

# Capacity Bottleneck Squeezed By Downstream Processes

by Eric Langer and Joel Ranck

Capacity bottlenecks for biopharmaceutical manufacturers are moving toward downstream purification areas, and producers are increasingly recognizing the need for a broader strategic perspective when investing in production improvements. Companies are finding that addressing production problems ad hoc and solving capacity problems individually can simply push their bottlenecks along to other links in the production chain. Biopharmaceutical manufacturers have been working to increase capacity, address upstream production problems, and improve yield for many years. Successes have been evident: Capacity use is down, and production is generally at a healthy level according to the *3rd Annual Survey of Biopharmaceutical Manufacturing Capacity and Production* (1). In the survey, biomanufacturers and contract manufacturers (CMOs) projected a 48% general expansion over the next five years in mammalian and microbial production. Some of that is likely to be constrained by bottlenecks in separation and purification.

Upstream production efficiencies and yield improvements have, in effect, created more capacity. Methods of filtering and purifying product streams are now the focus of attention for many manufacturers and suppliers. Changes on the downstream side in material recovery and purification are

growing more urgent. However, such changes may not be as fast-moving or revolutionary as the industry would like.

“You don’t have the same opportunity for dramatic changes downstream,” said Scott M. Wheelwright, PhD, president of Strategic Manufacturing Worldwide. “We are likely to only see incremental changes. On the downstream side the challenge is how to handle that amount of protein. To date, there have not been a lot of advances. People still rely on chromatography, but there hasn’t been much capacity increase. We’re still limited in our ability to process protein.”

Constraints may be particularly acute in monoclonal antibody (MAb) manufacturing, where product titers continue to increase. “The main bottleneck is how the protein A MAb purification process can be adapted to cope with the high yields of product without resorting to unfeasibly large columns with large inventories of protein A,” says John Liddell, PhD, head of separation science for Avevia Biotechnology. Liddell explains that for non-MAb protein purification, challenges arise in the lack of any general platform purification approach and the necessity to approach development of purification schemes case by case.

Although the third annual survey pointed to purification as a critical issue, it found that among CMO



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respondents, another major factor expected to affect capacity is lack of financing for production expansion (indicated by 52% of CMO respondents). Key areas to address in preventing capacity constraints continue to be optimization of cell culture systems to increase upstream performance (noted by 54.2% of respondents), as well as improving downstream purification performance (43.8%).

As manufacturing scales increase, so will the problems associated with downstream purification. Of respondents using mammalian cell culture, about 11% indicated that their production capacity was greater than 75,000 L. By comparison, in 2002–2003, only three companies had more than 50,000 L of mammalian cell culture capacity.

According to the survey, the industry's current five-year projection for production capacity is now significantly lower than the projections were in 2003. In that year, the survey's five-year projection suggested that capacity would expand 69% by 2008. Overall capacity use by biopharmaceutical developers and contract manufacturers has declined since then. In 2005, use of existing capacity decreased 8% compared with 2003. The decrease is a result of continued industry expansion and improvements in yield at existing facilities. The survey noted that despite an overall decrease, some segments of the industry—including larger biopharmaceutical developers—continue to experience capacity constraints.

A significant factor reducing the demand on capacity is that biopharmaceutical developers are seeing results from efficiency-based research and development aimed at producing greater yields. This has two effects: It can open existing capacity for organizations such as CMOs, and it can reduce the additional capacity requirements for producers who then can expand into the extra capacity generated by those efficiencies.

Capacity use for all biomanufacturers using mammalian cell culture systems is currently 68.8%. Use for microbial fermentation is 60.5%. As a comparison, a statistical release from the US Federal Reserve showed that capacity use for all US industries in July 2005 was 79.7% (2).

### **A SYSTEMS APPROACH TO MANUFACTURING**

A more systematic, strategic approach to investments in manufacturing improvements may be required to assure smooth implementation of production improvements, especially in regulated manufacturing. Recent process advances have been stymied to a large extent by legacy systems whose efficiencies cannot easily be improved for regulatory reasons.

Some experts agree with Liddell's assertion that a systems approach to manufacturing design and implementation is the way to overcome bottlenecks. Currently, novel technologies and advances tend to move the bottleneck from one area to another. Proponents of a systems approach advocate that operations and facilities management will soon take on a more important, strategic approach to biomanufacturing. They say that as the industry matures, incremental piecemeal improvements in production (especially in a regulated environment) will become inefficient and expensive in the long-run. But can (should?) a systems approach be taken if the technology is not available?

"Absolutely," says Adam Goldstein, engineering manager for downstream process development for Amgen. "If you have higher outputs and smaller tanks, it's going to go downstream. You have to consider how the whole system will react." Goldstein sees the downstream issue not as one that can be solved by larger columns or multiple runs that accommodate larger volumes. Instead, he says that column sizes should remain fixed, and the challenge should be for the resin vendors to develop products that can handle more proteins.

"Columns are not going to get bigger and bigger," says Goldstein. "The way things are done now is to run multiple elutions over a column and then gang them up. But it's not the prudent thing to do. A better solution is to get a higher number of protein loads on the columns themselves. It's the resins that should have higher capacities."

In a systems approach, manufacturers would be expected to project and anticipate how future upstream production improvements (such as implementation of disposable products) might further increase their manufacturing output. Managers would be expected to integrate downstream improvements and developments into their systems and projections. Technologies such as

disposable chromatography may help break the purification bottleneck.

"Disposable technology has allowed tankage to be largely replaced at early phase by disposable systems," says Liddell. "Developments in this area are likely to continue to consider more of the process such as chromatography and control systems and have a significant effect on the throughput that can be achieved in an early phase facility."

### **ADDRESSING BOTTLENECKS**

Systems approaches and new technologies may help solve some capacity issues, but new developments may necessitate training for such enhancements to fully reach their projected potential. Most respondents to the BioPlan Associates survey said that increased attention to training would have an overall impact on ultimate capacity. However, only 35% of respondents planned on implementing new training programs. Goldstein thinks the emphasis should be on initial hiring processes. The ability to hire the right person at the right location is more of a problem for the industry than training is at the moment. "We are doing a lot of hiring right now," he says. "For us it's hard to find qualified people to work in the lower cost-of-living areas and hard to get qualified operators to move to the high cost-of-living areas." Amgen hired 70 new employees in November 2005 and plans to add more than 100 in early 2006. "Training internal staff isn't really an issue," Goldstien says. "We always need to train, but the capacity issues will not require us to do any retraining."

Establishing a systems approach to production may help prevent future bottlenecks over the long term. Production improvements in one area, however, will not make a whole train go faster. The entire system needs to be considered, and everyone needs to be included to find ways to improve production in every area.

### **Downstream Improvements:**

Protein refolding could present another opportunity for improvement,

particularly in microbial processes. “You have a limit of concentrated protein in the refold buffer,” said Wheelwright. “If you have higher expressions, it doesn’t help in the refold buffer. That remains a challenge unless we come up with better ways to refold.” A potential alternative would be refolding in-line, where protein is injected into a flowing stream and mixed in a pipe. However, the technology has not yet been worked out. Wheelwright feels that “We will see incremental improvements downstream. We have much better columns, better design. We’ve seen improvements in resins and changes in ownership of the big players. It’s unclear what impact the changes in ownership will have in downstream development.”

In the short term, developments in purification and recovery technologies may be useful, such as using disposables in downstream applications in chromatography or resins that have greater protein capture capabilities. To be realized, such developments are likely to require expanded vendor–manufacturer collaborations. Such arrangements have been hampered in the past by intellectual property and confidentiality issues. As improvements in downstream processing happen, however, the industry will fully realize the upstream gains it has achieved through greater bioreactor productivity, higher titers, and greater volumes.

## REFERENCE

1 Langer E. *3rd Annual Survey of Biopharmaceutical Manufacturing Capacity and Production*. BioPlan Associates: Rockville, MD, 2005.

2 Federal Reserve Statistical Release: Industrial Production and Historical Capacity; [www.federalreserve.gov/releases/G17](http://www.federalreserve.gov/releases/G17). 🌐

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