondents were asked to indicate their current production capacity for various systems. Capacity use among producers using mammalian cell culture averaged 76.4%. For microbial systems, capacity use was somewhat lower: 71%. Producers using plant systems averaged 59% of capacity (Table 1). Those figures are consistent with the US industrial capacity use average of 81.3% for the period 1972–2002 (1).

Respondents' Perception of Overall

Industry Capacity: In addition to providing input about their own capacity, respondents were asked to estimate, based on their first-hand knowledge, the current industrywide, worldwide level of production in biopharmaceutical manufacturing. The perceived average biopharmaceutical industry capacity use is 79%.

OUTSOURCING CHALLENGING, SOPHISTICATED PROJECTS

Most drug developers today prefer to manufacture their biopharmaceuticals in-house. Retaining the institutional knowledge gained from building manufacturing capacity is one reason. Other factors in determining whether outsourcing makes sense include previous experience in

manufacturing similar products, the company's overall corporate philosophy regarding outsourcing, and willingness to relinquish control and QA responsibilities to a contract manufacturer. Even start-ups tend to strongly consider in-house production, especially multiple-product companies with strong pipelines. Said Lonza's de Witt, "Outsourcing makes a great deal of sense for start-ups and for companies with products in scale-up production, through phase II."

Small and early-stage producers may have a somewhat different perspective on the value of in-house production compared with large, established pharmaceutical concerns. Watkins, for example, believes that most therapeutic companies should at least strongly consider in-house production, "Outsourcing makes sense if you are a one-product company or if you have a very thin product development pipeline. For companies with three or four products in their pipelines, all two or three years apart, it makes more sense to bring that manufacturing competence in-house. Also, retaining the value in capital and organizational knowledge is more attractive to investors. They will be more likely to invest in a company with a facility than in one with a CMO contract."

Interestingly, survey respondents report that the number of manufacturing projects to be outsourced will increase over the next five years. For example, 21% of mammalian cell culture production is outsourced today. By 2008 respondents expect that outsourcing of mammalian cell cultures will more than double to 44% of all production in that segment.

Nonetheless, overall capacity for outsourced production will grow only modestly. Indeed, the percentage of respondents outsourcing the great majority of their production (80–100%) will decrease from 13.2% today to 10% in 2008.

On the other hand, the percentage of companies outsourcing some of their

production (1–49%) will grow from 8% today to 30% in 2008. That suggests that contract manufacturing organizations are going to be seeing more of the tough, technically challenging projects. **Because companies will keep the easy projects in house? Please clarify.**

That will give CMOs with effective teams able to tackle technically difficult projects a competitive advantage. The expertise for basic biopharmaceutical in-house production is becoming more readily available, and more technically challenging projects are expected in the future. CMOs able to meet the needs of the changing production environment may be in greater demand. Those specializing in more challenging projects and smaller niches may also be at an advantage. Some of those areas will likely involve complex purification processes or yield variables. Others may include gene therapy, cell therapy, and other difficult projects.

WHAT TO EXPECT

The industry will experience several dynamics working simultaneously over the next several years. For instance, partnering arrangements between developers and manufacturers are more likely, and increasingly creative ways to fund facility development may arise. If financing remains tight and companies continue to outsource fewer large projects, consolidation among CMOs will increase. Some of that consolidation may happen as larger therapeutic developers with manufacturing capabilities create codevelopment arrangements with smaller developers with compatible products. Large producers such as Biogen-IDEC are able to attract more companies to become development partners or participate in similar licensing arrangements **than smaller producers. ???**

Biopharmaceutical companies and contract manufacturers recognize that as new products barrel through the development pipeline, it will take more than physical capacity to meet production demands. If

biotherapeutic manufacturing capacity is to keep pace with the products coming out of the pipeline over the next five years, financing for manufacturing scale-up and production will become a high priority. Companies will need to become increasingly creative and strategic in their partnering to optimize their overall production given their potential financial constraints.

Additional capabilities in yield, purification, and performance will be required to produce new recombinant products. In the past, capacity was increased by adding capital and fermentation equipment. During the next five to ten years, increased production will more likely be the result of technical improvements, optimizing existing capacity, and partnering with companies that have idle capacity. Biopharmaceutical manufacturing is becoming more sophisticated. Improving the yields and technical skills of biomanufacturers appears to be the focus today and raw, physical capacity appears to be moving to the back seat.

REFERENCE

1 *Industrial Production and Capacity Utilization*. Federal Reserve Statistical Release G.17; 14 November 2003; www.federalreserve.gov/releases/G17/Current/default.htm. 

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