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Are Downstream Problems Finally Being Resolved?

Key problem areas decline, but industry continues to demand new DSP technologies

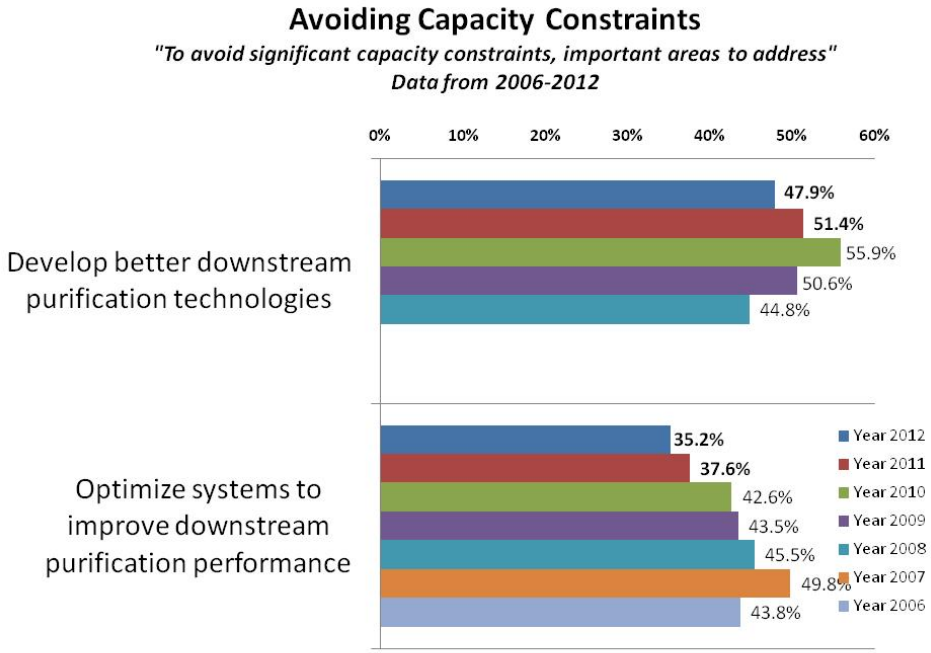
Downstream purification problems for biomanufacturers finally appear to be improving. Over the past six years, the demand for better purification has topped the list of biomanufacturing areas in need of fixing. This year, however, it appears that purification woes, though still a hot topic, are cooling off.

After seven years of measuring the impact on capacity of specific biomanufacturing operations, preliminary data from our *9th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production[1]* shows that both activities associated with optimizing internal DSP processes, as well as evaluation of external, novel DSP technologies is holding steady or declining. This is likely the result of incremental improvements in process design, and the on-going impact of excess industry capacity. Despite these incremental improvements, downstream processing remains a top area of concern.

This year, as last, 'Develop better downstream purification technologies' took the top spot, with (47.9% this year vs 51.4% in 2011). Each year, the survey reports trends among ~375 biomanufacturers. On the rise this year is the demand for vendors to 'develop more cost effective disposables,' (46.5 this year, vs 39.5% last). Some of this demand for single use devices is for less expensive filtration, and for single use chromatography columns. Continuing the trend over the past six years, internal focus on improving downstream productivity may be paying off, as the factor, '*Optimize systems to improve downstream purification performance*' once again declined. This year, just 35.2% of respondents expect internal DSP tweaking to reduce capacity problems, compared to nearly 50% of the industry in 2007.

We also compare responses from contract manufacturing organizations (CMOs) and biotherapeutic developers. For the past 7 years, downstream issues have taken the top spots among biotherapeutic developers in terms of areas that need fixing. Among CMOs, however, the need for better purification technologies is even more acute: Last year, for example, nearly two-thirds (62.4%) of CMOs identified this area, making it far and away the leading area for upgrades. Not surprisingly, CMOs are very interested in better, more cost-effective single use (disposable) devices. Nearly 50% of CMOs are looking for disposable options, and this goes for downstream technologies, as well.

Figure 2: Selected Areas to Address to Avoid Capacity Constraints, 2006-2012



Source: 9th Annual Report and Survey of Biopharmaceutical Manufacturing, Preliminary Data, Report release date: April 2012, BioPlan Associates, Inc. www.bioplanassociates.com

FOR LAYOUT

Answer Options	Year 2012	Year 2011	Year 2010	Year 2009	Year 2008	Year 2007	Year 2006
Develop better downstream purification technologies	47.9%	51.4%	55.9%	50.6%	44.8%		
Optimize systems to improve downstream purification performance	35.2%	37.6%	42.6%	43.5%	45.5%	49.8%	43.8%

These data suggest that the impact on capacity over the past few years is declining. *According to Dr. B. Bloggs, at ____, (Longmont CO), "We have experienced an improvement in our downstream processing as a result of relatively intense focus on individual process steps, and incremental improvements in how our existing equipment is being used." [Quote to be confirmed]*

Downstream Advances Contributing to Capacity Improvement

Our annual study sought to identify the magnitude of bottlenecks created by downstream processing problems, and determine whether advances in DSP were affecting overall capacity. Currently, 68.5% of industry respondents believe their facility is experiencing at least some degree of capacity bottleneck as a result of downstream processes (2011 data). This represents a marked decrease from 2009 when 74.5% held DSP responsible for

bottlenecks. Overall, the impact of downstream bottlenecks is leveling off: in 2011, about 20% of respondents indicated that they expected no bottlenecks, only a slight increase from the 17% in 2009.

Chromatography Problems Remain a Factor

Chromatography operations take a leading role in downstream processing. These steps tend to be expensive, and challenging to optimize, implement and operate. Capacity constraints resulting from chromatography columns and related purification steps appear to be slightly improving. This year, in 2012, just 13.7% of biomanufacturers reported "significant" or "severe" constraints at their facilities owing to column chromatography (from 14% in 2011, and 20.2% in 2008).

While chromatography resins have benefited in recent years from improved dynamic binding capacity, improvements to chromatography operations have not kept pace with the dramatic improvements in bioreactor expression levels. Indeed, while our data suggests that compared to previous years, the impact of chromatography and other downstream operations pose less of a constraint, relative to the other operations, chromatography is still the major hurdle in downstream processing.

Industry Begins Move to Alternatives

With downstream purification issues clearly still impacting capacity, respondents appear willing to change the way they approach their production processes. According to Dr. Scott Wheelwright, President of Strategic Manufacturing Worldwide, manufacturers are seeking lower cost operations by "deleting steps, switching to lower cost resins (such as substituting ion exchange for protein A), and increasing the use of membrane processes." [2]

Indeed, this year, more than 3 in 5 respondents said they were at least considering alternatives to protein A to reduce costs in new production processes, up from 53.2% last year but relatively consistent with 2009 attitudes (59.2%). Although the proportion considering alternatives to protein A for existing production units has dropped from 27.1% in 2009 to 22.1% this year, our data suggests that some of those respondents may have moved from consideration of alternatives to action. This year, 15.7% of respondents said they will actually be moving away from protein A for existing scale-up or commercial projects over the next 12 months. This compares to 7.85% last year and 12.6% in 2009 who stated the same.

Better Technologies on the Way

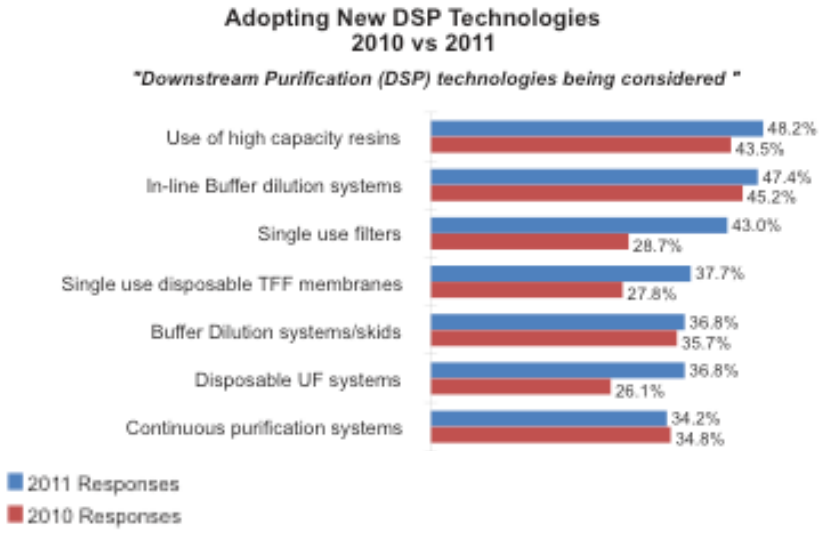
Numerous new technologies are being advanced, and many end-users are actively evaluating their applicability. We are seeing improvements in purification technology

that are likely to continue to move the industry away from capacity problems, such as membrane separation technologies and greater capacity binding resins.

This year, respondents indicted 21 different technologies that are being considered as alternative new DSP solutions. We evaluated the percentage of facilities considering new downstream processing technologies, specifically we asked, *"Which new downstream purification (DSP) technologies are you actively considering, to address capacity bottlenecks?"* Most of the novel downstream processing technologies that were being evaluated in 2010 are being considered by an even larger percentage of respondents today.

For example, we find a strong, and steadily growing interest in high capacity resins (48.2% in 2011 vs 43.5% in 2010), and in-line buffer dilution systems (47.4% vs. 45.2%). In addition, single use filters are growing rapidly (43% vs. 28.7%), as are disposable UF systems (36.8% vs 26.1%). A growing number are considering using filters instead of resin chromatography (29.8% vs. 23.5%) or seeking alternatives to chromatography (28.9% vs. 23.5%), although the most rapid growth has been in the consideration of single use-prepacked columns, which grew from only 1% of respondents last year to 31.6% in 2011.

Figure 3: Selected New Downstream Processing Solutions: 2010-2011



Source: 8th Annual Report and Survey of Biopharmaceutical Manufacturing, April 2011, BioPlan Associates, Inc. www.bioplanassociates.com

Drug innovators vs CMOs: CMOs typically undertake a greater number of manufacturing projects and campaigns and are often more capable of assessing new technologies in a

greater number of situations. As such, CMOs showed greater interest in emerging technologies such as:

- In-line buffer dilution systems (65% CMOs vs. 44.1% developers);
- Single use filters (55% CMOs vs. 40.9% developers);
- Buffer dilution systems/skids (45% CMOs vs. 35.5% developers);
- Continuous purification systems (40.0% CMOs vs 33.3% developers); and
- Membrane technologies (30.0% CMOs vs 23.7% developers)

Drug innovators/developers indicated they were more willing to assess the following technologies:

- Use of high capacity resins (49.5% developers vs. 45% CMOs);
- Centrifugation (31.2% developers vs. 20% CMOs); and
- Disposable UF systems (37.6% developers vs. 35% CMOs).

US vs European biomanufacturers: On almost every new downstream technology area, a larger proportion of US respondents reported looking at new technologies vs Europeans. For example, more US respondents are evaluating use of high capacity resins (50.7% US vs. 42.4% W Europe), single use filters (47.8% vs. 39.3%), single use TFF membranes (46.4% vs. 30.3%), and centrifugation (33.3% vs. 18.2%). The only areas in which Western Europeans display a clear preference is continuous purification systems (48.5% W Europe vs. 29% US) and moving beds (18.2% vs. 11.6%). This is not unexpected. US respondents' greater propensity to examining new technologies mirrors the increased impact they are feeling from downstream processing: this year, 78.6% of US respondents said they were experiencing at least minor downstream bottleneck problems, compared to just 54% of Western European respondents. Indeed, Western European respondents were almost twice as likely as their US respondents to report no bottlenecks at all (27% vs. 14.7%).

Conclusion

Novel downstream technologies are emerging and many in the industry are assessing potential opportunities for more efficient manufacturing. As these new technologies make it into clinical and, ultimately, commercial scale manufacturing, we expect to see a more rapid adoption rate. Especially as the new downstream technologies, using novel materials, find greater regulatory acceptance. In previous studies we attempted to evaluate respondents' awareness in alternative novel DSP technologies. In those studies we found relatively few respondents with knowledge of options beyond membrane technologies. Further, relatively few biomanufacturers had opinions about which downstream technologies would be likely to yield major improvements.

Our data suggest this is changing relatively quickly, especially in areas where capacity constraints are impacting costs and productivity. Single use devices, such as disposable columns and media are just one area of future improvements. According to Dr. Stefan Schmidt, CSO, ERA Biotech, "single use and disposable chromatography units will be the most important trend in the next 5 years. In that timeframe, this will be adopted by the majority of manufacturers, thus impacting price and efficiency."

This is a highly regulated industry, and many biomanufacturers approach new technologies slowly. There may be a relatively long learning curve as the industry evaluates and adopts alternative technologies. Even so, our data indicate that the conditions are ripe, and the industry is actively dealing with DSP problems both through increment improvements, and by evaluating novel alternatives to current downstream technologies.

References:

1. 8th Annual *Report and Survey of Biopharmaceutical Manufacturing Capacity and Production: A Survey of Biotherapeutic Developers and Contract Manufacturing Organizations*, BioPlan Associates, April 2011, 490 pages.

2. 9th Annual *Report and Survey of Biopharmaceutical Manufacturing Capacity and Production:* BioPlan Associates, Preliminary data; release date April 2012.

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Survey Methodology: The 2011 eighth 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 352 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 31 countries. The methodology also encompassed an additional 186 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.