

Managing Biopharmaceutical Manufacturing Capacity in 2007

Changes in Demand and Capacity Projected Through 2011

by Eric S. Langer

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Biopharmaceutical manufacturers are doing a better job planning for capacity than in years past, and their methods used for planning are maturing. By necessity, companies are implementing more effective capacity management techniques, and planning for future requirements is being considered at more strategic levels within most organizations. The results have been a smoothing of capacity use shifts and an improved ability to forecast capacity and outsourcing needs.

These trends are shown in the results of the recently released *4th Annual Report and Survey of Biopharmaceutical Manufacturing and Capacity and Production* (BioPlan Associates, Inc.) (1). Capacity utilization (a measure of how effectively manufacturers and industries are using their fixed assets) for all biopharmaceutical manufacturing systems declined or remained level in 2006. The report included responses from 337 biomanufacturers and CMOs from 29 countries. It encompassed an additional 157 direct suppliers of materials, services, and equipment to this industry. It compared biotherapeutic developers with CMOs, and US with European respondents, benchmarking responses from 2003 through 2006. The survey includes analysis from eight industry experts and covers issues such as current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, and hiring issues. This year, about 49% of respondents were



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from the United States, and 40% were from Europe. Other countries represented included Canada, Sweden, Switzerland, Denmark, Belgium, Netherlands, India, Austria, France, Ireland, Italy, Portugal, Finland, Australia, Spain, Korea, Argentina, Puerto Rico, Vietnam, Taiwan, Slovakia, Russia, New Zealand, Malaysia, Czech Republic, and Cuba.

Employment and training: The leveling-off of fluctuations in manufacturing capacity suggests that companies are using their existing capacity more efficiently and are planning more effectively for increases and shifts in their demands for additional capacity.

Capacity utilization can also be an indicator of demand shifts and how

effectively manufacturers adapt to unanticipated increases and decreases. In the biopharmaceutical industry, companies must project years into the future to build facilities. Because many pipeline products may ultimately never be approved, it is challenging to forecast future capacity needs. Capacity utilization trends help in planning for production capacity expansions and outsourcing. In addition, suppliers to the industry, training and education organizations, and job seekers have an interest in utilization rates because sales trends, job availability, and costs of production are affected by such shifts.

According to Bob Adamson, vice president of global process and product development at Wyeth Biopharma,

“Manufacturers are planning their capacity better today than they had in the past. They are using multiple methods to avoid capacity crunches, including improving their yield and titer so they can make better use of existing capacity. They are also integrating their overall manufacturing planning and decision-making with all business, production and regulatory areas. These approaches are smoothing out fluctuations in demand, which can optimize production processes and reduce the need for costly excess capacity during periods of unanticipated high production requirements.”

CURRENT CAPACITY UTILIZATION: BY THE NUMBERS

In 2006, biopharmaceutical manufacturers producing in mammalian cell culture had more available capacity than in previous years. Capacity utilization was running at 63.9%, compared with 68.8% in 2005 and 76.4% in 2003. Yeast and insect systems showed similar declines. For microbial fermentation, capacity utilization climbed slightly from 60.5% in 2005 to 61.9% in 2006 (compared with 71% in 2003).

By comparison, the overall (cross-industry) US national percentage of capacity rate for September 2006 was 81.9% (2). Historically, the average use rate between 1972 and 2005 for all industries was 81.0%. In 2001–2002, the US industry utilization rate hit a low of 73.9%. A year before, the September 2005 rate was 79.1%.

The 2006 overall capacity utilization for mammalian systems continued to decline despite continued strong sales growth in the biopharmaceutical industry. This may be the result of process improvements at existing facilities, including upstream yields and performance. More capacity may be available at biopharmaceutical companies. In mammalian cell culture and microbial fermentation, both CMOs and biopharmaceutical companies report capacity utilization of 60–65%. This relatively low level of use will help prevent industry-wide shortages. Available capacity is not evenly

Figure 1: Respondents' facility locations

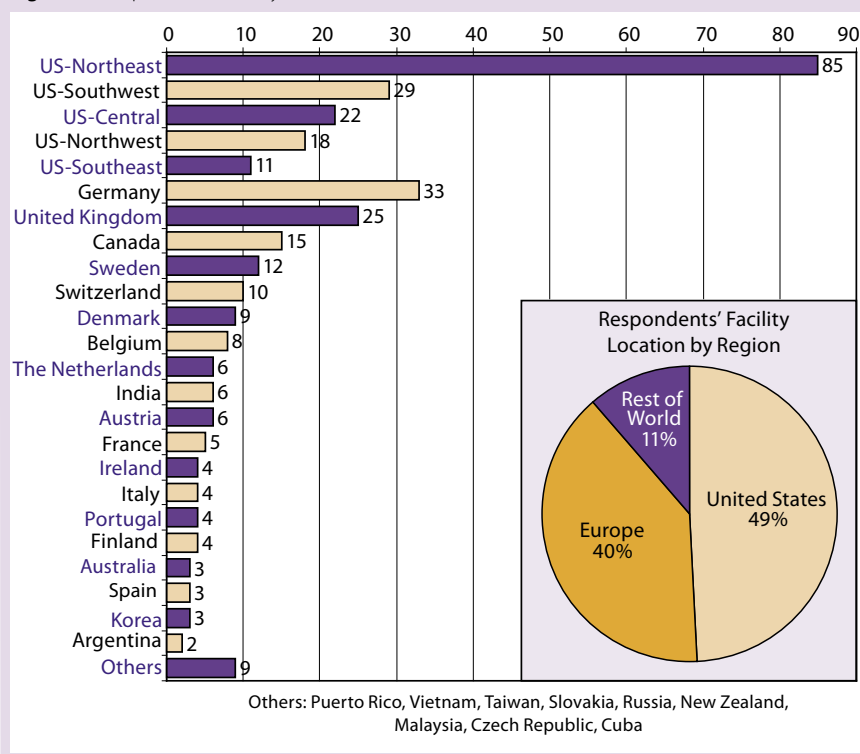
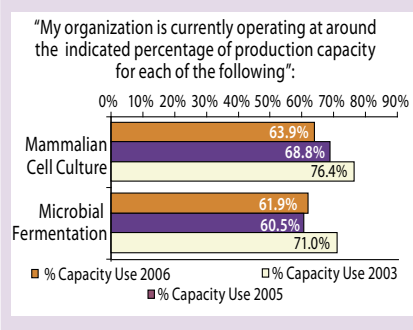


Figure 2: Average production as percentage of operating capacity, by system, 2006, 2005, and 2003

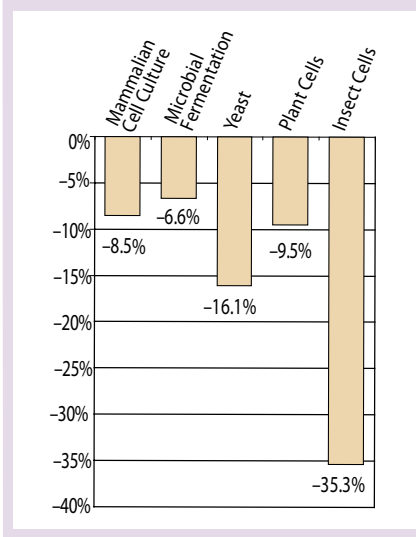


distributed, however, and some organizations continue to experience capacity problems as market demands for their products increase.

The higher level of capacity use for mammalian and microbial production systems indicates that their production planners are doing a better job relative to those of other systems (e.g., yeast and insect). Larger production scales associated with microbial and mammalian systems are needed to recoup the high investments associated with their facilities.

Biomanufacturing capacity utilization in 2006 remains significantly below cross-industry standards and far off of capacity utilization rates of 2003. The additional manufacturing capacity today

Figure 3: Chart showing the impact of design decisions on potential savings and costs as a function of the time of the decision

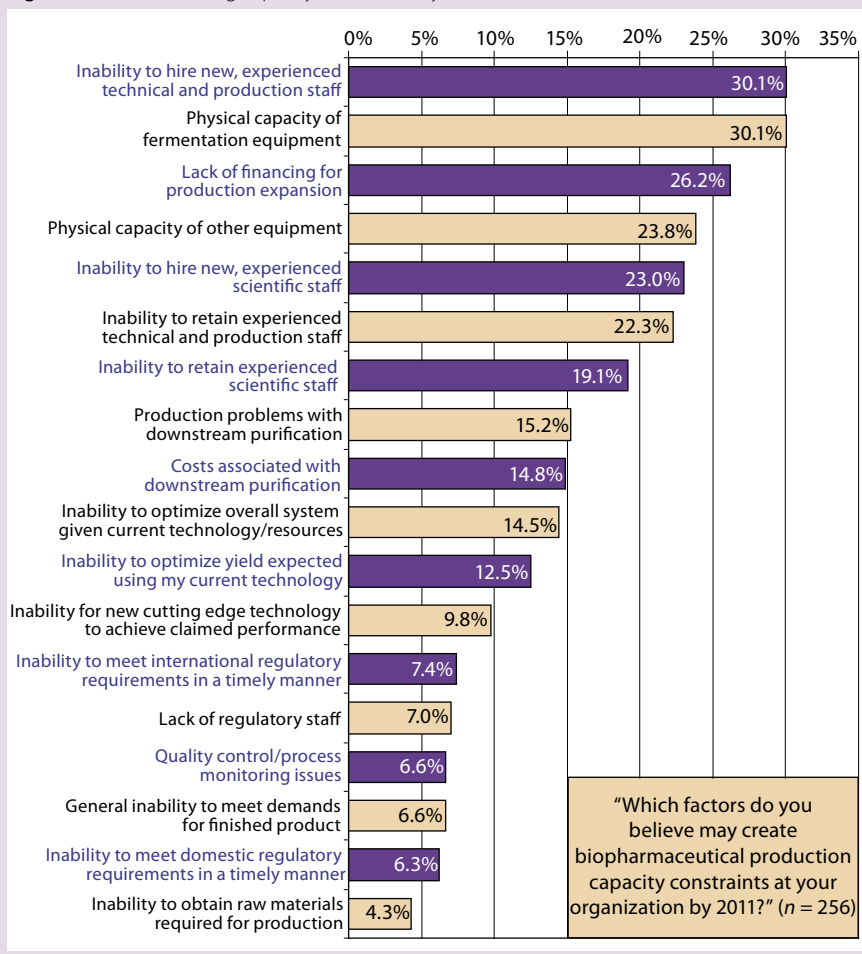


means that idle capacity may be more quickly available to those seeking it. For CMOs, utilization rates for most biopharmaceutical manufacturing systems have stopped their decline, and there remains more capacity today than in 2003. In that year, capacity use exceeded total US industry use by as much as 2%.

PLANNING FOR CAPACITY

The risks of ad hoc manufacturing planning have proven unacceptable to

Figure 4: Factors creating capacity constraints by 2011



managers and investors. Advancements in tools used to plan production and measure performance have led to more consistent planning processes. Evidence of this was suggested in the results of this year’s report.

Biomanufacturers are improving their ability to manage capacity through different means, including more effective analytical projections, partnering and outsourcing with CMOs, using advanced technologies including improvements in yield and downstream performance, using modeling and other tools to better forecast production, and incorporating more sophisticated long-term supply-chain management. These areas address strategic requirements for cost reduction and capacity management.

“Biopharmaceutical manufacturers are using multiple approaches to manage capacity projections, including ever increasing product titers, downstream yield improvements, and creative relationships with CMOs,”

according to Brandon Price, president of Falconridge Associates in Cary, NC. “Product titers averaged less than 1 g/L five years ago. They are often in the 2–3 g/L range now — equivalent to a 3–5 fold increase in capacity without the need for any new facilities.”

Wyeth’s Adamson echoes this approach. “Wyeth’s contribution is to focus on production efficiency. We are creating a ‘Super CHO’ cell line for example, that has transformational capabilities with respect to production improvements. These lines are achieving dramatic improvements in production in CHO systems.”

The use of contract manufacturing is one way biopharmaceutical companies are managing their production planning. According to Tom Ransohoff, senior consultant at BioProcess Technology Consultants, “Two of the primary ways firms are strategically addressing capacity management are by increasing the use of contract manufacturing

organizations to add to their internal capacity and by strengthening their capabilities for supply chain management. One concrete example is the recently announced deal between Genentech and Lonza related to the Porrino, Spain, and Singapore sites. This example demonstrates Genentech’s increasing use of CMOs to provide them with improved flexibility to access future capacity as needed.”

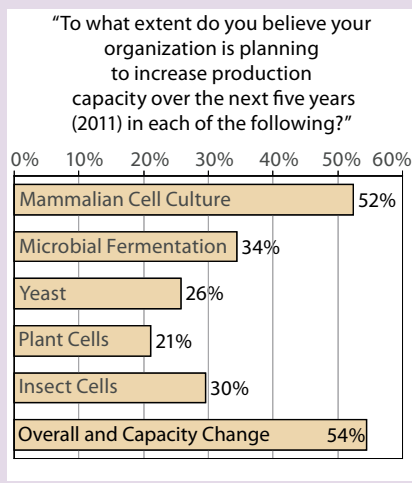
Planning and modeling software tools used to forecast demand are available in many forms. From off-the-shelf software such as Microsoft Project to highly complex, in-house-build programs, more probability assessment tools are becoming available. “It’s really a risk management issue,” says Parish Galliher, CEO of Xcellerex, a CMO in Marlborough, MA. “There is no single software tool used within this industry because most organizations need to tailor their planning tools to their own facility and pipeline. ‘Demand uncertainty’ is the key factor, and it is incredibly variable for companies with big pipelines. This results in hugely variable solutions. As a CMO we have similar variability in planning for drug demand.”

CHANGES IN CAPACITY UTILIZATION

Capacity utilization continues to decline for mammalian cell culture systems, but it appears to have reached a plateau for microbial and other systems. Mammalian cell culture capacity dropped 14.5 percentage points from 76.4% in 2003 to 63.9% in 2006 (a compound average rate of decline of –8.5%). Microbial fermentation capacity declined from 71.0% in 2003 to 61.9% in 2006 (CAGR –6.6%). Insect cell capacity use declined the most dramatically, from 70.4% in 2003 to 29.4% in 2006 (an average decrease of over 35%).

CMOs working with mammalian cell systems have slightly more available capacity compared with biotherapeutic developers (61.8% use for CMOs, compared with 64.3% use for the biopharmaceutical manufacturers). CMOs working with

Figure 5: Planned production increase by 2011; average industry percent capacity increase for each system



microbial systems have slightly less capacity (63.6% use for CMOs compared with 61.5% for biopharmaceutical manufacturers).

By comparison, in 2005, biotherapeutic developers were indicating a significantly higher percentage of capacity use for both mammalian cell culture and microbial fermentation than were CMOs (82.8% for mammalian and 76.8% for microbial systems in 2005). That suggests that biotherapeutic developers may now be experiencing a lightening of their internal capacity crunch, even as demand for biotherapeutics continues to grow. It may be the result of significant additional manufacturing capacity coming on-line in 2005 and improvements in productivity, yield, and operational efficiencies.

CURRENT CAPACITY CONSTRAINTS

In the survey, 35.6% of respondents “Agreed” or “Strongly Agreed” that their organizations were experiencing significant capacity constraint issues today.

In 2001, the capacity crunch resulted in building new capacity and improving production. Building has declined since then, even as the industry has continued to grow. Recent expansions have created a comfortable level of excess capacity. However, that may change over the next five years, and CMOs are planning for greater capacity expansion than are biomanufacturers. This is consistent

with CMOs’ separate concerns about future capacity shortages, as is outlined in the report.

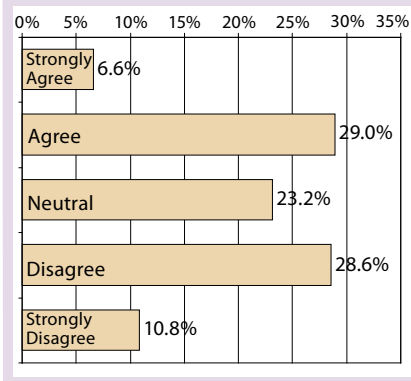
Both CMOs and biotherapeutic developers are experiencing capacity constraints. However, more CMOs are experiencing “very significant” constraints — at nearly double the rate (11.9% for CMOs compared with 5.6% for developers). This is the reverse of what was occurring in 2005, when 17.6% of biotherapeutic developers experienced serious capacity constraints compared with 6.5% of CMOs. Again, this may reflect an ongoing trend for larger biopharmaceutical companies to rely more on CMO capacity and also for early stage biotherapeutic developers to avoid establishing manufacturing infrastructure.

CAPACITY CONSTRAINTS BY 2011: ON THE RISE

We asked respondents from biopharmaceutical manufacturing and CMO facilities whether they expect some capacity constraints over the next five years. Of all respondents, 51% “agreed” or “strongly agreed” that they will experience capacity constraints. This compares with 42.3% in 2005 and 44.0% in 2003. The number of respondents fearing capacity constraints in five years was up by

As with last year’s results, inability to hire new, experienced technical and production STAFF topped the list, with more than 30% of respondents indicating this will be a major factor in managing production capacity.

Figure 6: Perceived capacity constraints, 2006 (“I believe that our organization is experiencing significant production capacity constraint issues today”)



>8% from 2005.

In a comparison of CMOs with biotherapeutic developers, by 2011 a greater percentage of CMOs believe their organizations will experience significant capacity constraints: 57.1% of CMOs expect capacity constraints in five years compared with 46.6% of biotherapeutic developers. This suggests that capacity constraints are more likely to occur among CMOs. Again, perceptions may reflect growing expectations of use of CMO capacity.

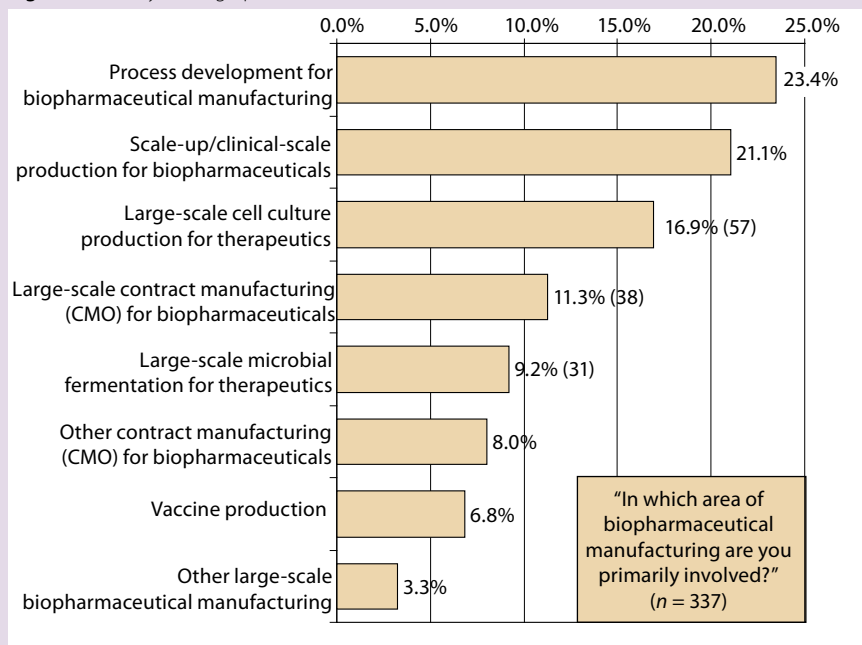
CAUSES OF FUTURE CAPACITY CONSTRAINTS

The major factors affecting organizations’ production capacity over the next five years may include problems in hiring production staff and fermentation equipment capacity. As with last year’s results, “inability to hire new, experienced technical and production staff” topped the list, with more than 30% of respondents indicating this will be a major factor in managing production capacity. Problems of capacity associated with downstream purification in 2006 were up significantly from 2005. The increases in bioreactor productivity are generally expected to increase constraints from downstream processing steps and are likely to account for this increase.

CMOs AND BIOTHERAPEUTIC DEVELOPERS

CMOs tend to be more concerned about manufacturing process performance and costs, whereas the

Figure 7: Survey demographics



Organizations this year are beginning to watch for signs of near-term capacity constraints, and they are applying greater **RESOURCES** to their forecast planning and modeling.

issues of early development, training, and regulatory issues are of more concern to biopharmaceutical companies. CMOs may be focused more on process improvements because they are expected to provide greater manufacturing efficiency and plant use to keep costs down. This allows CMOs to remain competitive and profitable (Figure 4).

Respondents were asked to identify areas that must be addressed in the future if the industry is to prevent significant capacity constraints. The top area in 2006 was "optimize systems to improve downstream purification performance." This was indicated by

nearly half (49.8%) of respondents in 2006 and by 44% in 2005.

PLANNED FUTURE CAPACITY EXPANSIONS

On average, respondents indicated that they plan to increase overall mammalian cell culture production capacity by 52% by 2011. For microbial fermentation, respondents plan to increase production by an average of 34%. This represents a small drop in expansion projections for both systems compared with 2005 data.

We compared expansion plans of CMOs and biotherapeutics developers. In 2006, CMOs in both mammalian cell culture and microbial fermentation expect larger increases in production capacity over the next five years, compared with biotherapeutic developers. CMOs using mammalian systems believe their facility will increase production capacity by an average of 63%, whereas biotherapeutic developers expect an increase in production capacity averaging 50%. With microbial fermentation, CMOs projected an increase in production capacity of 43%, compared with 32% for biotherapeutic developers through 2011. Last year, CMOs were projecting only a 47% increase in mammalian system capacity over five years (through 2010). Biotherapeutic developers last year were projecting a 61% "five-year"

increase for mammalian cell culture capacity (by 2010).

BETTER, MORE EFFECTIVE FORECASTING MODELS

Both biotherapeutic developers and CMOs recognize the need for improvements in production, planning, and forecasting. With today's pipeline of new products in development, there will be no shortage of need for more accurate models and production improvements. As in other, more mature manufacturing industries, as supporting technologies improve (e.g., upstream yield and downstream efficiencies), suppliers and manufacturers focus on developing effective forecasting models.

Despite a reduction in production capacity constraints in recent years, biotherapeutic developers and CMOs are benchmarking production and capacity performance against industry norms. Organizations this year are beginning to watch for signs of near-term capacity constraints, and they are applying greater resources to their forecast planning and modeling. The report suggests that reliance on CMOs is expected to grow as their capacity provides support for biotherapeutic developers by reducing total risks associated with building additional capacity for regulated products that may not reach the market. The cost of capital facilities will continue to drive new process innovations that decrease total requirements for fixed capacity.

REFERENCE

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

2 US Federal Reserve Statistical Release: *Industrial Production and Capacity Utilization*. 17 October 2006, www.federalreserve.gov/releases/G17/20061017. ☉

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