Pharmaceutical Technology
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Issue Date: February 2012
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Biopharmaceutical Industry in 2012: Optimism on the Rise

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The biopharmaceutical industry is starting 2012 with good reason for optimism. Based on preliminary results from our 9th Annual Report and Survey of Biomanufacturing[1], both biologics manufacturers and their vendors are spending more, demanding better technologies, and expressing greater optimism than at any time in the 9 years we have been assessing this industry.

The healthcare segment, including biotechnology and pharmaceuticals, are enviably insulated from many of the economic problems faced by industries. In addition, this year our study finds substantial optimism, with a whopping 37.3% of suppliers to this industry indicating that their company did either 'better' or 'much better' than expected in 2011. Even more relevant, 49.4% expect they will do 'better" or 'much better' in 2012. This broad optimism appears to be translating to increased spending, stronger R&D budgets, more capital expenditures, and more hiring.

Industry Growth Rate

In the annual study we measure sales growth among vendors. This is a leading indicator of how the overall bio/pharma industry is doing, as vendor sales is based on derived demand for materials for production of biologics. If vendors are doing well, and are optimistic for the future, the biopharma industry is likely to follow. Supplier respondents indicated that, on average, sales growth to this industry is currently at around 14% annually. This compares to 13.0% in 2010, and 14.1% in 2007.

Biopharmas' Budget Trends

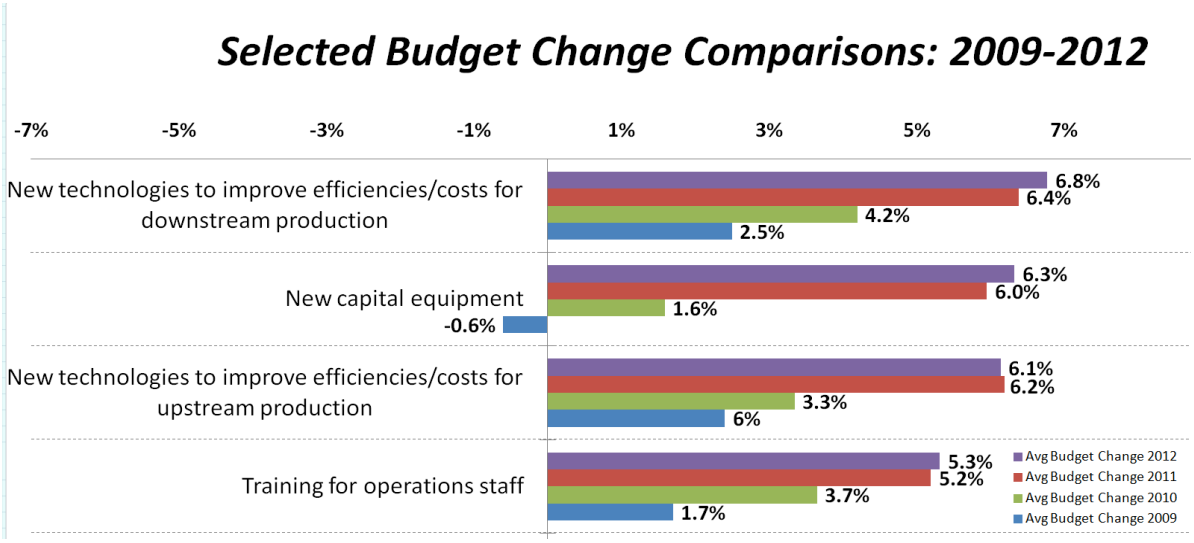
Budgets are also a good indicator of industry strength. And budget estimates for 2012 are, once again, up strongly for areas such as acquisition of new technologies, capital equipment, and training. In fact, early returns from respondents to BioPlan's 9*th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* [1] are projecting increases in all 12 areas measured in 2012, except for outsourcing. This budget bump clearly indicates a healthy continuation of investment and spending trends seen over the previous 3-4 years. Spending this year, in particular, is occurring in:

- New technology
- Capital equipment
- Process development and optimization.
- Personnel training and development

Across all departments, both budget trends and R&D/NPD efforts are leading indicators of economic constraints being loosening. This is especially evident in areas of expenditures that improve process performance. Our annual survey documents and analyzes how the rebounding and maturing biopharmaceutical industry is moving forward despite recent global economic challenges.

Our data suggest that the biopharmaceutical manufacturing sector may be even more recession-resistant than other healthcare areas. Budget estimates for 2012 are, once again, up strongly for acquisition of new technologies, capital equipment, and training. In fact, early returns from respondents to BioPlan's 9th *Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* [1] are projecting increases in all 12 areas measured in 2012, except for outsourcing. This budget bump clearly indicates a healthy continuation of investment and spending trends seen over the previous 3-4 years. (Fig. 1)

Fig 1: Selected Data: Average Change in Biomanufacturers' Budgets 2009-2012



Source: (Selected Data) Preliminary 9th Annual Report and Survey of Biopharmaceutical Manufacturing, Release Date: April 2012, BioPlan Associates, Inc. www.bioplanassociates.com

Macro Pharmaceutical Industry Trends

The trends above are, in large part, resulting from global shifts that continue to drive the bio/pharmaceutical industry. Below are broad industry trends we project in 2012.

Biopharmaceutical markets: The worldwide market for biopharmaceuticals continues to expand and at a more rapid rate than for pharmaceuticals in general. The world market for biopharmaceuticals is now about >$140 billion, with >$100 billion involving recombinant proteins/antibodies[2]. This includes over 430 biopharmaceuticals, including over 300 recombinant proteins/antibodies, currently approved in the U.S. and/or Europe. The biopharmaceutical market has been and is expected to continue to grow about 15%-18% annually, definitely a very healthy rate considering the state of the world's economy. It is

this rather steady overall growth rate that is driving much current investment in biopharmaceutical R&D.

Biopharmaceutical Approvals: Despite increasing biopharmaceutical sales, the number and rate of biopharmaceutical approvals in the U.S. has been relatively poor in the past few years (12 biopharmaceuticals entering the U.S. market in 2011). The 2011 approvals were even fewer in number than the relatively poor results in 2010 and 2009, (see www.biopharma.com/approvals_2011.html). This weak showing for biopharmaceuticals is in contrast with FDA reporting in November near record overall *pharmaceutical* approvals. The 2011 FDA biopharmaceutical approvals are listed in Table 1.

Table 1. FDA Full Biopharmaceutical Approvals in 2011**

Product	Company	Date	Indication
VEGF Trap, rDNA (Eylea)	Regeneron Pharmaceuticals Inc.	11/18/2011	age-related macular degeneration
Asparaginase/fungal (Erwinaze)*	EUSA Pharma Inc.	11/18/2011	acute lymphoblastic leukemia
Cord blood stem cells (Hemacord)	New York Blood Center, Inc.	11/10/2011	hematopoietic stem cell transplantation
CD30 mAb, rDNA--monomethyl auristatin E (Adcetris)*	Seattle Genetics, Inc	8/19/2011	Hodgkin's lymphoma
Scorpion Immunoglobulin F(ab)2 (Anascorp)*	Rare Disease Therapeutics Inc.	8/3/2011	scorpion stings
Fibroblasts, autologous (laViv)*	Fibrocell Science, Inc.	6/22/2011	nasolabial fold wrinkles (smile lines)
CTLA4-Ig, rDNA (Nulojix)*	Bristol-Myers Squibb	6/15/2011	kidney transplant rejection
Albumin, human (Kedbumin)*	Kedrion, S.p.A.	6/3/2011	multiple albumin supplementation indications
CTLA-4 Mab, rDNA/Medarex (Yervoy)*	Bristol-Myers Squibb	3/25/2011	melanoma
Adenovirus Type 4 and 7 Vaccine	Teva Pharmaceuticals	3/16/2011	vaccination of U.S. military personnel only
B-cell-activating factor Mab, rDNA (Benlysta)	Human Genome Sciences Inc.	3/9/2011	systemic lupus erythematosus
Factor XIII, human (Corifact)*	CSL Behring	2/17/2011	Factor XIII deficiency

*orphan designation
**Full BLAs excluded from consideration include biologics routinely manufactured by local/regional blood centers (e.g., Plasma, Red Blood Cells) and biologics approved as diagnostics, e.g., allergy test antigens.

Approval-related Innovation and Progress: The good news, particularly for patients and the health care system, is that 2011 FDA biopharmaceutical approvals involved much genuine innovation and advances, with nearly all products being approved for either new indications for which no treatments were previously available or for indications for which the last product approval was granted well over a decade ago. A record number (8) products were approved with orphan designation. Recombinant antibodies are a leading area for biopharmaceutical development. The large number of recombinant monoclonal antibody (and -like) products that many companies are relying on for future products may finally be starting to enter the market.

Approvals-related Problems: Largely due to the limited markets for these orphan and other approved products, 2011 U.S. approvals will not have as much industry economic impact as is likely needed in the long-term. Only 2 of the 12 approvals are expected to eventually reach blockbuster (>$1 billion/year) sales levels

Company and country approval trends: Illustrating the trend towards internationalization of manufacturing, a record number-four- (33%) of newly-approved U.S. biopharmaceuticals are manufactured outside the U.S. -- in the U.K., Germany, Mexico and Italy. This includes the first product manufactured in Latin America receiving FDA approval – a scorpion venom antitoxin (equine immunoglobulin F(ab) fragments), Anascorp, manufactured by a Mexican company.

Biosimilars (biobetters / biogenerics): With patents expiring for most established, successful, biopharmaceutical products, development of biosimilars is accelerating worldwide and will change the industry landscape. This will likely involve the entrance of many new manufacturers. Most of this activity is targeted to introducing these products in the U.S. and European markets, but many products are being developed by foreign companies, if only initially, for marketing in lesser-regulated domestic and international markets. There will likely be multiple biosimilars (and biobetters and biogenerics) for each currently successful biopharmaceutical, the number of biopharmaceuticals in the market and the number of biopharmaceutical manufacturing facilities will rapidly increase, perhaps doubling in the next 5 years. Many biosimilar/biobetter/biogeneric developers are adopting state-of-the-art expression systems and other manufacturing platforms. Biosimilars are competing with products being manufactured using 20-year-old technology. However, despite the technical advantages, drug innovators have long ago having paid-off manufacturing facilities. As such, biosimilar/biobetter/biogeneric developers will have to compete on the basis of price, and adopt aggressive cost-cutting technologies to effectively compete with the original biologic, and other biosimilar manufacturers. Although over a dozen biosimilars have received European Union (EU) approval, no biologics have yet been approved as biosimilars by US FDA. Our global facilities analysis, www.top1000bio.com [3], indicates that biosimilar/biobetter companies are present in virtually every biotechnology-capable region, including Latin America, Korea and other areas that have yet to be significantly involved in major Western biopharmaceutical markets. For example, among the nearly 400 organizations involved in biosimilars/biobetters development, over 30 companies are based in India and 14 in China.

Internationalization: The (bio)pharma industry continues to expand its presence worldwide, particularly in developing countries. With (bio)pharmaceutical markets growing faster in developing vs. developed countries, both vendors and drug developers recognize they cannot ignore these market opportunities. This trend toward internationalization is being driven by the need for prudent expansion of infrastructure and presence in new markets, and for opportunities for cost savings through outsourcing and off-shoring of activities, including R&D, which are traditionally performed in established high-tech regional clusters.

Internationalization of Manufacturing: Biopharmaceutical manufacturing is expanding and growing worldwide, with much of the growth involving new capacity

being added at existing foreign facilities and new entrants in developing countries pursuing biopharmaceutical development and manufacture. This is illustrated by BioPlan's *Top 1000 Global Biopharmaceutical Facilities Index* (www.top1000bio.com), which ranks over 1,000 global biopharmaceutical manufacturing facilities in terms of capacity, employment, and production. Although the U.S. and Western Europe remain the leaders in biopharmaceutical manufacturing capacity, over 37% of bioreactor capacity is now operating in other parts of the world, including nearly 10% in Japan and the Pacific Rim, 9% in China and over 8% in India.

Internationalization of R&D: Large international (Big Pharma) companies continue their expansion and or off-shoring of R&D. This included multiple companies announcing major, multi-$100 million, investments in new R&D centers in China, such as Merck Serono's $225 million, 4-year commitment in Beijing.

Demand for Local Production of Biologics: Companies are developing manufacturing strategies that include internationalization. Western product developer companies are joining with local companies. Local manufacture of vaccines, for example, contributes to the country's scientific/technical infrastructure, providing high-end jobs and lower product manufacturing costs and prices, and providing assurance of continued availability and price stability. Many foreign countries learned severe lessons several years ago when they could not purchase supplies of H1N1 influenza vaccines, even for government, military and essential staff vaccinations.

World Standardization of Manufacturing: As more biopharmaceutical manufacturing is performed worldwide, product developers are increasingly working to standardize their products, with this requiring standardization of their manufacturing processes. More companies are prudently planning for manufacturing in more facilities worldwide, including in developing countries increasingly desiring indigenous manufacturing. With more facilities expected to manufacture the same product, this is requiring companies to standardize and simplify their manufacturing processes, such that they can be reliably performed with consistent product produced even within facilities in lesser-developed counties.

Internationalization of Single-use Manufacturing: The trend towards more worldwide disseminated and standardized manufacturing is contributing to the increasing adoption of single-use/disposable bioprocessing equipment. Single-use systems allow processes and products to be developed, standardized and the same manufacturing systems shipped and installed at multiple facilities. Some companies, with major vaccine manufacturers among the leaders, are starting to think more in terms of selling full manufacturing and technology packages, including all needed equipment and technology transfer, not finished end-products, to foreign countries seeking local manufacture of vaccines for domestic distribution. Companies, such as GE and Biologics Modular, are developing fully modular, drop-in-place-type, equipment pre- or simply-installed, single-use

bioprocessing-based facilities largely aimed to this emerging market for pre-packaged biopharmaceutical manufacturing facilities.

Single-use Bioprocessing Technologies: In 2011, single-use/disposable bioprocessing systems further increased their dominance for the manufacture of biopharmaceuticals for pre-clinical R&D and clinical testing. In fact, one can now conclude that single-use systems dominant non-commercial-scale biopharmaceutical manufacturing in most regions. Single-use systems are increasingly being adopted for upstream manufacturing, such as adoption of single-use bioreactors and other upstream equipment. Despite dominance within pre-commercialization manufacturing segments, single-use systems remain a relatively small market, e.g., capturing only ≥10% of the overall bioreactor market, compared to fixed stainless steel equipment. Stainless steel remains the preference for commercial GMP manufacturing. In as short as 10 years (about how long its reported takes a biopharmaceutical to reach the market), about half or even more of new commercial biopharmaceutical manufacturing systems can be expected to be largely or fully single-use based.

Microbial manufacturing: Most industry attention in recent years, including blockbuster products and manufacturing technology development, has concentrated on mammalian cell culture-produced recombinant proteins. Mammalian cell culture capacity and facilities continue to dominate worldwide biopharmaceutical manufacturing, as shown by the *Top 1000 Global Biopharmaceutical Facilities Index[2]*. In contrast, microbial manufacturing remains relatively stable, with few new technologies, and few major bioprocessing equipment developers announcing novel devices. However, a confluence of trends is contributing to increased use of microbial (bacteria, yeasts, other fungi, etc.) host cells for recombinant proteins manufacture.

Outsourcing: Companies of all sizes worldwide continue to increase their outsourcing, particularly R&D and manufacturing. This includes increasing use of contract research organizations (CROs), particularly for high-throughput screening, other lead identification and toxicological studies, and use of contract manufacturing organizations (CROs) for preclinical, clinical and increasingly for commercial manufacturing. Based on the BioPlan annual survey of biopharmaceutical manufacturers, among 24 areas of outsourcing covered in the survey, the primary outsourced activities included product characterization testing, with 70% of biopharmaceutical companies outsourcing at least some of this activity. Other tasks now routinely outsourced include validation services (69%), toxicity testing (65%), analytical testing/bioassays (61.1%) and fill/finish operations (60.0%). Relatively few companies have outsourced all of their manufacturing, but nearly one-half of surveyed manufacturers expect to increase their budgets for biopharmaceutical CMO outsourcing.

The Economy: The worldwide economic downturn in recent years continues to impact the biopharmaceutical industry. Yet, with continuing growth in its underlying sales

revenue, the industry has managed to remain largely insulated from severe economic problems. Financial issues continue to affect most companies, including the major international (Big Pharma) companies that are the source for most biopharmaceutical R&D, with many having to deal with their most profitable products coming off patent. However, spurred by their interest in new, profitable products, biopharmaceutical R&D continues to increase. This includes a record amount, ≥$70 billion, being invested by the pharmaceutical industry in R&D, about 90% sponsored by the largest international companies, with an increasing number and percentage of pharmaceuticals in the development pipeline being biopharmaceuticals (vs. chemically-manufactured drugs). Thus, biopharmaceuticals provide more exclusivity, market monopolization and are increasingly attractive to the Big Pharma-type companies.

Mergers/Acquisitions: The trend for industry mergers, acquisitions and other corporate consolidation at all scales continued in 2011. This is particularly evident among large international companies that continue merging and purging – acquiring or merging companies, and then downsizing the merged company. Some companies, such as Merck, are moving from mergers/acquisitions in favor of more in-house and company-sponsored R&D. But the continuing trend of pharmaceutical company merging, combined with off-shoring of certain jobs and facilities, has resulted in relatively high (bio)pharmaceutical industry unemployment rates in the U.S.

Patent litigation: Patent infringement suits can be expected to increase, particularly as a large number of biosimilars (and biobetters and biogenerics) approach filing in the U.S. and other major markets. Major test cases, such as *Classen Immunotherapies, Inc. v. Biogen IDEC,* involve whether business methods patents include coverage of methods for determining the optimal dose of a therapeutic. Biopharmaceutical companies may soon need to consider yet another type of patent, in addition to those for composition-of-matter (e.g., sequences), formulations, uses, bioprocessing, reference standards, etc.

Summary

The bio/pharmaceutical industry is emerging from the current global economic situation into 2012 with a positive outlook. The industry is spending more, becoming more efficient, and, perhaps most importantly, expressing great optimism. With sales growth of between 14 and 18% this year, we will likely continue to see additional spending in new technology, capital equipment, and hiring.

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