

Elucidation

Quantifying Trends Toward Alternatives to Protein A

Survey Results

Problems associated with affinity purification in antibody production continue to increase as upstream cell culture expression levels improve. As a result, many vendors and users in the biopharmaceutical industry are working to identify alternative technologies that can replace tried-and-true column chromatography.

In a new study by BioPlan Associates, *5th Annual Report and Survey of Biopharmaceutical Manufacturing*, 434 global respondents pointed to the bottlenecks created by downstream processes as one of their most serious manufacturing problems today. 63.8% said their facility is experiencing some degree of such bottleneck. The problem has been growing over the past five years.

PROBLEM AREAS

Respondents identified 14 different areas where their facilities are facing significant downstream production problems. The top area, noted by nearly 47% of respondents, was column chromatography. That was followed by process optimization (33.1%), and validation (28.3%). To produce greater quantities of biologics in existing operations, companies need to remove the resulting bottleneck by improving recovery, raising capacity for chromatography resins, and changing to alternative processes that have higher throughput.

Planning for Downstream

Bottlenecks: How should companies plan to handle such bottlenecks, particularly considering that many survey respondents indicated the problem will only increase in the future? This planning issue hits most organizations twice: First, from the inability to make sufficient product in a current facility; second, from the cost of downstream processing and cost-cutting pressures.

Biopharmaceutical Developers and CMOs: The effect of upstream yield in creating purification bottlenecks is

particularly felt by contract manufacturing organizations (CMOs). This may be because many CMOs are working today with facilities constructed when downstream processing areas were matched to lower-yielding upstream processes.

We found that substantially more CMOs than biopharmaceutical developers are experiencing these capacity bottlenecks. Of CMO respondents, 68.8% said that downstream processing was causing "serious" or "some" bottlenecks today, compared with 42.5% of biopharmaceutical developers. Interestingly, 100% of CMOs expect to see at least some kind of bottleneck as a result of downstream purification over the next 12 months.

US and Western Europe: Although both US and European respondents said downstream processing was affecting their overall capacity, more European than US respondents indicated they were experiencing bottleneck problems (47.2% of European vs 35.3% of US respondents). Further, nearly a quarter (23.5%) of US biomanufacturers are experiencing no downstream bottlenecks, compared with only 11.1% of western European biomanufacturers.

DOWNSTREAM PROCESS ALTERNATIVES

One logical consequence of these pressures is a desire to move away from Protein A as an affinity chromatography ligand. The survey showed general agreement that downstream purification issues are important, and are changing production processes. Nearly 52% of respondents said that higher upstream productivity has forced significant changes to their downstream processing facility. More than 46% are considering alternatives to protein A to reduce costs in new production projects. At present, however, only 19% actually plan to move away from protein A for new production projects over the next 12 months.

The scarcity of potential solutions to the challenges of increasing capacity and lowering costs of downstream processing make shifting to alternatives difficult. For the time being, many industry experts predict that we will have to live with the high cost of chromatography, particularly Protein A. Because of regulatory concerns, end-users may not be pushing for alternatives with the gusto of less-regulated industries. Few companies want to be first to seek regulatory approval for a new idea.

Next Breakthrough Technology:

With relatively few real options open for breakthrough technologies, many survey respondents said that incremental improvements in chromatography will take place. But that will not achieve the doubling or tripling of capacity to match the upstream changes.

Respondents were asked to indicate areas where they believe major improvements in downstream purification will occur by 2012. Both this year and last, those responding indicated membrane technology as the area most likely to see major improvements for downstream purification over the next five years. Following were the development of MAb fragments and the development of synthetic proteins.

Opportunities for Improvement:

The overall conclusion is: There are opportunities for improvement as we face the challenges in downstream processing. For the moment, however, both drug innovators and vendors seem to be in a holding pattern awaiting the next major technical advances.

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