

Biotech boom

India's thriving biotechnology industry is threatened by a change in the law. Will the current high levels of investment be enough to secure its future? **K. S. Jayaraman** finds out.



Every year, on the presumed birthday of Krishna, the blue-skinned Hindu god, New Delhi's Mathura Road is choked with traffic. Buses, cars and bullock carts packed with devotees advance toward Vrindavan, where Krishna is believed to have been born 5,000 years ago.

This August, pilgrims to Krishna's legendary birthplace will pass an imposing three-story structure of sandstone and glass. Inside, at The Centre for Genomic Applications (appropriately shortened to TCGA, the letters of the genetic alphabet), white-coated scientists are devoted to a god of a different kind. On the centre's first birthday in May 2005, scientists acquired a new Hewlett-Packard supercomputer, the fastest in India, worth a whopping US\$2.2 million. Capable of four trillion operations a second, the computer places the centre among the ranks of international institutions such as the Wellcome Trust Sanger Institute in Britain and the

Institute for Molecular Science in Japan.

TCGA is the youngest of several biotechnology laboratories that have sprung up in India in recent years. It is a shared venture between the Chatterjee Group, a Kolkata-based industrial house, and two government agencies — the Council of Scientific and Industrial Research (CSIR) and the Department of Science and Technology — which shared the US\$ 5.7-million cost of construction.

The centre, which aims to provide world-class facilities for genomics and proteomics, is the first to be built by a public-private partnership. It also symbolizes the current revolution in India's biotechnology industry.

With fewer than 300 registered companies, the biotechnology sector is small but is gaining in global stature. According to the World Health Organization, India is the fourth largest producer of pharmaceuticals, and 66.7% of its exports go to developing countries. For example, the Pune-based Serum Institute of India,

once a small manufacturer of tetanus toxin, now makes 80% of the world's measles and DTP (diphtheria, tetanus and pertussis) vaccines (see 'A shot of success', opposite).

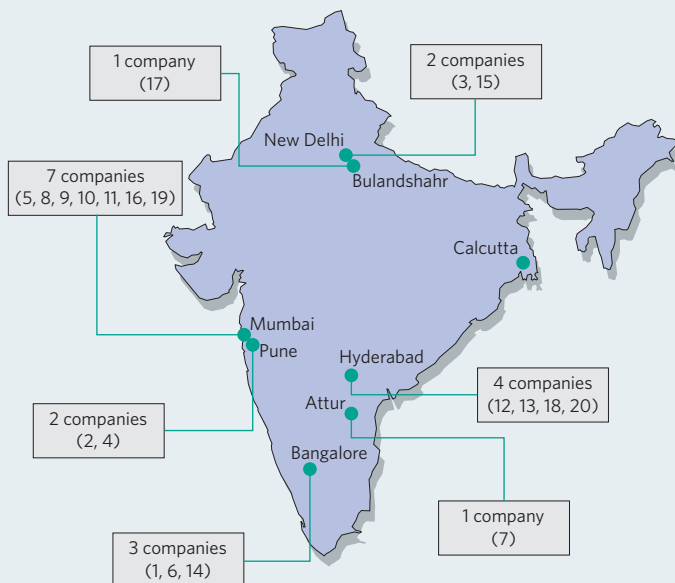
Other companies that have made a global impact include the Mumbai-based company Cipla, which rewrote the rules of the international AIDS drug market when, in 2001, it introduced inexpensive generic antiretroviral drugs. Strand Genomics in Bangalore has formed a partnership with Japan's MediBIC to develop informatics solutions for pharmaceutical companies in Japan. And Avesthagen, also based in Bangalore, has joined up with France's bioMérieux to develop diagnostic instruments for medical and industrial applications.

Profits soar

In 2003-04, Indian biotechnology companies together had a revenue of more than US\$700 million (see graphic, below). This year, they have surpassed US\$1 billion. "The biotech-

INST. BIOINFORMATICS, BANGALORE

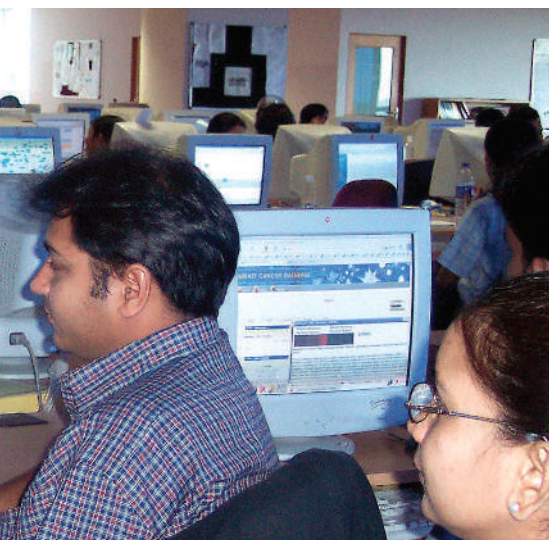
LOCATION OF TOP 20 BIOTECHNOLOGY COMPANIES



INDIA'S TOP 20 BIOTECHNOLOGY COMPANIES

Company name	Revenue 2003-04 (US\$million)	Revenue 2004-05 (US\$million)	Growth (percentage)
1. Biocon	115	148	29
2. Serum Institute of India	126	130	3
3. Panacea Biotech	34	50	46
4. Venkateshwara Hatcheries	20	43	114
5. Mahyco Monsanto	12	38	208
6. Novo Nordisk	25	31	23
7. Rasi Seeds	—	20	—
8. Aventis Pharma	17	19	15
9. Bharat Serums & Vaccines	18	19	2
10. Chiron Behring Vaccines	15	18	16
11. GlaxoSmithKline	14	18	28
12. Indian Immunologicals	13	17	28
13. Shantha Biotechnics	9	16	75
14. Novozymes	12	16	30
15. Eli Lilly & Company	15	16	1
16. Wockhardt	9	15	68
17. Bharat Immunologicals & Biological	5	12	147
18. Bharat Biotech	8	9	14
19. Advanced Biochemicals	7	9	31
20. Biological E	9	8	-6

Data from the ABLE-Spectrum Industry survey



World class: researchers from the Institute of Bioinformatics in Bangalore managed to characterize the human X chromosome.

nology sector is witnessing an impressive 40% annual growth,” says Kiran Mazumdar Shaw, chief executive of Biocon, Bangalore. “The profile of Indian biotech companies is undergoing a change and they are becoming international.” Biocon, the most profitable biotechnology company in India, this year posted revenues of US\$150 million, a 30% increase over the previous year.

Shaw, sometimes called India’s ‘biotech queen’, and several other company chiefs are quickly becoming household names in India. Five of them won this year’s Padma awards, the nation’s highest honour for civilians. “Never in the history of these coveted awards has a small section of the industry grabbed the entire limelight,” says N. Suresh, editor of *BioSpectrum* magazine, published in Bangalore.

The biggest boost to the biotechnology industry has come from the government itself. “Biotech is the government’s priority area,” says science minister Kapil Sibal. Less than a year after Sibal took office, the Department of Biotechnology (DBT) released an ambitious plan to create a biotechnology industry that would generate US\$5 billion in revenues per year and create one million jobs by 2010.

As part of its strategy, the DBT is planning to make it easier for foreign-owned companies to set up in India. Foreign investors have in the past had to knock on the doors of several different government agencies. But the DBT’s new plan is to set up a single independent authority to replace the committees at different ministries.

The DBT has also subsidized the construction of three biotechnology parks, including Genome Valley (see ‘Land for rent’, overleaf) and aims to help finance at least ten such parks by 2010. Together with the Ministry of Information Technology, the DBT plans to build the country’s first biotech/IT park. This

A SHOT OF SUCCESS

On a sunny Friday morning in January, the students of the Shiva Shivani School in Hyderabad were ushered, one by one, into a room where a doctor and nurse stood with syringes.

The school’s 470 students, ranging in age from 5 to 12 years, all received a shot of Shanvac-B, a hepatitis B vaccine produced by a local company, Shantha Biotechnics. At just Rs18 per dose (equivalent to US 40 cents), the vaccine is so affordable that scenes like this are commonplace.

Such widespread vaccinations were unthinkable early in 1997 when GlaxoSmithKline (GSK) sold its product at Rs500 per dose. But later that year, Shantha’s hepatitis B vaccine became India’s first recombinant product to be made indigenously in the healthcare sector. Today this vaccine is available in 52 countries and makes up 40% of UNICEF’s supply.

Varaprasad Reddy says he launched the company, named after his mother Shantha, after he heard multinational companies disparage India’s dependence on them for its vaccine needs. “India can position itself as an affordable base for producing vaccines for the entire developing world,” he says.

Shantha’s success inspired four other Indian companies to bring out their own hepatitis B

vaccine. As a result, GSK’s share of the vaccine in the Indian market has plummeted to 10% from a virtual monopoly (see graph, below). The Serum Institute, based in Pune, is the world’s largest manufacturer of the diphtheria, tetanus and pertussis vaccine, which now protects three out of ten of the world’s children, according to figures released by UNICEF. The Mumbai-based Haffkine Institute supplies 75% of India’s oral polio vaccine, and Indian Immunologicals in Hyderabad, already the world’s largest manufacturer of vaccines for foot-and-mouth disease, plans to make human vaccines against rabies, hepatitis B and measles.

“Not many people are aware that the United States is one of the largest importers of measles vaccine from India,” says Nirmal Kumar Ganguly, director-general of the Indian Council of Medical Research.

But Indian companies are only beginning to venture into original territory.

“It is true we have not made any new vaccine on our own,”

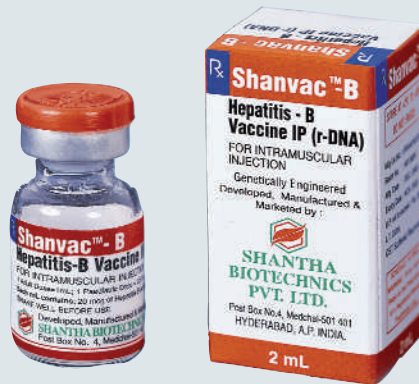
says Krishna Ella, managing director of Bharat Biotech.

To encourage innovation the Department of Biotechnology is supporting the development of 11 original vaccines. Four of these, for rotavirus, cholera, Japanese encephalitis and malaria, will enter clinical trials this year.

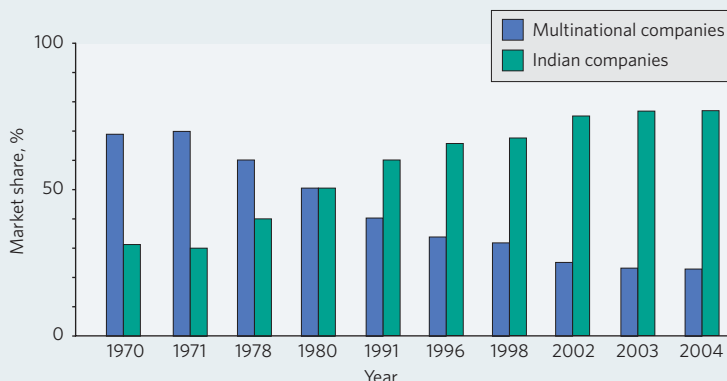
Outside of India, the number of companies producing vaccines has dwindled to 4 in 2005 from 26 in 1967. This reduction presents an opportunity for India and other developing countries, says Ganguly.

The Global Alliance for Vaccine and Immunization, launched by the Bill & Melinda Gates Foundation in 2000 is purchasing vaccines from Indian companies at low prices. In return, these companies are assured a long-term contract to guarantee revenue. The alliance has awarded contracts to the Serum Institute, Shantha Biotechnics and Panacea Biotech to make and test heat-stable vaccines.

K. S. Jayaraman



NATIVE COMPANIES DOMINATE INDIA'S PHARMACEUTICALS MARKET



LAND FOR RENT



K. S. JAYARAMAN

Beyond the gateway of the Biotech Park near Hyderabad the land lies empty. Companies are reluctant to build there until the infrastructure is complete.

“Welcome to Genome Valley”. The giant green-and-white sign stretches across the road on the way from the Hyderabad airport to this bustling south Indian city. But don’t blame the taxi driver if he meets your queries with a blank look — almost no one knows where the valley is.

Not too long ago, Hyderabad was dubbed ‘Cyberabad’, reflecting its strength in information technology. These days, it’s aiming for pastures new: the biotechnology sector. For now though, the ‘genome valley’ exists only in the minds of those who conceived it eight years ago.

The name refers to a 600-square-km area bound by an imaginary line that links nearly every institution in the city that has anything even remotely to do with science.

“I actually suggested that the whole of Hyderabad should be declared Genome Valley,” says Bhim Sen Bajaj, chairman of the southern chapter of the All India

Biotech Association. “They did not listen to me.”

In reality, Genome Valley is the Knowledge Park, 40 km from the city on 80 hectares of government land and set up by ICICI, a premier financial institution. There is no public transport to the area and, at one point, cars have to snake through muddy roads, occasionally interrupted by cows and hens.

The park offers modern modular laboratory units of approximately 300 square metres to rent. In the past six years, 13 companies have rented spaces, and an additional 7 have booked space.

A second area of the valley is the Biotech Park, which is intended for companies to use for manufacturing units. This park, which opened in 2001, has an impressive arched entrance to its 126 hectares — but it is almost empty. Officials say 19 companies have purchased plots and 7 have begun construction, but the promised infrastructure for these companies is not yet in

place. The water pipe was laid only a few months ago.

To make matters worse, builders are selling the land at about US\$112,000 per hectare, nearly ten times the government’s original price.

“I had no choice,” says S. P. Vasireddi, chairman and managing director of Vimta Labs, who is building a US\$10-million facility in a 4.5-hectare plot. “Land of this size is not available inside the city.”

For the moment, the valley has one undisputed king: Bharat Biotech, built by US-educated microbiologist Krishna Ella and his wife Suchitra. “Whenever a government guest wants to visit the genome valley, he or she is brought to our company,” says Seema Kumar, general manager of public relations for the company.

Bharat Biotech, which earned US\$10 million in 2004, produces vaccines, but the most used product at the company’s headquarters may not be one that

it manufactures itself. Instead it’s the anti-snake venom stocked in the first-aid kit. “The place is crawling with snakes,” says the company’s communication manager U. V. L. Ananda.

To help employees with the three-hour daily commute, Bharat Biotech operates shuttle buses to the city. In the meantime, there is no hospital, bank or police station nearby. ICICI bank is noted for its cash machines, but it has yet to set one up in its own Knowledge Park.

Bharat Biotech buys water from private tankers and generates its own electricity to operate its vaccine unit because the unit in nearby Turkapally village crashes at the slightest environmental disturbance, such as rain or lightning. The company has gleaming state-of-the-art technology, but no broadband Internet connectivity and, until recently, workers there could not use their mobile phones. Says one employee: “We do cutting edge science in such a primitive setting.”

K. S. Jayaraman

is expected to attract bioinformatics contracts from around the world and foster innovative companies.

“We not only want to build on the existing platform but expand the base to create global leadership in biotechnology,” says Maharaj K. Bhan, secretary of the DBT. “This will require larger investments.”

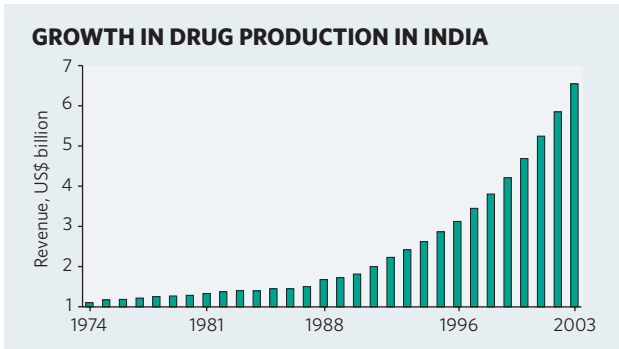
The science ministry has already announced a 50% increase in its budget over the past year for drug-discovery research and called for proposals from the industry.

To encourage small businesses, the DBT gives out grants of Rs5 million (US\$115,000) for proof-of-concept research and low-interest loans for subsequent product development and commercialization. Any money that companies spend on maintaining patents is also exempt from income tax.

Patent crackdown

One reason for this increased investment is that from 1 January 2005, a new patent law, which brings India in line with World Trade Organization (WTO) rules, came into effect. Indian companies will have to honour international patents and stop producing unlicensed generic drugs, a major source of their revenue over the past 30 years (see graphic, above).

The pharmaceutical industry’s research and development spending has shot up from Rs2 billion in 2000 to Rs8 billion in 2004, says D. G. Shah, secretary-general of the Indian Pharmaceutical Alliance. Chennai-based Orchid, which earned US\$82 million in 2004, is building a US\$15-million plant. Biocon is adding a US\$170-million research lab and manufacturing plant to its assets in



Bangalore. And Wockhardt, a large pharmaceutical company, last year built a US\$50-million complex — India’s largest — in Aurangabad. Nicholas Piramal India, which opened its US\$25-million research facility in September 2004, says it already has eight original products, including potential treatments for cancer and diabetes, in preclinical tests. Other generic producers such as Dr Reddy’s Laboratories in Hyderabad and Delhi-based Ranbaxy Laboratories are moving along this innovation route even as they continue to scout for patent-expired generics in the US market.

Still, “the odds are not in India’s favour in the innovation driven global drug markets”, says Prasanta Ghosh, a consultant to Cadila Pharmaceuticals in Ahmedabad and former adviser to the DBT. “We are nowhere compared with China, South Korea, Cuba or Brazil,” he says. “Our research has not gone into product development.”

Local companies will also have to compete on Indian soil with powerful multinational companies, others warn. Companies such as Merck and Bristol-Myers Squibb left India years ago because cheap copycat drugs cut into their profits. But with the WTO rules enforced to protect their patents, those companies will return, says Yusuf Hamied, Cipla’s chairman. “Multinationals will invade India in force and wipe us out in five years,” he warns.

Companies face other obstacles too. “Biology is extremely technology-driven and yet we do not make any instruments in this country,” says Syed Hasnain, director of the Centre for DNA Fingerprinting and Diagnostics in Hyderabad. “Except for flasks and syringes, every instrument is imported. We do not trust the local centrifuges, so we import even these.” Most institutes also have limited access to good animal-research facilities.

Another problem is the shortage of people trained in the latest techniques. India’s role in information technology is supported by the massive number of software experts in cities such as Bangalore, but such a pool of biotechnologists is not available.

When the Bangalore-based Institute of Bioinformatics (IOB) needs someone who knows the computer programming language Oracle, it can find a good candidate within a week. That’s because there are so many good programmers in the Industrial Technology Park, where the institute is based.

Akhilesh Pandey, a professor at the Johns Hopkins University, founded the IOB in 2002. In three years, it has published more than 40 papers, including several in high-impact journals. In April 2005, the IOB published its annotation of the X chromosome (H. C. Harsha *et al. Nature Genet.* 37, 331–332; 2005). The study, carried out in direct competition with Britain’s Wellcome Sanger Institute, marks the first time that any institute other than a genome-sequencing centre has characterized an entire human chromosome.

Training biotechnologists

With a booming biotechnology business and a demonstrated prowess in information technology, there should be a dozen such bioinformatics success stories in India. But even the big Indian pharmaceutical companies have been slow to adopt bioinformatics.

Although the country grants nearly 300,000 degrees and diplomas in biotechnology, bioinformatics and the biological sciences each year, companies struggle to find skilled staff. “Most of them get their degrees without seeing a biotech lab,” says Krishna Ella, managing director of Bharat Biotech International in Hyderabad. Most of those qualified also leave for greener pastures: up to 90% of those who finish their PhDs at the Indian Institute of Science go abroad. India needs to find ways to stem that massive brain drain, says Ella.

In the meantime, companies are wooing scientists to India from around the globe. According to estimates from the Indian Pharmaceutical Alliance, 10% of the new recruits at senior levels are expatriate Indians or foreigners.

Geetha Vani Rayasam, an IISc graduate, joined the Ranbaxy Research Labs in November 2004 after spending several years in Europe and the United States. Rayasam says many more like her would return to India if a few essential things were fixed. “There are several things that need to be improved, like a more professional approach, less bureaucracy and providing better salaries,” she says. “But the day is not far off when India might be leading the way in drug discovery.”

K. S. Jayaraman is Nature’s India correspondent.



Science minister Kabil Sibal is backing a plan to create a thriving biotechnology sector.

A. MANDAVILLU

SOURCE: THE WTO AND INDIAN PHARMACEUTICAL INDUSTRY, 2005