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CMOs and Biodevelopers Taking Different Approaches to DSP Problems: CMOs Get Serious About New Technologies

Eric S. Langer

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The biomanufacturing industry continues to have problems with downstream operations, as evidenced by the 7 in 10 (71.9%) respondents to our 9th Annual Report and Survey of Biopharmaceutical Manufacturing who report this year that they are seeing at least minor capacity issues due to their downstream processing. To evaluate the approaches the industry has taken to address these bottlenecks, we asked 302 biotherapeutic developments and contract manufacturing organizations (CMOs) about specific activities they have implemented to improve their downstream purification operations. Our results highlight some intriguing differences between how biotherapeutic developers and CMOs have been tackling these issues.

We found that a significant proportion of CMOs have used or evaluated membrane-based filtration technologies, compared to biotherapeutic developers (63.6% vs 38.5%, respectively). A similar gap exists between CMOs who say they have optimized running conditions for downstream operations.

Rounding out the top five activities undertaken by CMOs are 'cycling columns more frequently', 'investigating single-use, disposable downstream technologies', and 'negotiating harder with vendors' (each at around 45% of respondents). CMOs are more likely than biodevelopers to report undertaking each of these activities. Although the largest gap in these activities is in negotiating harder with vendors (45.5% of CMOs vs. 24.6% of biodevelopers). It not unexpected that CMOs are also out front when it comes to testing new technologies such as disposables.

While CMOs are trying out new technologies, such as membrane-based filtration technologies or single-use systems, biodevelopers are taking a process-driven approach. For example, they are 63% more likely than CMOs to have developed downstream processes with fewer steps (44.6% of biodevelopers vs. 27.3% of CMOs). They are also roughly 4 times more likely to have 'implemented process development to shorten cycle times' (36.9% vs. 9.1%) and to have invested in downstream process development.

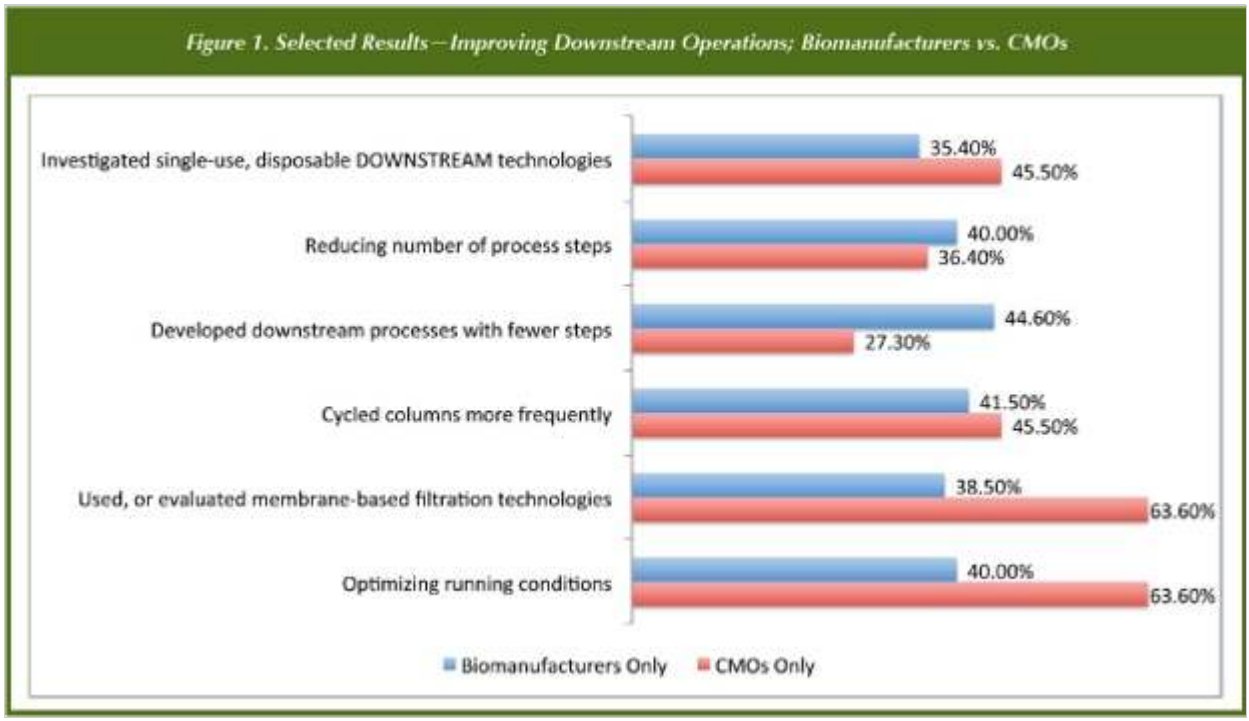
Overall, when we look at the results from CMOs and biodevelopers combined, and compare them to 2011's figures, we find that there has been a relative reduction in emphasis on implementing activities that improve downstream purification. This may suggest that the industry is gradually moving towards a better balance in its downstream capacity, and that recent downstream purification bottlenecks are beginning to abate. This may be the result of generally improved productivity in these operations, the implementation of better process monitoring, and/or improved technology adoptions.

Downstream Processing Becoming Less of a Problem for CMOs

Our report's data supports – to some extent – the view that the industry is moving away from serious bottleneck problems. This year, the proportion of respondents that reported "serious bottleneck today" as a result of downstream processing fell 3.3% percentage points, from 11.8% in 2011 to 8.5% in 2012. At the same time, the proportion reporting minor capacity and production problems rose from 21.3% to 25.6%, and the proportion reporting some problems rose from 35.4% to 37.8%. This suggests that while bottlenecks continue to occur, they are becoming less serious in nature as the industry adapts.

Comparing biopharmaceutical developers with CMOs reveals an intriguing development. This year, only one-quarter of CMOs felt that downstream processing was causing "serious" or "some" bottlenecking today. This is almost half the proportion that felt the same way last year (45.5%), and is also a significant step down from 2010 (38.9%), 2009 (60.7%), and 2008 (68.8%). On an even more encouraging note, none of the CMOs that reported at least "some" problems indicated that these bottlenecks were "serious." In 2011, 9.1% were experiencing "serious" bottlenecks, and 36.4% were experiencing "some" bottlenecking from downstream operations.

By contrast, biodevelopers appear to be having a more difficult time. This year, exactly half said they were experiencing "serious" or "some" bottlenecks today as a result of downstream processing. This is slightly up from 48.1% last year and 42.3% in 2010, though remains below 2009's high of 52.9%.



The difference in downstream bottleneck impact between CMOs and developers this year is the continuation of a multi-year trend, in which CMO bottlenecking has declined, while biodevelopers' issues have stayed relatively steady. The upshot of this is that while in 2008, CMOs were far more likely than biodevelopers to report at least some bottlenecks on account of downstream processing (68.8% vs. 42.5%), in the past 5 years, that script has flipped, to where biodevelopers are now twice as likely as CMOs to be reporting this level of bottlenecking (50% vs. 25%).

The decline in downstream bottlenecks at CMOs as compared to captive manufacturing plants can be attributed in part to CMOs tending to see new processes earlier than captive plants. CMOs are expected to fit new processes into existing plants, whereas captive plants are often purpose built for a particular product. Thus, a decline in the appearance of an

issue with CMOs suggests that they have developed and implemented solutions that resolve the issue.

Majority of CMOs Considering High Capacity Resins

CMOs adoption patterns, in many ways, are a leading indicator of which technologies will be adopted by the industry as a whole. The technologies that resolve downstream processing capacity constraints may be used first at CMOs. Our report already shows that CMOs and biodevelopers are experiencing different levels of capacity constraints, and have taken distinctive measures to improve their situations. When we asked respondents to identify the new downstream technologies they are currently considering (rather than have already investigated or implemented), we again found a significant level of disparity in the responses.

For CMOs, use of high capacity resins is the clear leader, with twothirds considering this technology this year. A majority are also looking at single-use disposable TFF membranes (55.6%), while a significant proportion are considering disposable UF systems and continuous purification systems (both at 44.4%).

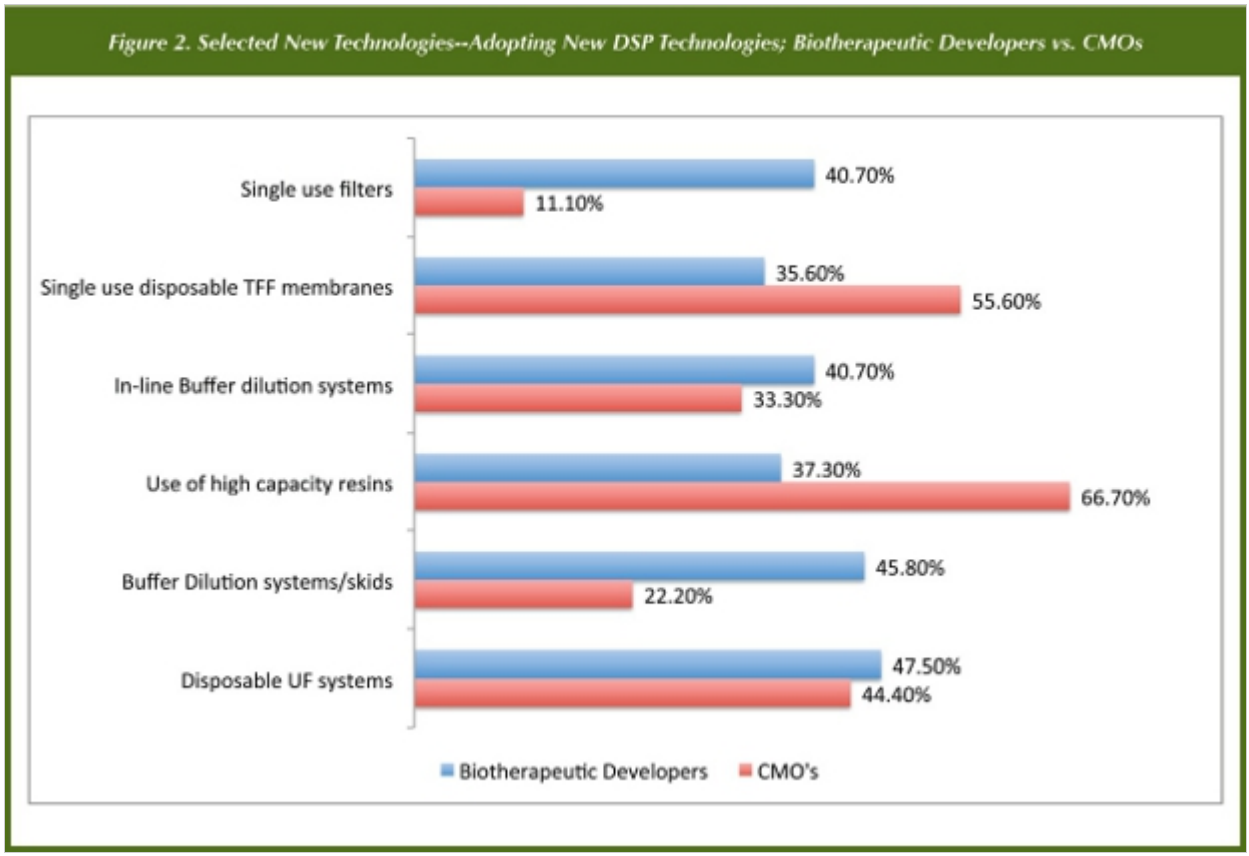
For the most part, these technologies are as actively evaluated or considered by many biodevelopers. Just 37.3% are considering use of high capacity resins, and 35.6% are looking at single-use disposable TFF membranes.

The leading new downstream processing technology considered by biodevelopers is disposable UF systems, cited by 47.5% of respondents (roughly on par with the 44.4% of CMOs also looking at this technology). The next-most popular technologies for biodevelopers barely resonate with CMOs: buffer dilution systems/skids (45.8% of biodevelopers vs. 22.2% of CMOs); and single-use filters (40.7% of biodevelopers vs. 11.1% of CMOs). There is more agreement on the potential for in-line buffer dilution systems (40.7% and 33.3%, respectively).

It is interesting to note that despite many differences in approaches, CMOs and biodevelopers seem to be relatively equal in terms of their active consideration of disposable UF systems. A closer look at our data reveals one potential reason why both groups are focusing some attention on this technology.

Impact of Purification Steps

When we examined the impact that specific purification steps are having over time on overall capacity, we found that ultrafiltration steps are becoming more challenging. This year, 8% of industry respondents (CMOs and biodevelopers combined) said that ultrafiltration steps are creating “significant” or “severe” constraints at their facilities. This is a noticeable step up from a range of 4.4%-6.6% of respondents from 2008 through 2011. In fact, this was the only purification step in which a greater proportion of respondents this year attributed at least “significant” capacity constraints than in any of the 4 years prior. For comparison’s sake, 10.2% this year said that depth filtration steps are contributing to at least “significant” capacity problems (against a high of 12.7% in 2008), and 17.5% said the same about chromatography steps (compared to a high of 21.6% in 2009).



Clearly, despite ultrafiltration steps contributing to the least amount of “serious” or “significant” problems, the trend is in a negative direction, while the trend for the other steps is either positive or stable. Indeed, it appears to be that respondents are upgrading the severity of the problems they encounter from UF purification steps: the uptick in those reporting “significant” or “severe” problems seems to be coming from the group who last year who were reporting “moderate” or “minor” constraints. Given the attention being paid to disposable UF systems by both CMOs and biodevelopers, this seems to be an issue that is affecting them on a similar level.

What’s to Come?

Data from our report suggests that while downstream bottlenecks may be abating – particularly for CMOs – the industry is by no means out of the woods when it comes to this issue. Even though only one-quarter of CMOs report “severe” or “significant” capacity constraints today, another quarter say they expect them within the next 12 months. This indicates that while a majority of CMOs have taken steps to fight this problem through process optimization, and adoption of solutions such as membrane-based filtration technologies, they are likely projecting still greater upstream productivity that will put additional pressure on their downstream operations. With new technologies emerging, and under serious consideration by CMOs, it will be interesting to track which technologies are ultimately adopted, and to what extent CMOs are able to continue their recent success in lessening the impact of downstream purification.

References:

1. *9th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, April 2012, Rockville, MD www. bioplanassociates.com*

Survey Methodology: The 2012 Ninth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production in the series of annual evaluations by BioPlan Associates, Inc. yields a composite view and trend analysis from 302 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations

(CMOs) in 29 countries. The methodology also included over 185 direct suppliers of materials, services and equipment to this industry. This year's survey covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time, and assesses differences in the world's major markets in the U.S. and Europe.

Eric S. Langer is president and managing partner at BioPlan Associates, Inc., a biotechnology and life sciences marketing research and publishing firm established in Rockville, MD in 1989. He is editor of numerous studies, including "Biopharmaceutical Technology in China," "Advances in Large-scale Biopharmaceutical Manufacturing", and many other industry reports. elanger@bioplanassociates.com 301-921-5979 www.bioplanassociates.com

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