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**Title: Innovation in Biopharmaceutical Manufacturing Advances:  
*Industry Wants More Innovation; Can Suppliers Continue to Meet Customer Needs?***

The biopharmaceutical industry has developed a voracious appetite for new technologies that increase productivity and improve performance. This year's 9<sup>th</sup> *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 a number of innovations and trends in bioprocessing in recent years and over the past decade. Partly the result of the recent global economic situation, our analysis shows that biopharmaceutical companies are increasingly turning toward their vendors for better ways to manufacture.

The biopharmaceutical industry has survived recent years' worldwide economic problems. As industry-wide revenue for biologics approaches \$150 billion, biomanufacturers are focusing on ways to improve performance. This year's study shows these companies are increasing budgets in every single category surveyed, but the biggest increases are going toward new technologies that improve productivity and performance. This will become increasingly critical with the coming of biosimilars, where the number of biopharmaceutical manufacturers and products will rapidly increase, with 5-10 or possibly more biosimilars or bio-betters likely for each successful established biopharmaceutical product (3). Our study indicates that vendors are aware, and are meeting the challenge. Trends in innovations in bioprocessing, including ever-increasing yields, have played a major role in allowing the industry to remain healthy and growing, with productivity constantly increasing.

**Industry Wants More Bioprocessing Innovations**

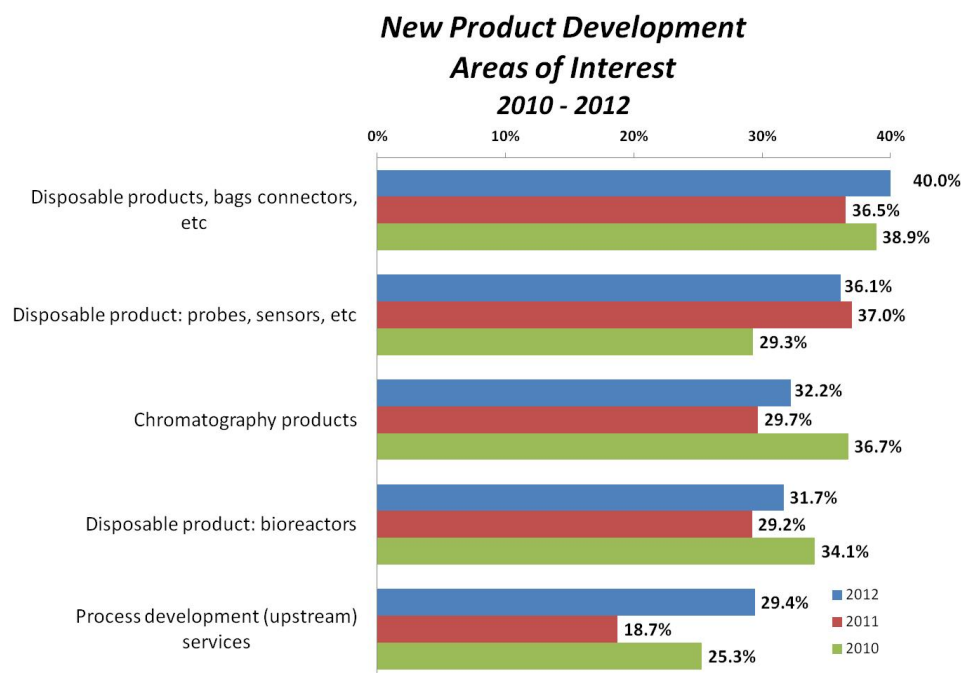
This year when asked about average budget changes from 2009-2012, those surveyed reported the highest budget increases were for "New technologies to improve efficiencies/costs for downstream production," with an average 6.4% increase reported, and "New technologies to improve efficiencies/costs for upstream production," with an average 6.0% increase reported. It is significant that survey data indicate that increased productivity, rather than cost-cutting, is now the leading concern to industry. The industry has clearly avoided the death spiral of constant cost-cutting, and with increased yields other improvements in recent years, has enjoyed steady increases in productivity and cost-savings.

But industry clearly continues to want and expect more bioprocessing innovations from its suppliers, as shown in Figure 1. This particularly includes improved single-use/disposable

bioprocessing systems. In terms of interests in new products and their development, the largest portion of respondents this year cited disposable bags and connectors (40.0%), followed by probes, sensors, etc. (36.1%), chromatography products (32.2%), bioreactors (31.7%), and purification products (28.9%). Note, much or most of the interest in improved sensors, bioreactor, purification and other equipment involve single-use. In services, process development upstream topped the desired services (29.4%). Stainless steel equipment remained near the bottom of the list, with only 10% indicating desiring new products developed in this area. Areas of interest demanded by industry end users as requiring improved technology this year included:

- Disposable products, bags connectors
- Disposable product: probes, sensors
- Chromatography products
- Disposable product: bioreactors
- Process development (upstream) services
- Disposable product: purification
- Process development (downstream) services
- Analytical assays
- Analytical development
- Separation products, general
- Process development for formulation
- Control systems
- Cell line services
- Disposable product: controllers
- Validation services
- Design of experiments
- Stainless steel equipment
- Reagents/supplements

**Fig 1: Selected Areas, New Product Areas of Interest, 2010 - 2012**



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

**DATA FOR YOUR LAYOUT PEOPLE**

	2012	2011	2010
Disposable products, bags connectors, etc	40.0%	36.5%	38.9%
Disposable product: probes, sensors, etc	36.1%	37.0%	29.3%
Chromatography products	32.2%	29.7%	36.7%
Disposable product: bioreactors	31.7%	29.2%	34.1%
Process development (upstream) services	29.4%	18.7%	25.3%
Disposable product: purification	28.9%	37.9%	34.9%

The industry has developed an interest in single-use systems, and is seeking improvements. According to the study, a common cause for dissatisfaction with current single-use bioreactors, liners and other equipment is that they are not robust enough. For example, single-use equipment is still not adaptable to the more extreme mixing, heat and other conditions involved with most microbial (vs. mammalian cell), e.g., E. coli and yeast, culture.

When asked to rate the factors responsible for creating improvements in bioprocessing in the past 12 months, the largest portion cited “overall better control of processes” (72.6%), followed by “improved downstream production operations, and use of disposable/single-use devices. Overall, the areas most cited as having improved performance within the past year involved process and production control and operations.

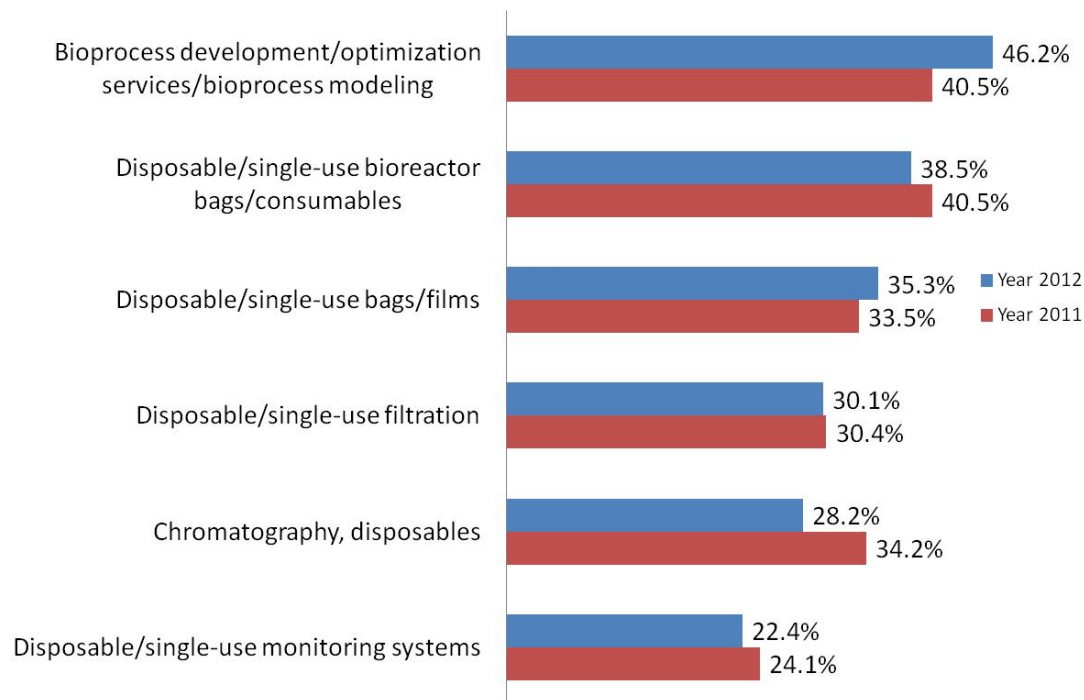
### **Vendors Are Responding With R&D**

Our annual global study includes a separate module for industry vendor professionals, with 185 participating. To evaluate how well vendors’ R&D match industry needs, we asked about budget changes in 2012. Vendor respondents reported an average increase of 1.9% in basic R&D for product development, 2.4% for hiring new staff, sales budgets up 4.3%, and capital equipment purchases up 3.4%. It is highly significant that vendor budgets, like those of developers/manufacturers, have increased this year in every area surveyed.

Survey data show that vendors are concentrating much of their R&D on improved and new single-use equipment, including responding to industry demands. Areas where vendors report developing new technologies or products are shown in Figure 2. The largest portion, near half (46.2%), of vendors report working on bioprocess development/optimization services/bioprocess modeling, followed by disposable/single-use bioreactor bags/consumables (38.5%) and a host of other specific areas of single-use equipment. New bioprocessing-related services are coming, with 40.5% of vendors indicating that “Bioprocess development services,” including bioprocess design and optimization, is the next New Product Development area, followed by disposable chromatography with 34.2%. Also, vendor expectations for financial performance are up this year, with a nearly three-quarters (74%) reporting expecting better performance in 2012 vs. 2011. So, vendors are continuing to both see and are supporting innovation and growth in the biopharmaceutical industry supply market.

**Fig 2: Selected Areas, Top 6 of 38 New Technologies Vendors Working on, 2010 – 2012**

**"Top NEW TECHNOLOGIES or NEW PRODUCT DEVELOPMENT areas your company is working on in biomanufacturing ?"**



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

**FOR YOUR LAYOUT**

	<b>2012</b>	<b>2011</b>
Bioprocess development/optimization services/bioprocess modeling	46.2%	40.5%
Disposable/single-use bioreactor bags/consumables	38.5%	40.5%
Disposable/single-use bags/films	35.3%	33.5%
Disposable/single-use filtration	30.1%	30.4%
Chromatography, disposables	28.2%	34.2%
Disposable/single-use monitoring systems	22.4%	24.1%

A few of the dozens of areas of R&D among vendors in 2012 include:

- *Animal-free media components*
- *Bioreactor control*
- *Chromatography, alternatives to Protein A*
- *Cell line optimization*
- *Sensors and probes*
- *Culture media optimization services*
- *Expression systems: Mammalian, CHO alternatives*
- *Monitoring systems*
- *Culture media supplements*
- *Controller systems*
- *Testing/assay services: Impurities detection*
- *Expression systems: Bacterial*
- *Expression systems and platforms*
- *Finishing: Lyophilization*
- *Testing/assay services: Raw materials testing/glycosylation analysis/ Viral clearance/Biosimilarity testing/Cell lines*
- *Finishing: Packaging materials*
- *Expression systems: Yeast/fungi*

## Bioprocessing Innovations and Trends

The biopharmaceutical industry has emerged from recent years of economic challenge in a healthy state, unlike many other industries. Improvements in bioprocessing over the past decade have played a major role in keeping the industry healthy and growing. The largest increases continue to be in areas that involve process improvement and productivity. A number of related 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 shown improvements in process yield.<sup>(2)</sup> Just 10 years ago, commercial mammalian cell culture yields of several 100 mg/L were considered good. In the future, yields over 10 grams/L are expected. Survey data now show that the average commercial-scale monoclonal antibody (mAb) production yield is significantly higher this year and has grown steadily over the past 5 years.
- b) *Mammalian cell culture attained 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 standardized in-house systems.
- c) *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).
- d) *Cell lines*: Cell line engineering and product-specific expression optimization are now rather common, supporting higher yields and better product quality. This includes an increasing number of high-yield cell lines going off patent and becoming more widely available.
- e) *Sensors, automation, process control*: Major advances have been made in these areas, further contributing to process and quality improvements. This included single-use sensors and sensors for new analytes.
- f) *Bioprocess modeling*: Manufacturing systems can now be modeled, greatly facilitating process and facilities design and the removal of bottlenecks.

Throughout the pharmaceutical industry, biopharmaceutical development is increasing, including at the expense of small molecule drugs. Biopharmaceuticals are now about 40% of products in the pipeline and increasing. Biopharmaceuticals, with their high specificity, have shown themselves to be more likely to gain approvals and once marketed are more profitable. Improvements in bioprocessing, including ever-increasing yields and other innovations, have played a large role in industry continuing to move into biopharmaceutical development.

A decade ago, the biopharmaceutical industry was facing a capacity threat, with dire predictions common. One respected analysis noted, “*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 (4)."* Inadequate manufacturing capacity was projected as success of more monoclonal antibodies reaching the market. Now, a decade later, it is clear that an industry-wide capacity crunch did not develop, in part, because process improvements, including the trends cited above, both bailed out the industry and fostered growth.

Now, contrary to pessimistic predictions, biopharmaceutical manufacturing capacity supply and demand are in a healthy equilibrium, with no major shortfalls, 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 demand. Survey data show that mammalian cell culture capacity utilization rates have leveled off in recent years and are now flat at 61%-62% in 2012 and recent years, down from 76.4% in 2004.

### **Conclusions:**

The biopharmaceutical industry, particularly all important bioprocessing and the manufacture of its products, has experienced significant increases in productivity. These have contributed to the industry surviving both a potentially serious or even fatal shortfall in manufacturing capacity and recent years' economic problems. With industry and supplier budgets up, more investment increasingly being devoted to biopharmaceutical (vs. drug) development, and with more future incremental and, perhaps, even revolutionary, e.g., comparable to single-use equipment, advances likely, the industry can expect continued growth and vitality.

### 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](mailto:elanger@bioplanassociates.com) 301-921-5979. [www.bioplanassociates.com](http://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*