10 years of biomanufacturing: Industry maturity shown in the shifts toward process improvement

Bioprocess International

Anne Montgomery

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The biopharmaceutical industry is emerging from four years of economic challenge in a very healthy state. Process improvements over the past decade have played a major role in keeping the industry healthy. Although earlier this decade most companies were more concerned about quickly getting their drug products to market than about strategically controlling costs of operations, according to our recent study, this has changed in most areas of manufacturing.

In fact, although this year companies reporting overall increases in every budget area surveyed, the largest increases continue to be in areas that affect process improvement, and productivity.

This year's *9th Annual Report and Survey of Biopharmaceutical* Manufacturers from BioPlan Associates, with responses from 302 bioprocessing professionals in 29 countries, as well as 185 suppliers to the industry, reflects major advances in bioprocess improvements over the past decade.

To get an idea of how far the industry has progressed, consider the following J.P. Morgan "*State of Biologics Manufacturing"* analysis:

> *"Demand for [biopharmaceutical] manufacturing capacity will exceed current capacity by a factor of four by 2005….We may also see delays in the development and commercialization of some products due to a lack of adequate clinical and commercial supply…Considering current manufacturing economics, products that must be chronically dosed at levels greater than 5 mg/kg/week may not be commercially viable unless major advances in biologics manufacturing processes are made (2)."*

Such analyses exemplified the widespread concerns that persisted a decade ago that the biopharmaceutical industry was facing an impending crisis of inadequate manufacturing capacity. These concerns were prompted by the anticipated success of more monoclonal antibodies reaching the market, with these products requiring repeated high doses (lots of protein). Now, a decade later, we can see that the widely-forecast industry capacity crunch did not develop, in part, because process improvements both bailed out the industry and fostered growth.

In our study this year, when asked about expected capacity constraints at their facility within 5 years (2017), only 6.8% of respondents reported likely severe constraints, while 51.1% reported

either no constraints, or just minor problems. Trends in expectations for capacity constrains over the past nine years have continued to point toward process improvement and de-bottlenecking. These optimistic projections should also be considered in context with the expected bioprocess expansions being planned. Respondents also reporting an average expected 51.0% increase in mammalian over the next five years, and 35.8% in microbial systems' production. In fact, 23.8% of respondents expected to double their mammalian production capacity in the next five years.

What appears to be restraining the industry today, compared with 10 years ago, typically involves unit operations. For example, when asked about key areas to be addressed to avoid capacity constraints, 57.5% cited the need for better downstream purification technologies and half (49.7%) cited need for more cost-effective single-use equipment.

In fact, recombinant monoclonal antibodies are now the industry's most important and profitable products, with annual sales about $45 billion, larger than the entire biopharmaceutical market a decade ago. And the industry has a very healthy pipeline of products in development. For example, the industry now reports over 900 biopharmaceuticals in the U.S.-targeted pipeline, including 300 monoclonal antibodies (4). And economics now actually favor biopharmaceuticals over small molecule drugs, with about 40% of all pharmaceuticals in R&D now being biopharmaceuticals and this percentage increasing as the largest companies increase investments in biopharmaceuticals vs. drugs. This situation would have been unimaginable just 10 years ago. According to our analysis at www.top1000bio.com, there are now over 1,000 facilities worldwide manufacturing biopharmaceuticals at, or near, clinical scale (5).

Advances Contributing to Process Improvements

The past decade's process improvements have made the biopharmaceutical industry more efficient, productive, flexible and profitable. These advances have resulted in bioprocessing improving by perhaps orders of magnitude in the past decade. Major trends that have contributed to improved bioprocessing over the past decade include:

a) *Expression systems:* Even legacy expression systems from the 1980/90s, such as CHO, yeasts and E. coli, have experienced major improvements in process yield.(6) Just 10 years ago, commercial mammalian cell culture yields of one or at most several 100 mg/L were considered good, while commercial manufacturing yields of several grams/L are now commonplace, and yields over 10 grams/L are expected in coming years. Our survey data now show that the average commercial monoclonal antibody (mAb) production yield is now 2.4 grams/L, while yield for late-stage clinical manufacture is 2.85 grams/L.
b) *Mammalian cell culture attains dominance:* Mammalian expression systems use now thoroughly dominates the industry. Classic microbial, including E. coli and yeasts, systems are being displaced as companies increasingly adopt mammalian as their

preferred in-house systems, and as costs for manufacture in mammalian systems increasingly match those of simpler microbial systems.

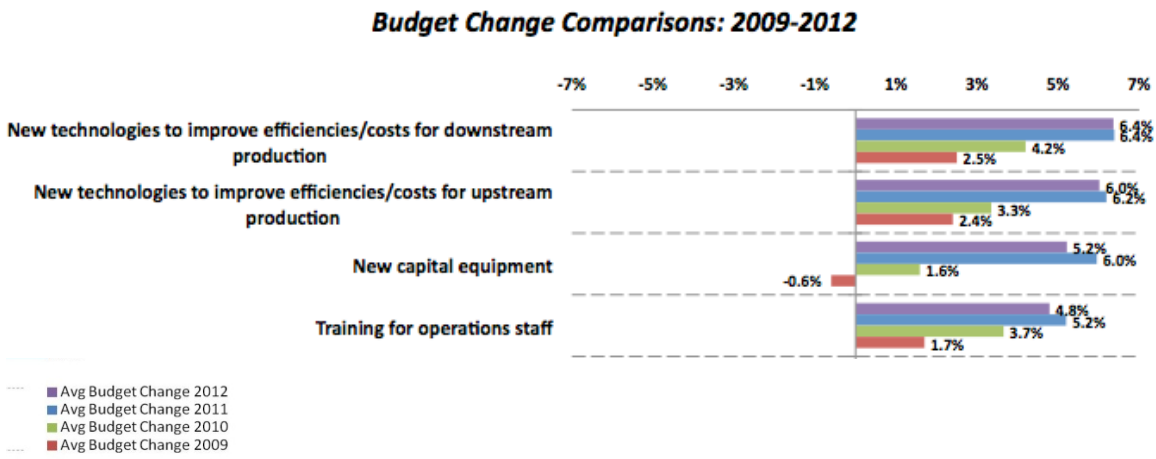
c) *Cell lines:* Cell line engineering and product-specific expression optimization are now rather common, supporting higher yields and better product quality.
d) *Single-use/disposable systems:* Preclinical, clinical and other pre-commercial manufacturing is now dominated by single-use/disposable equipment; and single-use equipment is now on the verge of being adopted for commercial manufacture (3). This includes trains of 1-2000 L single-use bioreactors expected be used rather than very large, e.g., ≥10,000 L, fixed stainless steel bioreactors. Overall, our survey respondents now report spending an average of over $250,000 per facility just for single-use bioreactors.
e) *Sensors, automation, process control:* Major advances have been made in these areas, further contributing to process and quality improvements.
f) *Bioprocess modeling:* Manufacturing systems can now be modeled, greatly facilitating process and facilities design and the identification of bottlenecks.

Improved bioprocessing will increasingly support growth in the biopharmaceutical industry. The industry will expand greatly in coming years, particularly in terms of numbers of marketed products and manufacturers, as biosimilars (and biobetters and biogenerics) enter the world markets. For example, over 900 biosimilars/biobetters are in the development pipeline and we can expect 5-10 or even more follow-on products entering the market for every currently successful biopharmaceutical coming off patent. With biosimilars expected to compete on the basis of price, particularly with each other, their developers must adopt highly cost-effective technology to keep manufacturing costs low, with many adopting and pushing the state-of-the-art. New bioprocessing technologies, such as the industrialization of plant expression systems, will enable the manufacture of products at costs as low as pennies per dose (7).

Some of these approaches and enabling technologies have been in development for years. For example, Brian Hatch, Consultant Biologist, at Eli Lilly & Co., notes, “The continuation of "platform" approaches to product development…will begin to really bear fruit in the coming decade…Bioprocesses developed with a "platform" approach…actually cost less to produce, as they utilize existing facilities with the capitol costs diluted among multiple products.”

Budgets are one way to evaluate how companies are actively investing in process improvement. In our study, we measured changes in 12 budget areas this year. Figure 1 shows selected industry responses from 2009 to 2012 regarding budgets for new technologies and equipment. Increases in investments in both new upstream and downstream technologies were reported this year, and there is an overall trend indicating future increased investments in process improvements. Overall, developers and CMOs are expecting a 6.4% increase in this year’s budgets for new technologies to improve downstream production, and a slightly smaller 6% increase for innovative products to improve upstream production.

Fig 1 Selected Results: Budget Trends, 2009 - 2012

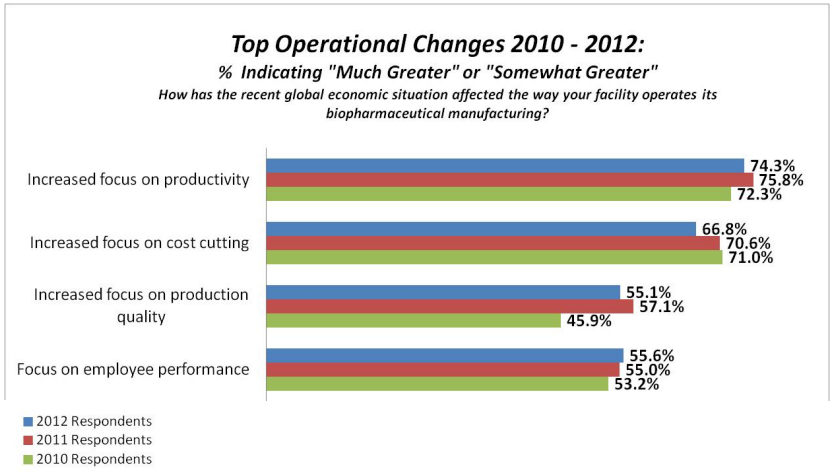


Source: 9th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, April 2012, BioPlan Associates, Rockville, MD

Process Improvement Areas

This year, again, we found that companies are continuing to build their manufacturing capabilities, but are doing so more strategically, with process improvement a major area where companies are applying resources. In fact, 74.3% of biopharmaceutical manufacturers reported focusing on 'productivity' to a 'Much Greater' or 'Somewhat Greater' extent, with this ranking number one and even beating "increased focus on cost savings" (66.9%) It is very significant that industry is now more concerned with improving productivity, rather than cost-savings and cuts. The focus on productivity was particularly stronger among U.S. (77.1%) vs. European (66.0%) respondents.

Fig 2 Selected Results: Operational Changes, 2010 - 2012



Source: 9th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, April 2012, BioPlan Associates, Rockville, MD

Separately, when asked *"How much have each of the following improved biomanufacturing performance at your facility over the past 12 months?,"* the largest portion, 72.6%, cited *overall better control of processes*, followed by *improved downstream operations*, and *use of single use devices* (both cited by 67.2%). Following was *improved upstream operations.* This suggests that the industry continues to place a high priority on process control and improvements to increase its manufacturing performance**.** When comparing the responses from US/European vs. rest-of-the-world (ROW) companies, ROW biomanufacturers are devoting their attention and seeing the most improvements in more basic aspects of process control and development, while U.S., and European companies report improvements in more specific areas and, particularly, those involving optimization rather than bioprocessing basic operations. This indicates that the ROW is actively catching up with manufacturers in US and European countries.

Industry Capacity Utilization in Equilibrium

According to the 9th Annual Survey, industry utilization and the supply and demand for bioprocessing capacity appear to currently be in a healthy state of equilibrium, with no major problems, such as products not being manufactured to due to lack of capacity, and no major complaints of excess capacity, as indicating by CMOs reporting steady and growing demand. In recent years, capacity utilization has remained flat, unchanged, for mammalian cell culture systems (at around 61-62%), while there have been decreases for microbial, including yeast, fermentation, with microbial fermentation utilization falling for the first time below 50%. Since 2004, capacity utilization for mammalian cell culture systems has dropped significantly, 14.7 percentage points from 76.4% in 2004 to 61.7% this year; while over the past six years, mammalian cell capacity utilization has flattened out, changing by at most by only a few percentage points since 2006. This year's data show that developers are operating at higher mammalian system utilization rates than CMOs, while CMOs are operating at higher rates than developers for all other systems.

Conclusions

It can be seen that the biopharmaceutical industry has experienced significant, even radical, overall process improvements in the past decade. These have contributed to the industry's health, including avoiding severe capacity constraints and surviving recent years' economic problems, with there currently being a healthy balance of bioprocessing supply and demand and the industry poised for even more process improvement-driven growth. A number of industry participants have noted, however, that the current advances are unlikely to remain static. For example, Sourav Kundu, Director, Process Development, at Amgen notes, "I see is the need to shorten the development and commercialization timelines…The industry will have to respond through increasing efficiency, performing risk based prioritization of tasks, developing comprehensive compliance programs all the way back to development and technological advancement." To achieve continued future improvements will require the concerted efforts of both suppliers and drug developers.

References:

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About the Author:

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

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 encompassed an additional 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.

NOTE: IMPORTANT TO INCLUDE THIS SO READERS UNDERSTAND HOW THE STUDY WAS CONDUCTED