

Pharmaceuticals: Cash Injection for Biologic Drugs

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Leading pharmaceutical and generic drug manufacturers are injecting dramatically more money into biologic drugs in a bid to push up profitability. As the market for biologic drugs--also known as bio- therapeutics--grows, the opportunities for contract manufacturing of biologics will grow, industry experts say.

the biotechnology industry raised \$55.8 billion in 2009 to fund start-up companies that are developing novel biotherapeutics, despite the meltdown of venture capital and volatile stock market conditions in the past 18 months. Cash entering the sector last year represented a hike of 85% compared with the \$30.1 billion raised in 2008, says G. Steven Burrill, head of industry investment and analyst group Burrill & Co. (San Francisco).

Sales from commercially sold biotech drugs are also on the rise. "We expect a decent growth rate of 15%-20%/year [in biologics] for the next few years." says Phil Sheibley, head of the North American pharma practice at Accenture. Sales of biologic drugs total \$85 billion/year. Sales of biogeneric drugs could triple in three years from \$17 billion in 2008, Sheibley says.

A portion of the new money coming into the sector is inevitably making its way through to contract manufacturers. The biologics contract manufacturing market is expected to grow "at an average compounded annual growth rate of 16% over the next five years and reach \$5.4 billion," says William Downey, president of HighTech Business Decisions (San Jose, CA), a market analyst group. "We estimate that the market in 2009 was roughly \$2.6 billion." Downey draws his figures from HighTech's annual report on the sector, which in 2009 featured interviews with 48 directors of biomanufacturing at pharma and biotech firms, and representatives of 29 biopharma contract manufacturing organizations (CMO).

However, "in the near term, supply has overtaken demand," Downey says. "For microbial fermentation and mammalian cell culture only, capacity is estimated at close to 1 million liters. Process yields have improved from new and better technologies. Expansion plans put in a few years ago also factored in excess supply. As a result, the industry capacity utilization rate trended down in 2009, and is in the mid-70% range. Supply and demand always self-adjusts, and the directors that we spoke with expect utilization to climb up to a healthy level in the mid-80% range in 2011. Capacity is expected to grow more than 40% over the next few years," Downey says.



Borgas: Demand dropped in 2009.



Sheibley: Contract sales will grow.



Maier: Boosting development capacity.

Some industry players interviewed by HighTech say the emergence of generic biologic drugs, also known as biosimilars, “will expand the market, which will create opportunities for smaller CMOs,” Downey says. The likely downside will be pricing pressure and a [negative] impact on profitability, Downey adds.

An increase in biologic drugs manufacture in Asia is another trend affecting contract manufacturers. “There is a good chance a big pharma player has a presence [in biologics] in Asia,” Sheibley says. “Some generics players are getting into biosimilars, and to spread the financial risk probably they will form alliances or become contract manufacturers.” Pfizer’s recent deal with Strides Arcolab (Bangalore, India) for the production of generic steroid injectables is an example of the shift of activity in biologics toward Asia. “It’s one small example but there is lots of activity in China and India,” Sheibley says. Manufacturing in Asia represented only a small percentage of the global market until recently, but the region is now responsible for manufacturing at least a double-digit percentage of total biologic drugs production, Sheibley says. “Overall, expect growth in contract manufacture,” he adds.

A number of key players in the Indian pharma industry have identified contract biopharma production as a major opportunity. India’s biotech sector could become a \$10-billion/year industry by 2015, Kiran Mazumdar-Shaw, chairman and managing director at biotech firm Biocon (Bangalore) says. Ranbaxy Laboratories (Bangalore), India’s biggest pharma company, signed an agreement in the past few weeks to buy biologic drugs and vaccines product rights and a biologic pharmaceuticals manufacturing facility from Biovel Lifesciences (Bangalore). The deal will give Ranbaxy access to all of Biovel’s products, pipeline, intellectual property, and know-how, as well as a manufacturing facility at Bangalore. The facility includes pilot plants, a commercial unit for producing two biologic drugs simultaneously, and downstream processing facilities. The deal provides Ranbaxy with an entry into the manufacture of vaccines. “With an increasing focus on prevention of disease, the importance of the vaccine market has never been greater,” says Ranbaxy CEO and managing director Atul Sobti. “The vaccine and biotherapeutics business will be an important part of our growth strategy.”

Reliance Industries is also growing its activities in biologics manufacture, in part through Reliance Genemedix (London), an AIM-listed subsidiary that Reliance acquired in 2007 to develop biosimilar drugs. Reliance is part of the way through a \$62-million investment program to expand Genemedix’s activities.

Sigma-Aldrich Fine Chemicals (SAFC) Biosciences, a Sigma-Aldrich subsidiary, says it sees opportunities for growth across a range of biopharma product areas and that it is in an investment phase. “We see the chance as much as anybody that there is a need for services on the biologics side,” says David Backer, director/business development and marketing at SAFC Biosciences. “We are not a ‘Lonza,’ making large volumes of monoclonal antibodies but we are in smaller, specific applications,” he says.

SAFC Biosciences produces viral vaccines and viral vectors, as well as reagents and media for biologic drugs. The company will bring online a site to produce high-potency, small-molecule pharmaceuticals via a fermentation process that has the capability to manufacture recombinant therapeutic proteins.

SAFC is working with a string of biotech partners to develop production processes for next-generation vaccines that will be used to treat a range of diseases including cancers, and for therapies for the central nervous system, heart, and eyes. “The field we are in is very edgy,” Backer says. “It’s a new phase of business that requires some really interesting technologies.”

The recent squeeze on funding from venture capital (VC) firms is having an effect. "VCs have not been spending much money and this has impacted on early-stage projects," Backer says. SAFC Biosciences saw slightly higher financial growth for full-year 2009 than in 2008. The company sees "potential improvement" for the second half of this year. "I am cautiously optimistic," Backer says.

Demand from biologic drug producers continues to grow for SAFC's media for manufacturing biologics. "We are now receiving media-formulation requests from the largest players," Backer says. SAFC Biosciences also is developing a cell-line technology platform for manufacturing biologic drugs that is starting to draw interest from biotech producers. The technology is based on a system invented by Sangamo BioSciences (Richmond, CA), for which SAFC has an exclusive worldwide license. The technology, "zink finger," features a protein that can turn genes on or off. "It allows us to knock in or out certain genes and increase certain cell lines for production," Backer says. "It's about improving productivity." Sangamo and SAFC have finalized contracts for zink finger technology, but "it's very early days for talking with pharma companies," Backer says.

SAFC is not yet a major supplier of biologic drugs but it is interested in expanding in this sector through acquisition. "Stay tuned," Backer says. "We have not ruled out a bio acquisition this year."



SAFC: Expanding its offering across the biologics field.

Lonza and Boehringer Ingelheim are the clear leaders in biologics contract manufacture, dwarfing the activities of companies such as SAFC. However, Lonza says it suffered last year because of a drop in demand for its large-scale contract services. Another emerging issue for the company is that recent "orders were very short term," says CEO Stefan Borgas.

Biologics generate about half of Lonza's custom-manufacturing income. The company's custom-manufacturing Ebit, before special charges, fell 14.3% in 2009, to SF239 million (\$222 million) compared with the year earlier, on corresponding sales down 6.2%, to SF1.4 billion. Biopharma activities were "at the bottom end of acceptable," Borgas says. Biopharma capacity utilization fell below 70% in 2009, from about 77% in 2008 and about 95% in 2006-07.

Lonza expanded its biologics pipeline to more than 200 active projects in 2009, from fewer than 150 in 2008, despite the drop in custom-manufacturing volumes. Pipeline growth was due predominantly to a doubling in the number of pre-clinical projects secured by the company to about 80, compared with the previous year. "We asked ourselves: 'do we have a strategy problem?'" Borgas says. "We are convinced that we don't. There is nothing fundamental that we have to change," he says.

Seeking to take advantage of the biosimilars market's potential, Lonza in early 2009 formed a joint venture with generic drugs leader Teva Pharmaceutical Industries (Petach Tikva, Israel). The jv has a "good handful of projects" in development. "Feedback from the U.S. FDA at the highest level tells us that they will have a regulation for this in 2011," Borgas says. Additional clinical trials will be required at a cost of \$40 million/drug if U.S. regulations are not in

place by 2011. Lonza plans to sink SF300 million into the biosimilars jv and predicts the business will be profitable from 2015, with the first product launch scheduled for 2014.

Privately owned Boehringer Ingelheim showed in its most recent financial results, for the first half of 2009, that it was struggling to grow its biologics business. The company recorded total contract-manufacturing sales of €382 million (\$522 million) for the first half of 2009, with no change from the year-earlier period. Flat contract biopharma sales last year contrast sharply with growth of 22.8%, to €569 million achieved by the company in 2008. The firm's activities range from manufacturing and high-yield expression systems to product "fill and finish."

Slow growth is not an issue for contract manufacturer Avecia Biologics (Billingham, U.K.), which has had a "good year [with orders] from biotech, and new business from pharmaceutical companies," says Stephen Taylor, commercial director. "Certainly, I don't see any decline in outsourcing."

Generic pharma producers' move to make biosimilars is unlikely to increase competition for contract manufacturers, Taylor says. "I don't see the biosimilar guys as a threat," he says. But they will need good process technology, which "could become another opportunity."

Avecia Biologics' became a subsidiary of Merck & Co. on February 1, having been sold by its former private equity owners Cinven (London) and Investcorp (New York). Avecia will carry out projects for Merck & Co., and for Avecia's customers. "Very clearly we will not walk away from any of our existing customer contracts," Taylor says.

In another private equity deal, Signet Healthcare Partners (New York) acquired a majority stake in Pfenex, the biologics processing technology business of Dow Chemical, last December. The business has its headquarters in San Diego, CA. Dow says it continues to hold a "significant minority stake" in the business.

Pfenex, under the leadership of Bertrand Liang, has broadened its focus from biologic process technology through the company's bacteria-based expression technology system. "We expect to create value in R&D in the lead protein space, and in areas such as research proteins, reagents, and biosimilars," Liang says.

Pfenex's expression technology enables the identification of a production strain making active, soluble, and high-quality protein, through a fermentation process lasting 12 weeks that easily scales to large volumes. This "is unparalleled in the industry," Liang says.

The character of recombinant proteins in today's drug-development pipeline is changing, Liang says. "There are fewer truly native human proteins in the pipeline and many more chimeric proteins that have been engineered for function," he says. "Just as there was no expression platform paradigm 20 years ago for the expression of monoclonal antibodies, there is no expression paradigm for these engineered chimeras today. Traditional platforms like yeasts or *E. coli* lack the flexibility and depth of the Pfenex platform to address the challenges of expressing these proteins that have no evolutionarily defined path to folding like native proteins do," Liang says.

New technologies are emerging in the downstream processing production phase. Pall Life Sciences (Port Washington, NY) introduced earlier this month a vibration-based filtering technology that it says can cut costs and simplify process design by combining harvesting and clarification steps. "The stable permeate flow and improved protein transmission we can achieve with this technology contribute to better process economics," says project manager Nathalie Pathier.

Wacker Chemie says its biologics business is also in a growth phase, and that it is expanding capacity to meet higher demand. The business has been "developing very nicely" during the past year, says Thomas Maier, managing director at the Wacker Biotech subsidiary. The company predicts high double-digit percentage sales growth this year compared with 2009.

Wacker entered the biologics sector in 2005 and has progressed to making clinical-trial quantities of biotherapeutics. "A major driver [for customer demand] is the increase of our reputation due to the fact that we have supplied clients for clinical phase III and developed profound knowledge in process validation," Maier says.

Wacker has 300 liters of bioreactor capacity at its GMP facility at Jena, Germany that can produce more than 10 kg/year of bulk active ingredients. The company is poised to more than double space at Jena as part of a €15-million project that is almost completed. Wacker, as part of the same program, built an 18,000-sq feet process development facility that can supply non-GMP material for preclinical purposes. "A major focus of further investment will be our process-development capacity and early clinical supply since we see the most demand coming for these services," Maier says.

Maier is optimistic about prospects for the biologics business. "With the recent successful approvals of antibody fragments and the increasing pipeline of scaffold proteins, there is a growing need for manufacturing with microbial systems," he says.

The company says its biosecretion fermentation technologies using *E.coli* bacteria are gaining "more and more interest in the industry. Compared to mammalian cell production, the shorter fermentation batch times of 1-2 days, versus 12-16 days, are a major advantage," Maier says.

Companies providing raw materials for biopharma processing face mixed market conditions. Novozymes confirmed recently that North American sales for its biopharma materials dropped to an undisclosed level during 2009. However, the company says that its BioBusiness division, which includes biopharma materials, achieved a 6% increase in sales, to DK650 million (\$119 million), with a particularly good contribution from biopharmaceutical ingredients. The BioBusiness's 2009 sales from microorganisms were flat.

Merck KGaA announced last month that it had begun work on a €30-million plant to produce active ingredients and excipients for use in biopharmaceutical production processes, among other applications. The project will increase capacity by about 50% compared with production lines currently being used. Completion is expected in mid-2011. The expansion is a response to growing demand for final pharma and biopharma formulations, says Klaus Bischoff, head of the performance and life science chemicals division at Merck KGaA.

Investment capital entering the sector may have been too late to boost contract manufacturers' project pipelines in 2009, but improved prospects for 2010 are expected. "I think the worst is over," Lonza's Borgas says.