Downstream Production Challenges in 2007

Study Indicates Problems May Not Be Resolved Before 2011

by Eric S. Langer

Half of the biopharmaceutical industry believes the answers to future manufacturing capacity problems will be found by resolving downstream purification bottlenecks. Yet most people in the industry and its suppliers are unclear on what form such solutions will take — or where they will come from.

According to the *Fourth Annual Report and Survey of Biopharmaceutical Manufacturing and Capacity and Production* (**1**), a survey of 337 biopharmaceutical manufacturers, the top area that must be addressed for the industry to prevent significant capacity constraints is optimizing systems to improve downstream purification performance (indicated by 49.8% of respondents). As shown in Figure 1, this is up from 43.8% in the 2005 survey, which indicates increasing concern regarding the impact that purification is having on capacity and production.

Downstream Impact on Capacity

As recently as 2000, typical expression levels in mammalian cell culture were measured in hundreds of milligrams per liter. Today, greater than 1 g/L is common. And expression levels of 10 g/L are being predicted by industry leaders as a realistic goal during the next decade. As upstream yield and improvements in expression levels continue, downstream technical challenges are increasing. Current purification technologies will struggle to keep up.

The study indicates that downstream processing is not currently seen as a major capacity-limiting step. However, to prevent capacity constraints, improvements in downstream purification performance are viewed as the most important area to be addressed. This may suggest that the industry is forecasting impending bottlenecks. Manufacturers recognize that today's downstream headaches will be tomorrow's potential capacity failures. As manufacturing bottlenecks shift downstream, many in the industry are asking how to translate upstream success into downstream cost reductions and production improvements.

To assess the impact of bottlenecks on production capacity, respondents to the survey were asked to describe the effects their downstream purification processes were having on overall capacity, thus indicating the current magnitude of the bottleneck. The survey found that 17.4% strongly agreed that downstream processes were causing serious capacity problems (Figure 2). Overall, 43.5% felt that their facilities were experiencing at least some capacity bottlenecks resulting from downstream processes.

The impact of downstream purification is growing, and its effect on capacity is a bigger issue today than it was in 2005. Although the biopharmaceutical industry believes it should address this issue to prevent future capacity constraints, few clear solutions are appearing on the horizon.

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Biopharmaceutical Developers and CMOs: When comparing concerns about downstream purification among biopharmaceutical developers and contract manufacturing organizations (CMOs), we found that a substantially greater percentage of CMOs were experiencing capacity bottlenecks caused by downstream processes. In fact, 64% of respondents felt that downstream processing affected their overall capacity ("Agree" or "Strongly Agree") — compared with 39% of biopharmaceutical developers experiencing some such bottlenecks.

CMOs may be feeling the downstream capacity pinch more acutely than others in part because of upstream yield improvements. Some

Figure 1: Key areas to address for preventing capacity contraints within five years (abridged)

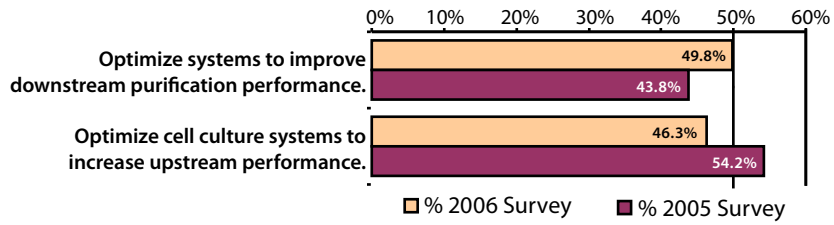
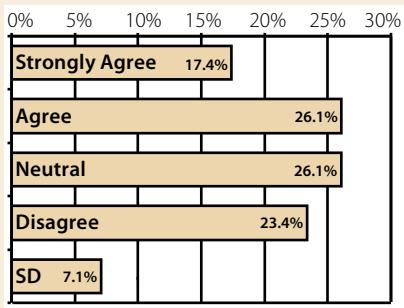


Figure 2: "For my facility, downstream processing is creating a serious capacity bottleneck to our overall production process."



* SD = Strongly Disagree

CMOs can now make more product using their existing tank capacity, which previously might otherwise have been a limiting factor. With increased yields from fermentation and cell culture, companies now have sufficient production capacity. In such cases, the limitations of recovery and purification may prove significant.

Where Are the Major Improvements?

Downstream processing is a hot topic, with special attention now being focused on its constraints. However, this general industry concern has not yet translated into commercialized innovations or products. It is debatable whether such innovations will come as stepwise, incremental improvements to current technologies or be introduced as "disruptive" technologies. What is not debated is that today's downstream technologies are not supporting the improvements in yield that are being realized.

"Innovation successes in downstream may not be just around the corner," says Yuling Li, director of purification sciences in process development at Human Genome Sciences. "For innovation to reach the commercial stage, we may still be years out."

"Yes," Li continues, "we need to optimize areas such as chromatography media, but the real breakthroughs will come from innovation. These downstream innovations may include membrane technologies, which are very promising in terms of improvements to throughput and capacity. They may also come from reoptimization of technologies such as aqueous two-phase systems, crystallization, and others. There are a number of technologies being developed today in response to the need for lower costs and higher throughput."

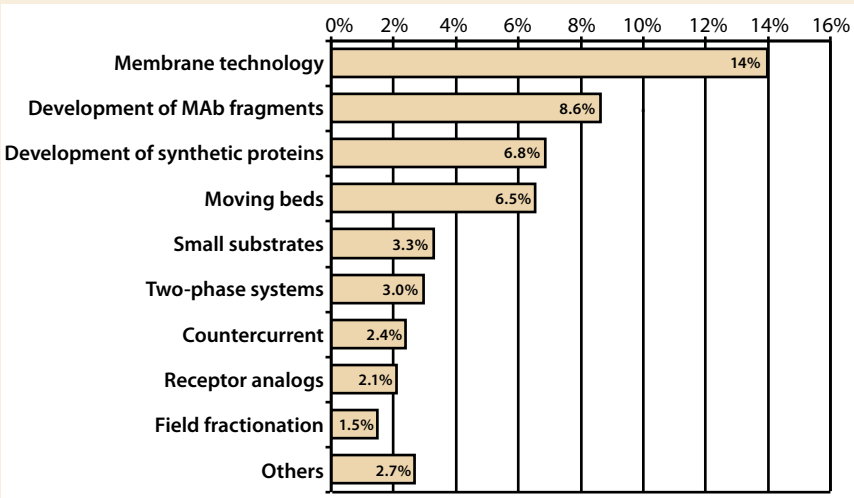
One difficulty in improving downstream processing involves diminishing returns on advances. In upstream (fermentation and cell culture) productivity, the theoretical room for improvement is limited only by the density at which cells grow. This is not so on the downstream side.

According to Geoff Hodge, vice president of process development and technology at Xcellerex, Inc., "with typical downstream yields for a monoclonal antibody process at ~60–70%, a twofold improvement in purification efficiency would be overly optimistic." He feels that significant improvements in purification will not be made by incremental, continuous improvements to current technology. Rather, the improvements will come from new technology developments. And these are currently in the hands of the technology vendors. Hodge believes that whereas the previous capacity crunch may have been averted in part by process development at the drug development companies, the next one will need to be addressed by their suppliers.

Here are some issues associated with downstream improvements:

• Membrane technology's adsorptive capacity, selective

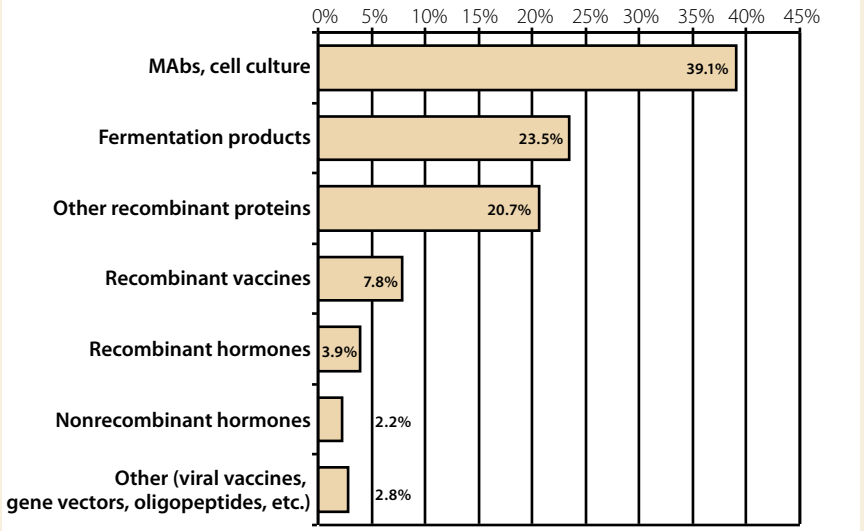
Figure 3: Areas where major improvements in purification may occur in the next five years (by 2011); percentage of the 47 respondents who had opinions on potential areas of improvement



Summary of Downstream Issues from Survey

- Knowledge about novel technologies is limited, and slow adoption rates are expected.
- Membrane technologies appear to be most familiar to their current users.
- Filter fouling and its economic impact on operational efficiency are primary problems associated with downstream purification.
- Cost of filters is a problem, but not seen as a primary issue.
- "Loss of product" is experienced by 54% of respondents, and they see that as a significant problem.
- CMOs may be more motivated to seek better purification technologies.

Figure 4: Downstream purification system design ("For which of the following classes of biopharmaceuticals is your primary downstream purification system designed?")



adsorption, and improved materials of construction

• Reducing the need for purification capacity by moving toward chemical synthesis of longer peptides and antibody fragments

• Simulated moving-bed technology for chromatography of well defined and large-scale products such as antibodies.

Downstream Innovation

Although lower costs and higher-capacity chromatography resins are often pointed to as ways to reduce cost and increase the capacity of downstream operations, current improvements do not address the magnitude of recent advances in upstream yields. The survey indicated that the largest expectation within the industry for improvement is membrane technology. However, even that technology received only a 14% response rate (Figure 3). According to Scott Wheelwright, president of Strategic Manufacturing Worldwide, "This low awareness in the industry suggests a general lack of knowledge regarding where advances will occur. This absence of consensus leads to the conclusion that a major breakthrough in technology may not be near."

Respondents to the survey were asked to suggest areas where major improvements in downstream purification would occur by 2011. Membrane technology was indicated as the area most likely to see major improvement over the next five years. Following that was the development of MAb fragments and the advent of synthetic proteins (by 8.6% and 6.8%, respectively). Because of the relatively limited knowledge among biomanufacturers and CMOs of potential opinions in new downstream technologies, the industry should be prepared for slow adoption rates with any new technology as well as a long learning and regulatory curve.

Microfiltration Problems: Concerns raised by respondents regarding microfiltration were interesting. About 10% claimed that very significant problems exist in all areas. Nearly two-thirds (64.5%) felt that the increased operating expenses from filter fouling is a significant factor. Such dramatic levels of user dissatisfaction could represent significant business opportunities for suppliers. Filter vendors today are responding to that situation.

Jerold Martin, senior vice president of scientific affairs at Pall Life Sciences, says that "The major problem experienced by biomanufacturers involving microfiltration steps is primarily lost productivity. If an operation has to be halted to change a filter, that time can equate to significant money."

In addition to the impact on operating expenses of filter fouling, other areas of concern were filter throughput, production scheduling, and the costs of filters. Interestingly, the actual cost of filters ranked fourth in terms of significance.

Downstream Purification Systems: As expected, most biopharmaceutical downstream purification systems are designed for monoclonal products (indicated by 39% of respondents to the survey as their primary system). Fermentation products were the primary system for 24% of respondents (Figure 4). "Other recombinant proteins" made up 21% of respondents' primary systems.

Membrane Technology

Membrane technology is one area in which respondents felt there would be opportunity for improvements over the next five years. Some respondents provided the following comments regarding their expectations:

• Higher capacities resulting from new membrane technologies
• Cost reductions
• More selective sizing
• Membranes ultimately replacing fixed columns
• Membranes improving binding capacity
• Increased selectivity and cleanability
• More resin types becoming available
• Membranes improving virus removal
• Single-step purification benefits
• Overall throughput improvements
• Better fractionation
• Better adsorbents and faster flow rates
• Broader applications (e.g., tangential-flow filtration and viral filtration)
• Effective DNA removal
• Membranes handling much greater titers
• Possibility of disposable chromatography
• Cost reductions from development of effective disposable membranes
• Columns replaced in flow-through modes
• Columns combined with membranes
• Charged columns as de facto disposables that achieve the resolution of packed columns
• Adsorption of impurities
• Frames standardization
• Mixed-mode separations (charge/size)
• Efficient capture modules
• Membrane adsorbers take over chromatography
• More scalable devices needed.

Moving Bed Technology

Respondents who felt that moving-bed technologies would see the most improvements would occur over the next five years provided the following input:

- Reduced column size
- Higher yields
- Continuous purification
- Much greater titers
- Easy setup and use
- Denser beads
- Robust: more cycles/resin volumes
- Usable with wider range of feedstocks
- Viable technologies developed
- Perhaps only for truly large-scale facilities
- Becoming a reality, now being put into processes
- Being used in MAb manufacturing
- Real feasibility with fragile, more complex biologics
- Not user friendly enough yet
- Make more usable for smaller systems
- Some moderate potential, but low likelihood of substantial successes

Survey Methodology

The fourth annual report and survey included responses from 337 biomanufacturers and CMOs from 29 countries (Figures 5–7). It compares biotherapeutic developers and CMOs and US and European respondents, and it benchmarks responses from 2003 through 2006. This annual evaluation yields a composite view from 337 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations in 29 countries. The methodology also encompassed an additional 157 direct suppliers of materials, services, and equipment to this industry. The 2006 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, hiring issues, employment, and training. Among respondents to the 2006 survey, 23.4% were primarily involved in process development specifically for biopharmaceutical manufacturing. Large-scale cell culture for therapeutics accounted for 16.9%, and large-scale microbial fermentation for therapeutics represented 9.2% of respondents.

Figure 5: "In which area of biopharmaceutical manufacturing are you primarily involved?"

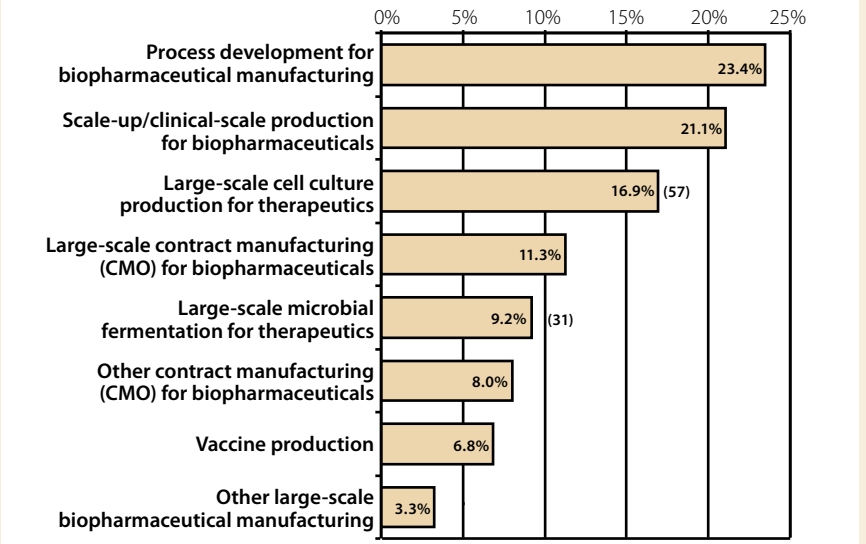


Figure 6: Respondents' facility locations (percentages add up to >100 because some respondents had facilities in more than one region)

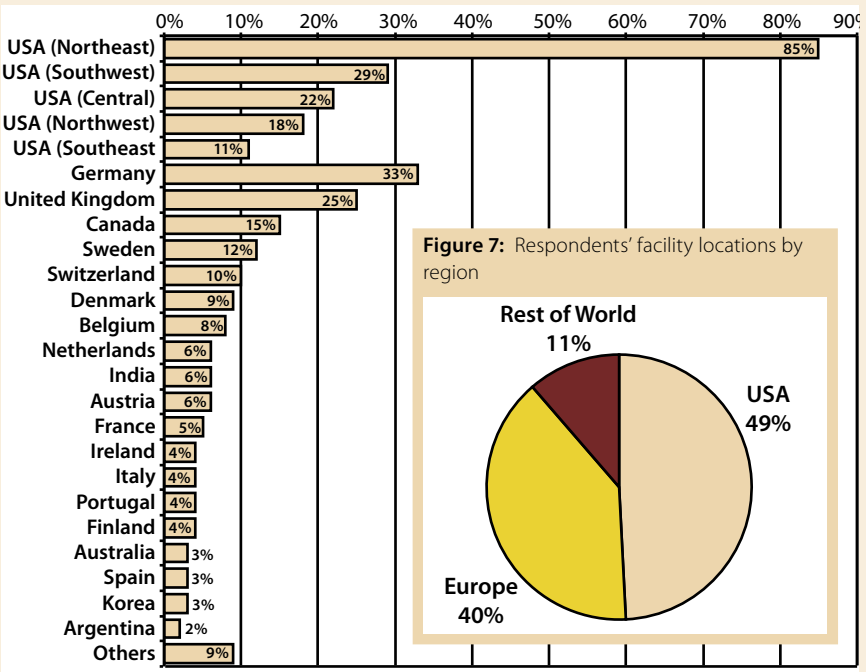


Figure 7: Respondents' facility locations by region

Reference

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

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