# Quantifying Downstream Capacity Crunch

## Column Resins Are Implicated by Many Experts as the Source of Biomanufacturing's Woes

*Eric S. Langer*

In today's biomanufacturing environment, downstream capacity has become a partial roadblock to nearly all CMOs (94%) and 61% of biotherapeutic developers (Figure 1).

Extensive data from 434 biopharmaceutical manufacturers in 32 countries is summarized in BioPlan Associates' just-released 5th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production. The report shows, among other trends, that biomanufacturing facilities are experiencing a dramatic increase in downstream bottlenecks.

In fact, in our previous study, fewer than half of all respondents indicated downstream processing capacity was a bottleneck. This year, the number of respondents expressing concern about the impact of downstream processes on their overall capacity grew to nearly two-thirds.

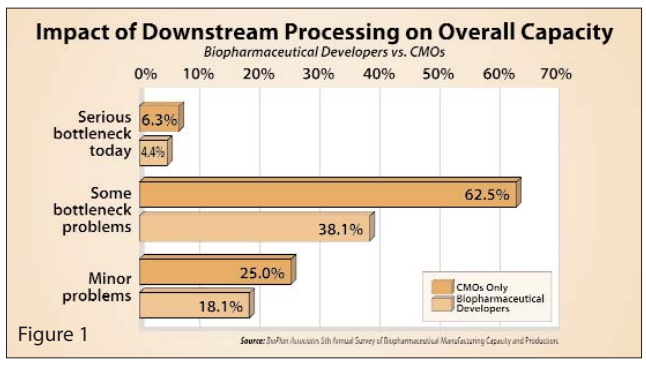

Figure 1

The problem appears to be more pronounced in Western Europe. Figure 2 shows that 75% of European biomanufacturers and CMOs are experiencing at least some downstream bottlenecks, compared with 61% of U.S. biomanufacturers and CMOs.

### Source of the Problem

Downstream purification covers a broad range of technologies. When we tested where the actual problems were located we found, not surprisingly, that column chromatography is causing significant problems at nearly half of all manufacturing facilities (Figure 3).

Other areas causing significant problems include: sensors and process automation, virus removal, tangential-flow filtration, sterile filtration, diafiltration, integrity testing, materials and pore sizes, and certification and suitability.

### Remedial Action

To help remove downstream production roadblocks, the industry's vendors and biomanufacturers are investing resources to address the problem. Much of this R&D is going into column resins.

Based on his years of experience in the industry, Adam Goldstein, senior manager, clinical operations purification development, Genentech (www.gene.com), said that the critical constriction causing production bottlenecks is the lack of high-capacity resins. "Current column resins can require as many as 10–12 loading cycles, which takes too

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Eric S. Langer is president and managing partner at BioPlan Associates.
Web: www.bioplanassociates.com.
E-mail: elanger@bioplanassociates.com.

BioPlan's 5th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production was conducted using web-based methodology, yielding a composite global analysis from 434 responsible individuals at biomanufacturers and CMOs, and 126 direct suppliers. The survey covers current and future capacity, capacity constraints and expansions, use of disposables, budgets, downstream purification, quality, batch failures, and training. Comparisons of production by drug innovators and CMOs, annual changes, and differences between U.S., Europe, and other major markets is provided.

# Downstream Capacity

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much time," added Goldstein. "If a resin existed that had 10 times the capacity, it could potentially cut the time involved in downstream purification by 80%."

Many vendors are already researching solutions. According to Amitava Kundu, associate director, process development at Genmab (www.genmab.com), "we are working with a resin manufacturer that has developed a novel approach to increasing binding capacity of resins. I can say that in a couple of years, I believe we will be using ion-exchange applications with binding capacities in excess of 100 g/L. These improvements will be to the existing basic bind-and-elute resins currently in use. The capacity improvements will come from interior pores and the way ligands are put on a bead so they are accessible to the protein of interest."

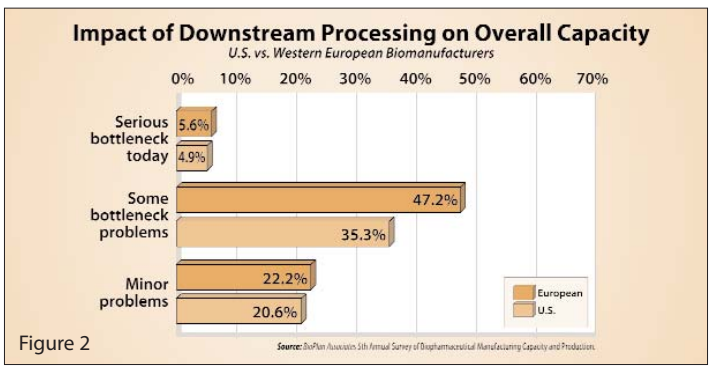

Figure 2

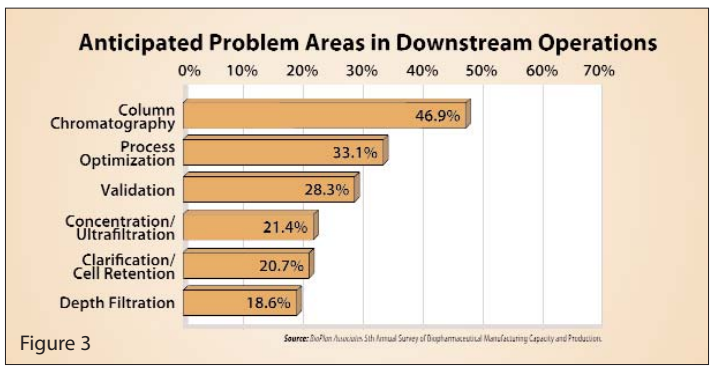

Figure 3

A top concern within the industry for many years has been the cost of chromatography steps for purification. This is driven by internal company pressures to reduce operating costs. Chromatography resin is a large expense that weighs heavily on balance sheets. And while manufacturers of chromatography resins warn that there may be few breakthroughs that lower the cost of these materials, more specialty resins may be produced that will ultimately lower the total cost of production by improving overall performance.

This is consistent with the views of Scott Wheelwright, Ph.D., president of Strategic Manufacturing Worldwide (www.smwbiotech.com). "Companies perceive they must increase the throughput of their operations. None of the respondents emphasized an increase in the volume of tanks, or even expanding the downstream operations. The interest is 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."

As we double or triple the amount of target protein produced in each bioreactor batch we need to adjust downstream operations accordingly. This year's survey shows that many in the industry expect this trend to continue, which will exacerbate downstream capacity problems. CMOs are particularly hard-hit because current volume bioreactors are overmatched to downstream processing areas that may have been built to meet lower yield requirements. Consequently, downstream areas are now undersized.

The BioPlan survey shows that there is a strong desire to move away from Protein A; concurrently there is a scarcity of potential solutions to increase capacity and lower costs of downstream processing.

Most likely, any breakthrough technology expecting to replace expensive chromatography, particularly Protein A, will need to address regulatory concerns in this very conservative industry. Relatively few companies, according to the survey, plan to migrate from Protein A. As such, in the short-term, we will probably see vendors offering incremental improvements in chromatography to match the upstream changes. GEN