



India's Biogenerics Industry

India has made great strides in the development of its biopharmaceutical industry

India's pharmaceutical manufacturers currently sell close to 30% of the world's generic therapeutics. Sales of generic versions of biologicals in India have grown rapidly, and that growth will likely expand into export sales over the next decade, according to the joint study, *Advances in Biopharmaceutical Technology in India*, (February 2008) by BioPlan Associates, Inc., and the Society for Industrial Microbiology.

Biogenerics represent a high-growth sector in India, where recombinant insulin, GCSF, interferon alpha, erythropoietin, monoclonal antibody (MAb) products and recombinant vaccines are manufactured by a number of domestic biotech companies. The costs of Western-made biopharma products remain out of reach for much of the world, and many of these products are close to losing their patent protections. To assist the Indian biotech industry in seizing this opportunity, the Indian government has streamlined some of its drug application and review procedures, and has offered strong tax incentives. As a result, India's biotech industry has been investing heavily in the development of facilities. It is expected that Indian biogenerics makers will soon receive their first approvals to manufacture products for the European market.

According to Ashesh Kumar, PhD, Head of Medipolis GMP, "Indian companies, such as Biocon, Dr Reddy's Laboratory, Intas Pharmaceuticals, MJ Biopharma, and others have the skills to develop and manufacture recombinant biotech products." These include hepatics [QA: hepatitis?] B vaccine, streptokinase, human insulin, G-CSF, EPO, HAH, interferon alpha-2a and MAbs for cancer & Hodgkin's lymphoma.



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BIOLOGICS MANUFACTURING IN INDIA

Following its generic pharma industry success, Indian policy makers plan to repeat this in the biogeneric sector. Indian biotech revenues, currently at about \$2 billion, are projected to reach \$5 billion by 2010. Already, nearly 60% of these revenues are from exports. 2005 was an important milestone for Indian biotechnology as revenues crossed \$1 billion. In India, the biopharma sector has two dominant segments: vaccines and biotherapeutics.

ROADBLOCKS TO BIOGENERIC DOMINANCE

The success demonstrated by India's small molecule generic drug industry may not be a easily duplicated for several reasons.

- The research infrastructure, academic network and overall talent pool are small compared to those supporting the traditional pharmaceuticals industry.
- There have been greater regulatory hurdles for biologics in major markets, in particular, the lack of bioequivalence laws in the US, and the lack until recently in Europe.
- The costs and the technical challenges of making biogenerics are higher than for traditional chemically-synthesized generics.

Yet India seems intent on developing a world-class biotech capability. Even in the early 1980s, when Genentech and other American biotech companies were just beginning to make headlines, the Indian government initiated a program to promote its own biotech industry. In 1982, the National Biotechnology Board was set up under the Ministry of Science and Technology, and became the Department of Biotechnology (DBT) in 1986. The DBT now spends close to \$200 million annually to develop biotech resources in the country, including the expansion and improvement of academic programs, the development of more and better infrastructure, the nurturing of

Table 1. Biotherapeutics in India and their manufacturers

| Biogeneric | Company | Product Name | Year of Launch |
|---|--------------------------|-------------------|----------------|
| Insulin | Wockhardt | Wosulin | 2003 |
| | Biocon | Insugen | 2004 |
| | Shreya Life Sciences | Recosulin | 2004 |
| Erythropoietin | Hindustan Antibiotics | Hemax | 2000 |
| | Emcure | Epofer | 2001 |
| | Wockhardt | Wepox | 2001 |
| | Ranbaxy | Ceriton | 2003 |
| | Intas Pharmaceuticals | Epoft and Erykine | 2005 |
| | Shantha Biotechnics | Shanpoietin | 2005 |
| Hepatitis B vaccine | Shantha Biotechnics | Shanvac B | 1997 |
| | Bharat Biotech | Revac B | 1998 |
| | Panacea Biotec | Enivac HB | 2000 |
| | Wockhardt | Biovac-B | 2000 |
| | Serum Institute of India | Gene Vac-B | 2001 |
| | Biological E | Bevac | 2004 |
| Granulocyte colony stimulating factor (G-CSF) | Dr Reddy's Laboratories | Grastim | 2001 |
| | Intas Pharmaceuticals | Neukine | 2004 |
| Streptokinase | Bharat Biotech | Indikinase | 2003 |
| | Shantha Biotechnics | Shankinase | 2004 |
| | Cadila Pharmaceuticals | STPase | 2004 |
| Interferon alpha-2b | Shantha Biotechnics | Shanferon | 2002 |
| rituximab (MAb) anti-EGFR (MAb) | Dr Reddy's Laboratories | Reditux | 2007 |
| | Biocon | BioMAB-EGFR | 2006 |

Source: Advances in Biopharmaceutical Technology in India, BioPlan Associates, 2008

biotech companies, and the improvement of technology transfer to businesses from universities and other non-commercial laboratories.

This enthusiasm for biotech springs partly from an appreciation that biotherapeutics represent the future of medicine. But Indians also see in biotech an advanced, high tech industry more in keeping with the image they expect of their country. Immensely proud of their world-class IT industry, Indians would like to mirror this in biotech, thus becoming "one of the nations to be counted" in the world com-

munity. And a natural step is for the country to become a major producer of generic biologics.

THE OPPORTUNITY

Blockbuster first-generation biotherapeutics developed in the west are already starting to lose patent protection in western markets, and in the next decade, even second-generation products will begin to go off-patent. The biogenerics markets in Europe and the US together could amount to more than \$15 billion in the next three years, at an average annual growth rate of close to 70%.

MAJOR PLAYERS IN INDIA'S BIOGENERICS INDUSTRY

India's biogenerics industry remains relatively small, and nearly all of the products marketed now or in the near future are accounted for by a handful of companies. There are four main players.

Biocon: India's first and largest biotech company was founded in 1978. Bangalore-based Biocon is now the largest biotech firm in Asia by market capitalization and the sixteenth largest worldwide. Biocon's existing biogenerics product line includes recombinant human insulin (Insugen), erythropoietin (Erypro), GCSF, and streptokinase. Most of Biocon's pipeline is now filled with innovative molecules, and it already markets a novel biologic, an anti-EGFR MAb (BioMAB-EGFR) for head and neck cancers. As Biocon's CEO, Kiran Mazumdar-Shaw, told Fortune a year ago, "Unfortunately, [analysts] still tend to categorize us as a generics company...We keep saying, 'Look, we're not interested in generic companies, because we're trying not to be one.'"

Dr Reddy's Laboratories: India's third largest pharmaceuticals company, Dr Reddy's was founded in 1984 in Hyderabad as a bulk pharmaceuticals manufacturer and soon grew to become one of India's best known generics makers. Among other ventures, Dr. Reddy's has manufacturing plants in the UK and a research facility in the US. The company currently markets only two biologics, both generics: Reditux, a version of Roche's blockbuster rituximab monoclonal against non-Hodgkins lymphoma; and Grafeel, a version of GCSF. Dr Reddy's announced in mid-2007 that it planned to invest \$20 million to expand its biogenerics capability, and expected to roll out one new biogeneric product per year for the next eight years. In 2001, the company had "ten recom-

binant products at different stages of development," but only two have made it to market so far.

Ranbaxy Laboratories/Zenotech:

Founded in 1961, Haryana-based Ranbaxy is India's largest pharma company. It recently decided to move towards biogenics by taking a large stake in Hyderabad-based Zenotech, an established biotech firm. The two companies now sell biogeneric versions of GCSF (Nugraf), and GM-CSF (Macrogen) and have an Interleukin-2 generic, a recombinant human growth hormone generic and a rituximab generic in clinical trials.

Shanta Biotechnics: Hyderabad-based Shanta, now 60% owned by Merieux Alliance, currently markets three biogenics—an interferon alpha-2b (Shanferon), a streptokinase (Shankinase), and an EPO (Shanpoietin). The company's biogenics pipeline includes a tPA product and a pegylated interferon for treating hepatitis C, although most of Shanta's R&D has been focussed on new biologics and vaccines. Shanta has been making a recombinant-protein hepatitis-B vaccine since 1997.

Wockhardt: Wockhardt, based in Mumbai, currently has six biogenics on the market in India: an EPO (Wepox) and a recombinant human insulin (Wosulin). Its pipeline includes an insulin glargine generic, interferon alpha 2b, and GCSF.

REGULATORY ISSUES

New regulatory guidelines enable a streamlined clinical trials and review process under a single National Biotechnology Regulatory Authority. However, India's biogenics manufacturers are less interested in India's market, or in other loosely regulated markets where consumers are relatively poor, than they are in the wealthy US and European markets.

The bioequivalence issue in the US is awaiting legislation that would amend Sec. 262 of the Public Health Service Act. Major health care legislation is unlikely in 2008, an election year, and passage of a standalone biogenics bill is also unlikely given the opposition by the PhRMA and other lobbying groups for innovator biotech companies. In late 2005, the EMEA gave final approval to basic guidelines for "Similar Biological Medicinal Products." Since then, it has approved two growth hormone biosimilars, Sandoz's Omnitrope and Biopartners' Valtropin, in early 2006, as well as Sandoz's EPO biosimilar in August 2007.

OUTLOOK

The opening up of the European biosimilars market marks the end of the beginning of the biogenics industry. Products made by India's biogenics makers or their western licensees will appear in European pharmacies as soon as their abbreviated clinical research requirements and EMEA reviews are completed successfully. Biogenics will ultimately take, and keep, a significant chunk of the global biotherapeutics market, as biotherapeutics themselves take a larger portion of the global pharmaceuticals market.

But in the near term, the biosimilars market isn't as appealing as it might seem. The lack of US legislative action so far, the unlikelihood of action any time soon, and the evident opposition to such legislation, reduces the available market. And it is far from clear that when such legislation is enacted, it will include terms that make the 'follow-on biologics' market attractive for India's generics makers.

Even in the European biosimilars market there is room for skepticism. Two of the first three approved biosimilars are competing against each other, and the more popular one of the two, Sandoz's Omnitrope,

Table 2. Top biotech organizations in India

| Rank | Company | Biotech sales (\$ million) |
|------|--------------------------|----------------------------|
| 1 | Biocon | 108.42 |
| 2 | Serum Institute | 106.05 |
| 3 | Panacea Biotech | 32.18 |
| 4 | Nicholas Piramal | 28.08 |
| 5 | Novo Nordisk | 12.78 |
| 6 | Venkateshwara Hatcheries | 19.01 |
| 7 | Wockhardt | 18.14 |
| 8 | GlaxoSmithKline | 17.28 |
| 9 | Bharat Serums | 17.21 |
| 10 | Eli Lilly and Co. | 14.56 |

has so far captured less than 1% of the European HGH market, despite being priced up to 25% less than the drug it was made to resemble, Pfizer's Genotropin.

For Indian companies, with their lower operating costs, a smaller piece of the pie may still be enough to justify their efforts. But some may elect to license development and marketing in western markets to western partners—as Biocon already has done for its GCSF biogeneric, in advance of approval. And as Biocon's evolution also has shown, biogenics may represent only a passing phase for some Indian biotech companies, who prefer to focus their R&D efforts on the creation of new and patentable biologics. Indeed, the same national pride that makes Indians want to excel at IT and biotechnology seems to make some of them anxious to outgrow the country's "cheap generics" reputation. Dr. Swati A. Piramal, the director of an R&D center for Nicholas Piramal in Mumbai, was quoted not long ago as saying, "Indian companies are no longer going to be just copycats. We want to take our rightful place at the head table with the developed nations." ♦