Indian Biotech on the Rise

by Gordon Feller

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Biotech in India is faring well. The country's highly educated community of scientists and researchers has benefited from strong government support and access to a growing infrastructure. Eight-hundred companies are active in the market; at least 50 of them work on advanced biotech applications. Key areas of expertise include research and production of vaccines, diagnostics, enzymes, and biopesticides. Approximately 60% of the industry is devoted to human health applications, 10% to agricultural biotech, and 30% to industrial applications, bioinformatics, and genomics.

Particular strengths in the Indian biotech industry include expertise in pharmaceutical manufacturing and fermentation technologies, skill in handling microbes and animal cells, experience with plant and animal breeding, growing expertise in bioinformatics, and solid infrastructure at numerous research centers.

Challenges for the industry include focusing publicly funded research efforts on particular strengths, increasing intellectual property protection, and improving the regulatory systems for both medical and agricultural products. Critics accuse the government of supporting research in areas that have already been perfected in other parts of the world and conducting unnecessary regulatory reviews of products already approved in Europe and North America. This "reinventing the wheel" has slowed progress for product approvals and in niche sectors of research that are particular strengths for India, including bioinformatics, pharmacogenomics, and seed research.

The Indian biotech industry is ranked third in the world in terms of stem cell research, primarily because both the government and private industry have invested heavily in research institutes to study human disease and search for treatments. Also, embryonic stem cell research has not generated the same moral debate in India as it has in the United States, Canada, United Kingdom, and other countries. In fact, an Indian bioethics committee determined that human embryonic stem cells may be harvested, with the full and informed consent of the donor, up to the fourteenth day of gestation.

Two research laboratories — the National Center for Biological Sciences (NCBS, www.ncbs.res.in) and the private-sector Reliance Life Sciences — have been identified by the United States Institutes of Health Research as having cutting-edge embryonic stem cell research. Despite such advanced work in stem cell research, India has not yet formulated a policy on human cloning. The government has decided to study the issue more closely and does not feel a need to rush because the capacity to clone a human does not currently exist.

The biotech industry in India is still emerging, and it is showing signs of significant growth potential. The country has a solid base of expertise, ties to Indian expatriots working throughout Europe and the United States, and strong government support for the biotech industry at both national and state levels. India has the largest number of English-speaking scientists in the world outside the United States and a highly educated and skilled workforce.

Governmental Oversight and Organization

The focal point for biotech within the national government is the Department of Biotech (DBT). The DBT is active on several levels, from providing support for government-funded research centers to working with various advisory committees to formulate India's biotech policy. Complete details of all programs and activities are available online at http://dbtindia.nic.in.

Components of the department include the following:

- The Scientific Advisory Committee for DBT (SAC-DBT), which advises the DBT on policy issues, new developments in the industry, and implementation and monitoring of new technologies
- A joint committee of the DBT and the Ministry of Agriculture's Indian Council of Agricultural Research (the DBT-ICAR), which supports growth and development of agricultural biotech
- The Recombinant DNA Advisory Committee (RDAC), which is responsible for establishing, reviewing, and updating biosafety guidelines
- Institutional Biosafety Committees (IBSC), which implement and enforce biosafety guidelines on specific projects in research centers, universities, and national laboratories
- The Review Committee of Genetic Manipulation (RCGM), which authorizes containment conditions for experiments, closed trials, and small-scale field trials, and monitors those trials to ensure that safety standards are met. The RCGM also approves import requests for products needed for experimental work, training, and research, such as etiologic agents and vectors, germ plasmas, and organelles.

Research Centers: Biotechnology in India is also supported by both public and private research centers, including the following.

The NCBS in Bangalore is owned by the Tata Institute of Fundamental Research, which was founded by industrial giant Tata. The NCBS has three potential stem cell lines that meet US funding requirements for embryonic stem cell research. However, the center has not yet decided whether it will collaborate with the United States in this field.

The Indian Council of Medical Research (ICMR, http://icmr.nic.in/home.htm) is the focal point for all medical and human health–related biotech research in India. The ICMR is funded through the Ministry of Health and includes 21 permanent research centers and institutes, six regional medical research centers, and a series of Centers for Advanced Research based on existing expertise and infrastructure at educational centers and other research institutes throughout the country. The ICMR also offers grant and scholarship funding for specific projects and conducts taskforce-based studies on time-sensitive projects. In 2003, ICMR received $30 million over five years from the Ministry of Health for genomics, stem cell, and structural biology research. The funding will be divided among various research centers and medical institutions under the direction of ICMR.

The Council of Scientific and Industrial Research (CSIR, www.csir.res.in) has 40 laboratories throughout India researching all areas of scientific inquiry. Biotech research is conducted at the Central Drug Research Institute, the Central Food Technologies Research Institute, the Center for Cellular and Molecular Biology, the Industrial Toxicology Research Center, and the Indian Institute of Chemical Biology.

The Center for Cellular and Molecular Biology (CCMB, www.ccmbindia.org) is focused on research and applications of modern biology. The CCMB develops biotech in India through basic and applied research, training, and industry collaborations. It also provides information for biological and biotech research. Key research areas include gene therapy, genomics, drug delivery systems, and the use of DNA chips in disease diagnosis. The CCMB was involved in developing the rDNA-based hepatitis-B vaccine now manufactured and sold by Shantha Biotechnics Ltd. and has worked with other companies to transfer technology and assist with collaborative research efforts.

Regulatory Changes and Complications

The regulatory system in India for biotech products has been criticized by the All India Biotech Association (AIBA) for being over bureaucratic and secretive. The AIBA has called for revisions to stimulate additional growth in the industry and has proposed a single national regulatory agency for all biotech products under direct authority from the prime minister and independent of the various government departments and ministries that are now involved.

Currently, biotech products must be reviewed by both district and state monitoring committees. Products are then reviewed by committees at the national level, including the DBT, the Department of Health, the Ministry of Agriculture, and the Ministry of Environment.

All pharma products, including biopharmas, must also receive approval from the Drug Controller General of India (DCGI) before they can be sold in the country. In general, phase III clinical trials must be conducted in India before approval is given. If a product has

not received marketing approval in other countries, some phase II trials may be required, but new drugs are not generally approved for sale in India until they have been approved in their country of origin. Some fast-track approval processes for drugs approved abroad and in desperate demand in India are available.

Companies seeking to manufacture drugs in India must acquire a license from the central government. Small companies — with investments of less than US$164,000 (7.5 million rupees, Rs) — must obtain a license from the state health authority.

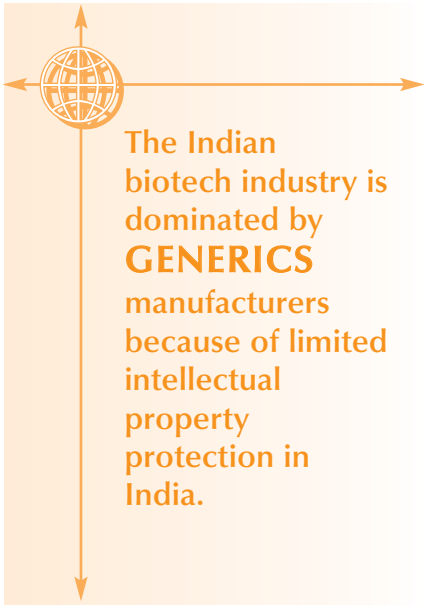
In January 2002, the DBT articulated priority research areas for government funding in biotech. These areas include vaccines based on genomic research for cholera, malaria, AIDS, rabies, and tuberculosis as well as biofertilizers, biopesticides, transgenic crops, and gene therapy for cancer treatment. A biotech "vision document" released in late 2001 outlines additional plans over the next 10 years, including developing edible vaccines for specific disease targets, testing and approving a series of GM crops, developing additional vaccines and diagnostic tools for major communicable diseases, and identifying and protecting biodiversity hotspots.

A new pharmaceutical policy announced by the government of India in February 2002 allows up to 100% foreign investment in all areas of the pharmaceutical industry except bulk drugs produced by the use of recombinant DNA technology, bulk drugs requiring in vivo use of nucleic acids, and specific cell and tissue targeted formulations. For more information, see www.techno-preneur.net/timeis/cgovt/pharmapolicy.html.

The Indian government has entered several agreements to foster additional biotech growth. For example, India has a biotech cooperation agreement with Indonesia to collaborate in the production of inexpensive medications and vaccines. The agreement includes provisions for research exchange and training opportunities for scientists.

Partnering Opportunities

Non-Indian companies are starting to partner with Indian companies doing drug discovery research and contract research and manufacturing. They are also establishing technology transfer agreements and strategic research partnerships with key research institutions.



Indian biotech companies already have the capacity to work on monoclonal antibodies (MAbs), synthetic peptides, and recombinant antigens. Foreign companies can also make use of India's vast and varied population for clinical trials and pharmacogenomics studies. Indian industry recognizes the value of the country's biodiversity and the diversity of its people for genetic research.

There are opportunities to produce and sell vaccines and therapeutics that respond to the needs of the millions of poor people in India. Simple, effective, and low-cost treatments for diarrheal diseases, influenza, tuberculosis, malaria, meningitis, and pneumonia will find a ready market in India. The market for diagnostics is also significant. Demand will increase for immunodiagnostics for tuberculosis, typhoid, malaria, and other microbial infections.

Multinationals from the United States and Europe are active in the Indian market both independently and in partnership with local Indian companies. GlaxoSmithKline, Novartis, Eli Lilly, Pfizer, Aventis, and Bayer are some of the leading multinationals successfully operating in India. Many foreign companies are focused on opportunities to collaborate with and sell products and services to Indian companies already established in biotech subsectors, including industrial enzymes and biopesticides.

Foreign companies that enter the Indian market early stand to benefit from increased growth and opportunities after 2005. Early entry and a solid foundation in the market will benefit those able to work within the current limitations of India's intellectual property laws. Companies currently active in the market are cautious when transferring technology and often sign confidentiality agreements with partner companies.

Intellectual Property Considerations

In the biomedical and pharma field, the Indian biotech industry is dominated by generics manufacturers. Because of limited intellectual property protection in India — patents are issued on the process but not the product — companies are able to work backward from the finished product to develop new processes and launch similar products.

Despite these limitations, India was the third most active developing country in terms of Patent Cooperation Treaty (PCT) applications filed before the World Intellectual Property Organization during 2002. According to a study by the Confederation of Indian Industry (CII), India's share of PCT applications has risen to 9.3% of the total applications filed by any country.

Given Indian strengths in producing generic medications, some companies are hoping to increase their capabilities in biotech processing and manufacturing in anticipation of a new series of biotech-based generic drugs. As drug patents on some of the earliest biotech drugs expire in the coming years, there will be a new market for biotech-based generics.

Key players in the biotech industry predict that the Indian biotech market will grow substantially after 2005 as a result of stronger intellectual property protection expected to be passed.

Geographic Distribution

The Indian biotech industry is focused in the south of the country in cities such as Bangalore in the state of Karnataka. Other clusters of activity are in the states of West Bengal, Maharashtra, Andhra Pradesh, Hyderabad, and Kerala. Bangalore is branding itself as a "biocity" and is promoting convergence and growth between its successful information technology industry and biotech, the result of which is a growing bioinformatics industry.

Following is a list of the activities of some of the most active private Indian companies.

Dabur India Ltd. announced in April 2002 that it established a molecular diagnostic laboratory at the Rajiv Gandhi Cancer Institute and Research Center in New Delhi with plans for additional facilities in Mumbai, Ahmedabad, and Chennai. The laboratories will use genomic and proteomic profiling to detect molecular changes in cancer patients. The company also manufactures and sells 22 anticancer drugs in India.

Reliance Life Sciences, part of the large conglomerate Reliance Industries, is designing and constructing a life sciences complex in Mumbai. The site will include research laboratories, greenhouses, and pilot manufacturing facilities. Some of the laboratories were built in 2002, and the entire complex is expected to be complete by the end of 2003. The company is active in areas of stem cell research, as well as plant and industrial biotech.

Sartorius, an Indian bioengineering company, is planning to establish an incubator and knowledge center in Bangalore to provide training, support for process scale-up, production for clinical trials, lab services, contract manufacturing, and other support services.

Biocon (Bangalore), India's largest biotech company, began operations in the late 1970s and manufactured enzymes to break down the pectin in fruit juice. The company has continued to work in fermentation and has developed state-of-the-art technology to manufacture a group of cholesterol-lowering drugs. Biocon is also developing genetically engineered medications, including anti-infectives.

Shantha Biotechnics Pvt Ltd. is a vaccine production company that has produced and successfully marketed a genetically modified hepatitis B vaccine in India. In April 2002, Shantha Biotechnics and Biocon announced a joint venture to manufacture and sell recombinant human insulin. The global patent on recombinant human insulin expires in 2003, and the two companies have formed their partnership to ensure a place in the market once the patent expires.

Bangalore Genei produces restriction enzymes, DNA polymerases, and modifying enzymes — all critical tools for genomic research. Before it established operations, these research tools were imported by Indian companies and research centers. The company now controls 30% of the Indian market for these products.

Dr. Reddy's Laboratory is a long-standing pharmaceutical company that has recently added a biotech division. The company has a licensing agreement with Novo Nordisk for diabetes therapeutic technology and is developing human therapeutic proteins through rDNA technology.

Panacea Biotech Ltd. a pharmaceutical company based in New Delhi, will produce and market a vaccine for anthrax developed with the Center for Biotech at Jawaharlal Nehru University and the DBT. The drug is expected to receive fast-track approval through the regulatory system.

Industry Valuations

The industry was valued at US$3.7 billion (Rs 172.5 billion) in 2001 and employed approximately 20,000 people. Growth is expected to top $6.7 billion (Rs 312 billion) by 2010. Sales of biotech products for both human and animal health care totaled $115 million (Rs 5.4 billion) in 2000 and are expected to reach $200 million (Rs 9.3 billion) by 2005.

The pharmaceutical market (both biotech-based pharmas and traditional pharmas) was estimated at $8 billion (Rs 372.9 billion) and is expected to grow to $37 billion (Rs 1.7 trillion) by 2010. The diagnostics market is valued at an estimated $75 million (Rs 3.5 billion) and is dominated by demand for monoclonal and polyclonal antibodies, tissue typing, clinical assays, and contract research. The vaccine market in India, valued at approximately $150 million (Rs 7 billion), is a key component of the biomedical sector. Other biotech medications on the market include recombinant insulin, human growth hormone, alpha interferon, blood clotting factor VIII, and medical proteins such as relaxin, rennin, and interleukins.

During the next five years, some analysts think that the total fresh investment flowing into India will reach $150 million to $172 million (Rs 7 to 8 billion). Even half this sum could rapidly change the biotech production scenario.

Venture capital for biotech in India is limited but growing. ICICI Venture Funds Management Co. Ltd. is India's largest venture capital company. It announced the creation of the ICICI Biotech Incubator Fund in March 2002 with a target size of $32 million (Rs 1.5 billion). The company has already invested in local industry leaders, including

Biocon and Avesthagen.

The DBT has also announced venture funding for small- and medium-sized biotech companies. Although the size of the fund has not yet been announced, it will be part of the Technology Development Fund program.

Future Prospects

Vaccines: Most conventional human vaccines are produced locally by Indian companies and laboratories. A substantial increase in the Indian production of newer, more effective human vaccines is widely expected. There is immediate demand for items such as cocktail vaccines of DPT with hepatitis B, hepatitis A with B, injectable polio vaccine, influenza, varicella, and meningitis vaccines. Technical capabilities exist in India in all these areas — and for that reason Indian companies and laboratories are focused on exploiting these opportunities. For instance, there is a strong commitment among Indian companies to increase the availability of typhoid vaccine. It is estimated that investments on the order of $6.4 million to $8.6 million (Rs 300 to 400 million) will be needed in India's vaccines sector during the next five years.

Diagnostics: The potential for large-scale use of diagnostics in India is substantial. Immuno-diagnostic methods for detecting

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Note: Site includes links and addresses to all 27 National Research Centers and all 46 research institutes.

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Note: Site includes links and addresses to all Regional Medical Research Centers, Centers for Advanced Research and Permanent Research Institutes.

Indian Associations

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Real Companies with Real Projects

The Glenmark Company has a team of 100 scientists focused on discovering new chemical entities. The company has two molecules in late preclinical development: GRC 3015, a PDE inhibitor for the treatment of asthma; and GRC 1087, a beta3 agonist for the treatment of diabetes and obesity. In addition, 10 products have been developed at the company's Formulation Research Center at Sinnar in Nasik and will be launched in the market in 2004.

Pharmaceutical and biotechnology company **Wockhardt Ltd.** plans to launch a 10,000 international-unit-per-day version of its successful biotech product Wepox aimed at the oncology market in 2004.

Seeking to emerge a global player in the biologicals market, **Bharat Biotech International** has lined up a number of products developed through collaborative research. The first of these would be the world's first vegetarian version of a nonbovine typhoid vaccine, christened Tybar. It was developed in collaboration with the US National Institutes of Health (NIH). Some other products slated for early launch include streptokinase, used for dissolving blood clots, and epidermal growth factor. Products such as vaccines for malaria, rotavirus, and insulin are still in the pipeline.

viral infections such as HIV, HBV, HCB, and papilloma and other microbial infections such as tuberculosis, typhoid, malaria, leishmaniasis, and cholera are increasing fast. Most diagnostic products are imported, although local skills could be sharpened and used to competitive global advantage. Diagnostics based on MAbs, synthetic peptides, and recombinant antigens or antibodies could be made locally using locally made raw materials. The investment in diagnostics during the next five years is expected to be greater than $10.7 million (Rs 500 million).

Bioactive Therapeutic Proteins: In India, 10 bioactive therapeutic protein products are approved for marketing: insulin, alpha interferon, hepatitis B surface antigen-based vaccine, GM-CSF, G-CSF, blood clotting factor VIII, human growth hormone, erythropoietin, streptokinase, and follicle stimulating hormone. Hepatitis B surface antigen-based vaccine recently began local production, whereas the others are still being imported. Indian biotech leaders believe it is possible to create a viable and globally competitive industry in India, and are convinced that a total investment of $17.2 million to $21.5 million (Rs. 800 million to 1 billion) could be necessary. The skilled labor exists locally, and the country's R&D infrastructure has been substantially upgraded.

Other Products: Opportunities for fresh investment also exist in setting up facilities focused on the fractionation of blood and blood products into cellular and noncellular components, sanitized immunoglobulins, albumin, and concentrates of blood clotting factors. Further production of MAbs, bioactive peptides, and effective biotech drug delivery systems are also areas for fresh investment. It is estimated that in all these areas — including blood fractionation — more than $21.5 million (Rs 1 billion) could be invested in the creation of local production facilities.

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