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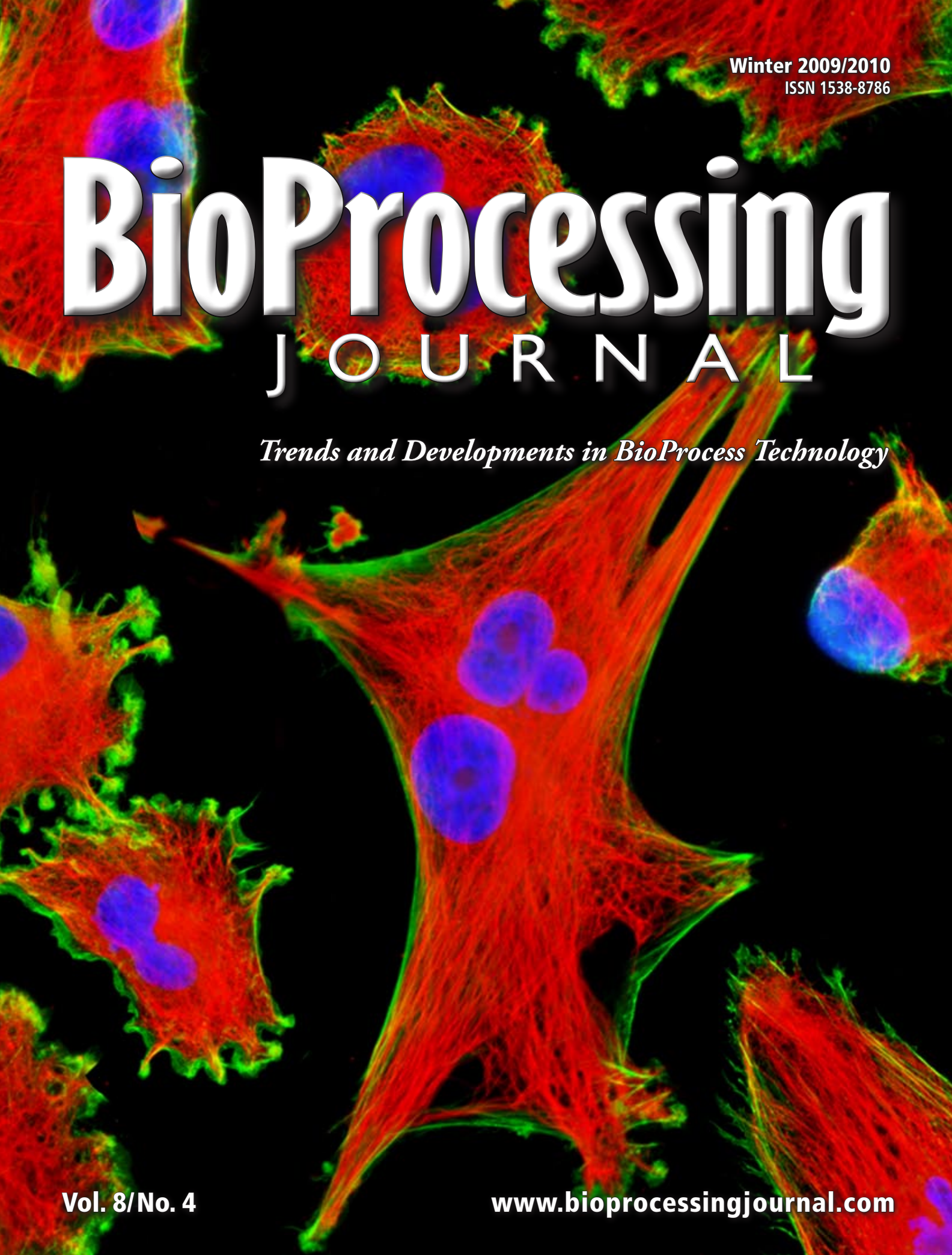

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Downstream Factors That Will Continue To Constrain Manufacturing Through 2013

By ERIC S. LANGER

Downstream processing is increasingly seen to be a capacity constraint for many biopharmaceutical manufacturing organizations. In our current study, nearly 75% of respondents reported that their facilities were experiencing some degree of capacity bottlenecks as a result of downstream processing. In comparison, 63.8% responded the same in the previous year. As the biopharmaceutical industry increases its focus on cost containment, product pricing, and healthcare reform, critical manufacturing operations have been pushed to center stage.

Over the past few years, downstream processing, which includes complex operations such as filtration of final products and chromatography operations has become increasingly challenging, from budgetary and operational perspectives. As upstream operations continue to improve, the ability of current downstream facilities to handle the additional load has led to strains and constrictions. The industry is open to new solutions although few alternatives to current processes have been presented. A number of promising innovative technologies are on the horizon, but it will be a few years or more before they debut in clinical or commercial production operations.

The impact that downstream purification has had on production capacity has become an increasingly important issue since 2006. According to our data, this has emerged as the primary area that the biopharmaceutical industry believes must be addressed to avoid current and future log jams. Our current study shows that manufacturers believe they will continue to face significant downstream processing problems this year and through 2013. As a result, downstream purification suppliers and R&D groups are putting increasing emphasis on downstream product research to resolve these chronic, growing problems.

Interestingly, for all biopharmaceutical manufacturing, upstream and downstream capacity constraints have both remained relatively light over recent years. Significant shifts are not expected through 2013. Despite the expectations of adequate overall capacity, many respondents still felt that there would be specific bottlenecks in physical capacity of downstream purification equipment, which poses the most serious threat to production. Unless breakthrough approaches to purification are developed and put into operation, downstream limitations will continue to plague the industry.

METHODOLOGY

We analyzed current and future trends in downstream processing (DSP) based on data from BioPlan Associates' *6th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production*.[1] We evaluated current capacity constraints, as well as expected constraints through 2013. The study provides a global outlook among executives at 443 biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 39 countries. This sixth in a series of annual evaluations is a web-based quantitative survey. To ensure broad, global coverage, it is done in conjunction with a number of association and media partners (see www.bioplanassociates.com). The study covers issues in biopharmaceutical manufacturing faced by global biotherapeutic developers and CMOs. Respondents are asked to answer 54 closed and open-ended questions associated with capacity utilization*, constraints, future expansions, emerging technologies, use of new technologies such as disposable (single-use) products, downstream purification problems, quality issues, batch failure rates, training and hiring issues, and other current manufacturing issues. We surveyed biomanufacturers involved in mammalian cell culture, microbial fermentation, yeast, plant and other systems. This year's study yielded a composite view from responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations involved in R&D, process development, scale-up production, and commercial manufacturing.

*The definitions of 'capacity' and 'capacity utilization' can vary. To ensure consistency, our study attempts to reflect the definition used by the US Federal Reserve Board, which defines 'capacity' in its surveys as: "*The maximum level of production that [an] establishment could reasonably expect to attain under normal and realistic operating conditions fully utilizing the machinery and equipment in place.*" It assumes normal downtime, maintenance, repair, and cleanup. In our study, respondents were asked to indicate at what percentage of total production capacity their facility is currently operating. This study methodology regarding capacity expansion is intended to provide directional information rather than quantitative volume analysis. That is, we are measuring perception of near-term growth rather than actual change in physical volume. For more information, visit www.bioplanassociates.com.

Eric S. Langer, MSB, *is President and Managing Partner, BioPlan Associates, Inc.*
2275 Research Blvd., Suite 500, Rockville, Maryland 20850 USA
Phone: +1 301-921-5979; Website: www.bioplanassociates.com; Email: elanger@bioplanassociates.com

Downstream Process Impact

The study asked respondents to define the impact that downstream purification processes had on overall capacity, and to identify the magnitude of the resulting bottlenecks (results shown in Figure 1). We found that 74.5% of respondents were experiencing it to some degree (compared with 63.8% in the previous year's study). This represents a 17% increase in the number of facilities experiencing downstream capacity bottlenecks at some level. Specifically, 8.1% of respondents agreed that their facility had "serious bottlenecks today" while 46.3% felt that they were experiencing "some bottlenecks." Only 16.8% indicated they expected none at all (compared with 21.7% last year).

Purification Step Capacity Constraints

This year, 80% of respondents felt chromatography steps created at least a minor capacity constraint. Further, 21.7% reported experiencing "significant" or "severe" capacity constraints due to chromatography column issues. Depth filtration was seen as creating "moderate" or greater capacity constraint by 32.9% of respondents (close to last year's 37.2%). Just over a quarter of respondents (27.4%) felt that ultra-filtration steps were creating at least "moderate" capacity constraints (versus 31.6% last year).

Emerging Problems in Downstream Purification

Respondents were asked to identify areas where they believe their facility will face significant problems in downstream operations (Figure 2). The top area, noted by nearly 63.9% of respondents, was "column chromatography" where costs, cleaning, validation and operation were once again identified as the lead DSP problem area by respondents by a very wide margin over other potential trouble spots. Perhaps due to column chromatography's rising significance, some other contenders appeared to recede in importance, including process optimization (26.2%) and validation (24.1%).

Western Europe versus United States

We also found significant differences in the impact that downstream processing has had on capacity when comparing US and western European biomanufacturers. While both US and European respondents are being impacted, significantly more Europeans indicated that they are experiencing bottleneck problems. Those problems are also being felt more acutely in Europe (62.3% of European vs. 48.4% of US respondents are experiencing "some" or "serious" bottleneck problems). In this year's study, European respondents with bottlenecks took a 15% jump, from 47.2% in 2007 to 62.3%. US respondents saw a 13% point jump from 35.3%.

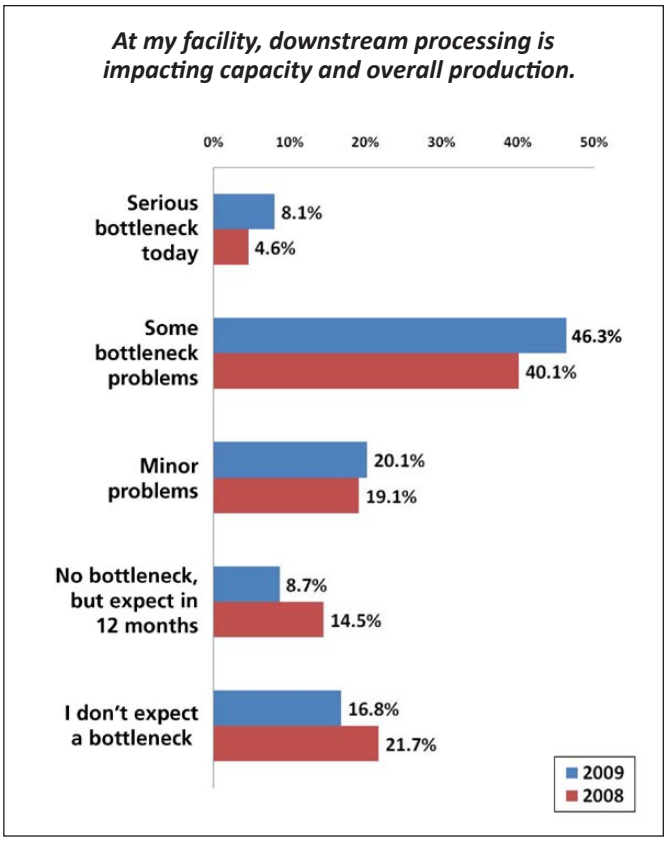

FIGURE 1. Impact of Downstream Processing on Overall Capacity

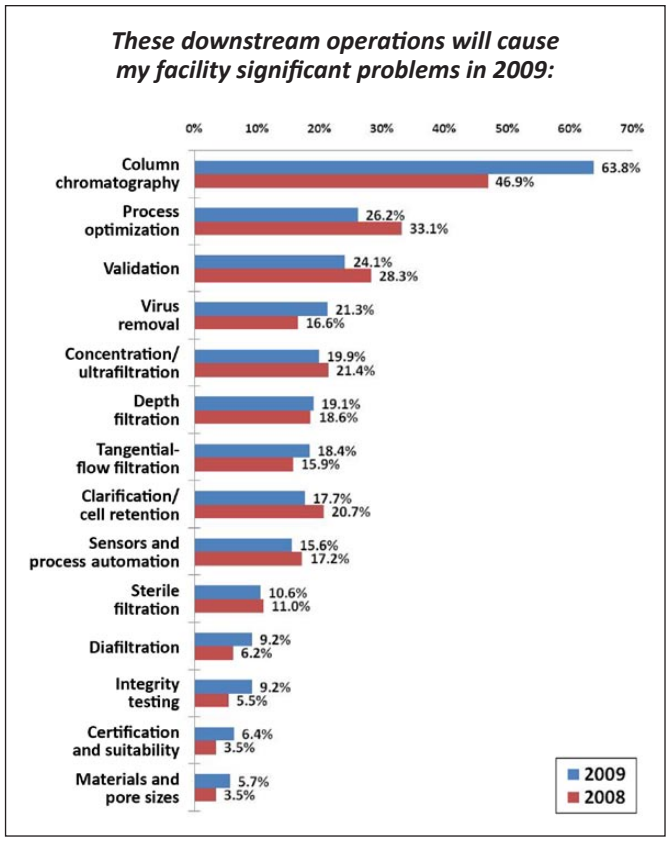

FIGURE 2. Problem Areas in Downstream Operations

Western European respondents indicated that, particularly for chromatography steps, the gap appears to be widening. Among European respondents, 33.3% felt that chromatography steps were causing significant or severe constraints compared to only 14.5% of US respondents, a 16% gap. Last year's numbers showed only a 4.6% difference (23.3% Europe, 18.7% US). For depth filtration, we found 10.4% of western European respondents indicated it was causing "significant" or "severe" constraints compared with only 3.8% of US respondents. In ultrafiltration, the numbers were small and relatively consistent (Figure 3).

Current Overall Facility Capacity Constraints

We compared the percentage of biomanufacturers experiencing capacity constraints, for any reason, so we could evaluate the relative constraints from DSP. In this year's study, we found that 17.3% of all respondents were experiencing "severe" or "significant" constraints at the commercial manufacturing level. In addition, 39.7% of them reported experiencing more than just "minor constraints." Clearly, there is more overall available capacity this year than last, at the commercial scale. In addition, 14.9% of respondents were experiencing "severe" or "significant" constraints at "later stage clinical manufacturing" (Phase 3), compared to 17% last year. At the "early stage clinical manufacturing" (Phases 1 or 2) level, 9.2% were experiencing "severe" or "significant" constraints, compared with 11.2% in the previous year. Based on these results, it appears that consistent levels of constraint continue in earlier phase production levels (see Figure 4).

Capacity Constraint Expectations by 2013

In the study, biomanufacturers were asked to predict the extent to which their facility is likely to experience production capacity constraints by 2013. Respondents seemed moderately more concerned about upcoming capacity constraints on commercial-scale production. About 22.9% expected "significant" or "severe" constraints in commercial production systems by 2013, compared to 18% (later stage) and 9% (early stage) clinical systems. This broadly reflects their perceptions of current production constraints although for commercial production, expectations of "moderate" or "minor" bottlenecks within five years were somewhat higher than the "moderate" or "minor" constraints perceived today. Last year, at all stages of development, a significantly higher percent of respondents predicted there would be "five years out" capacity crunches.

For example, 29.6% of respondents last year predicted that they would be experiencing "significant" or "severe" capacity constraints within five years. In this year's study, 22.9% of respondents indicated the same. Essentially half the number of respondents this year expected they will experience capacity constraints in five years, compared to a year ago. At that time, 19.8% of them predicted "no constraints" as compared to 40.2% this year. This also correlates with the drop in capacity utilization seen in this year's study, as shown in Figure 5 (on the following page).

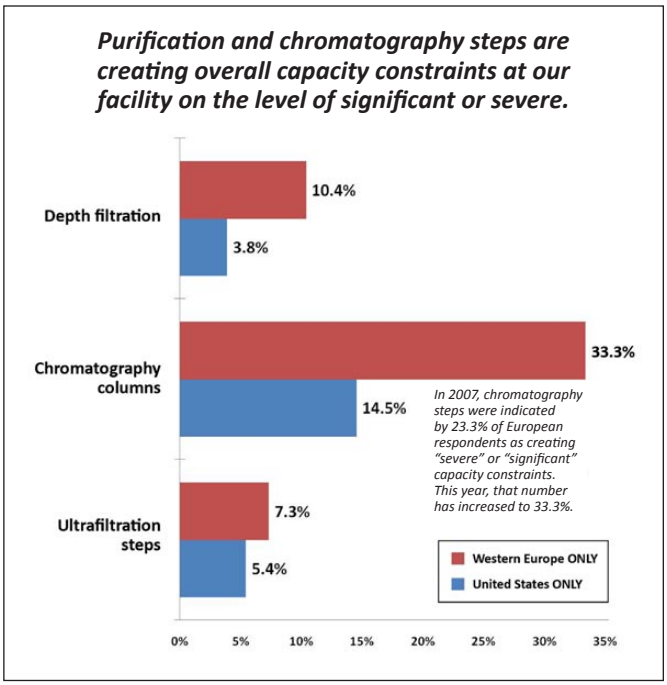

FIGURE 3. Impact of Purification Steps on Capacity – US vs Western Europe

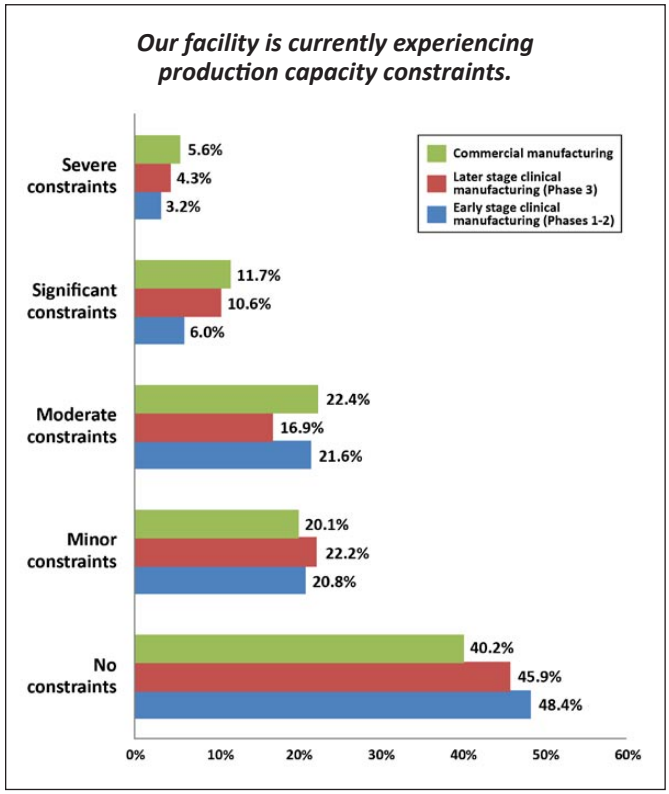

FIGURE 4. Capacity Constraints at Different Stages of Production

Factors Creating Future Capacity Constraints

We aggregated respondent data and identified 19 different major factors likely to constrain respondents' production capacity over the next five years. This year, biomanufacturers most frequently indicated factors affecting future capacity constraints including "physical capacity of downstream purification equipment" (30.5%), "costs associated with downstream purification" (26.9%), "lack of financing for production expansion" (26.3%), and "inability to hire new, experienced technical and production staff" (25.3%). Only 20% of respondents indicated they were "unlikely to see capacity constraints in five years." Downstream purification issues were clearly recognized as the current bottleneck. The top two concerns which involve DSP most likely explain the third ("lack of financing...") as shown in Figure 6.

Avoiding Future Downstream Capacity Constraints

Study respondents also identified areas to be addressed in the future if the industry is to avoid significant capacity constraints (Figure 7). Again, the top area to address, for the third year running, involved downstream purification. This year, "develop better purification technologies" was the greatest area identified with 50.6% of respondents feeling new technologies are required. "Optimize systems to improve downstream purification performance" followed with 43.5%. This was a top area of concern in 2007 and 2006, and second in 2005. One potential area for development is in more cost-effective disposables, which was third on the list of areas to fix to avoid capacity problems (by 39.6% of respondents). This suggests that improvements in disposable downstream technologies may be an important area of research for preventing downstream operations from being overloaded.[3]

Areas Where Major Improvements Will Occur in Downstream Processing

The survey also asked respondents to suggest areas where major improvements in downstream purification processes are likely to occur over the next five years (by 2013). Relatively few in the industry were able to respond (about 10%). Of those, half pointed to membrane and monoclonal-fragment technologies as possible areas for improvement. These results are almost identical to last year's. Membrane technology continues to be indicated as the area most likely to see major improvements for downstream purification. Following that was the development of MAb fragments and the development of moving bed technologies (by 4.7% and 3.8% of all respondents, respectively). It would appear that relatively few biomanufacturers and CMOs have firm opinions about which downstream technologies are likely to yield major improvements.

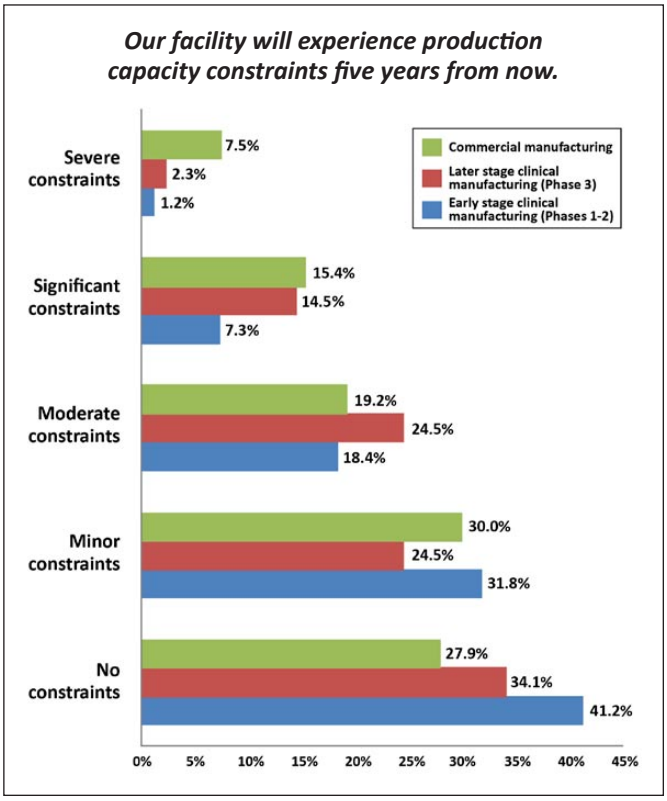

FIGURE 5. Expected Capacity Constraints in 2013

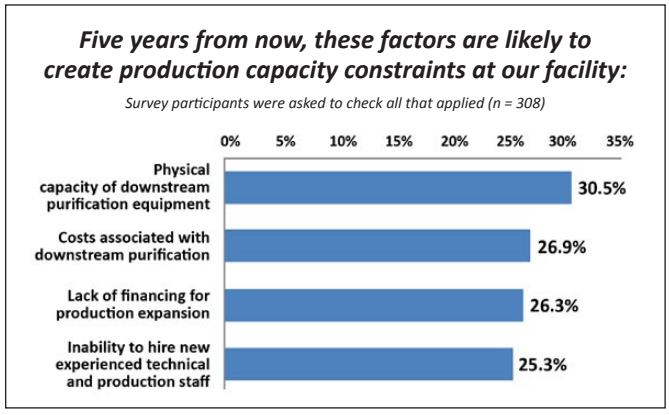

FIGURE 6. Factors Creating Future Capacity Constraints

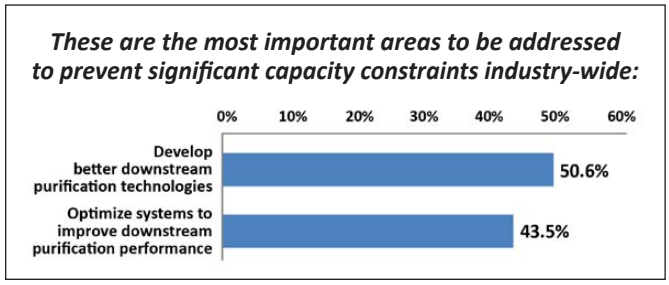

FIGURE 7. Key Areas of Concern Regarding Capacity Constraints

We summarize in this paper the trends associated with downstream purification and the effect that DSP steps have on capacity based on our recent global study. DSP has become an increasingly important issue since 2006. Today it is the primary area that biopharmaceutical manufacturers believe must be addressed to avoid continuing capacity constraints through 2013. The industry, both manufacturers, and vendors, are evaluating options and managing the development of improved downstream systems and novel technologies.

The key question is how companies and their suppliers will deal with downstream processing and future bottlenecks. A top industry concern for many years has been the general cost of chromatography steps for purification. In part, this is driven by internal company pressure to reduce operating costs and improve product margins: chromatography resin is a large expense that jumps out at company financial managers. Most managers recognize that major breakthroughs in chromatography are unlikely in the near future, and that any incremental changes are unlikely to dramatically lower the overall cost of manufacturing, or of these materials in particular. We are, however, seeing more specialty resins, including product-specific synthetic affinity matrices that are priced near those materials they are meant to replace, such as Protein A.

Respondents to the study provided comments regarding the impact on their overall capacity that downstream performance was creating. The primary areas of focus indicated by respondents were chromatography capacity and costs associated with purification. Others commented on lack of space. It appears that cost issues are pressuring the industry to produce more from existing operations. Thus, companies try to increase the capacity of downstream operations and increase throughput. Interestingly, none of the respondents emphasized expanding the downstream operations. The interest appears to be in pushing more product through a given facility.

The suggested means to increase throughput include improved recovery, higher capacity for chromatography resins, and process changes to alternative unit operations that have higher throughput. The technical change that has led to the bottleneck in downstream processing is the increase in fermentation and cell culture yields that has been achieved in the industry in recent years. We are seeing double and triple the amount of target protein produced and that product must correspondingly increase the burden on downstream operations. This trend in upstream optimization and performance is likely to continue, which will exacerbate the downstream capacity issues.

Where then may we find the opportunities for improvements in downstream capacity and cost? While there is a desire to move away from Protein A as an affinity chromatography ligand, there continue to be few potential solutions to the challenges of cost-effectively increasing capacity in downstream processing. Further, regulatory hurdles with any new technology will create delays in adoption of any new approach. Few companies want to be the first to seek regulatory approval for a new idea.

At least for the short term, the industry will likely have to continue to accept the high cost of chromatography. It is possible that a rational solution will not be presented until the DSP problem reaches a more acute stage and manufacturers more aggressively explore new technologies and alternatives. At present, few real options are open for breakthrough technologies. Incremental improvements in chromatography will continue, but will not match the doubling or tripling of upstream advances. There are a number of potentially promising technologies where we do expect to see improvement, including membrane processes. In fact, the majority of problem areas, and therefore the biggest opportunities for improvement, are in this technology.

What does the future hold? To achieve major improvements in DSP through 2013, membrane and monoclonal-fragment technologies are seen as possible areas for improvement. However, relatively few biomanufacturers and CMOs have clear opinions about which downstream technologies are likely to yield major improvements. Without a definitive roadmap, there may be less aggressive product development, slower evaluation and adoption of new technologies, and a relatively long learning curve for the industry.

In conclusion, there are many opportunities for improvements as we face the challenges in downstream processing, but there are relatively few prospects for major technical advances to solve our problems. As new biopharmaceutical products move through the pipeline, and cost pressures mount, downstream processing is clearly going to advance. We will, however, continue to face technical and regulatory challenges as we work to improve recovery yields and process throughput while decreasing operating costs.

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