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India Gets Big in Bio Manufacturing

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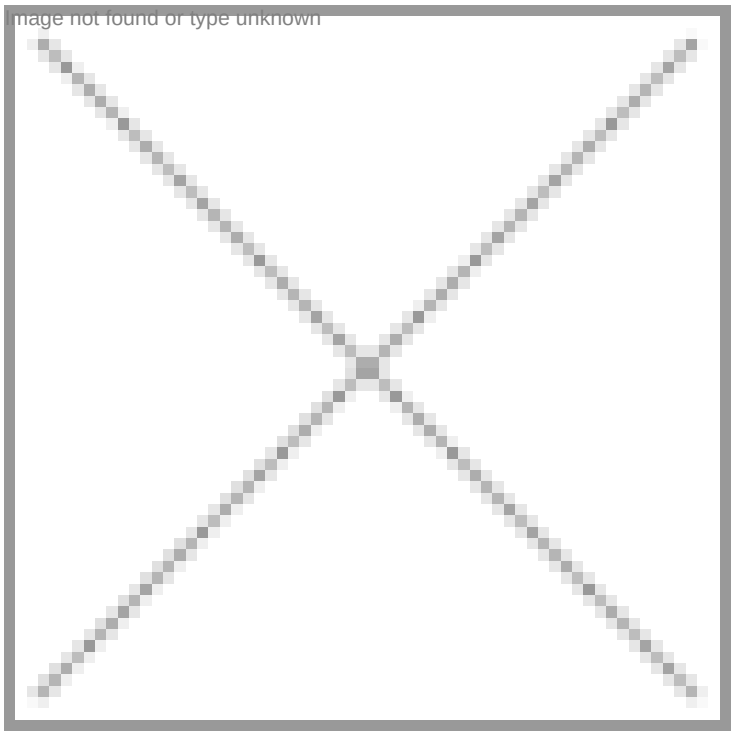
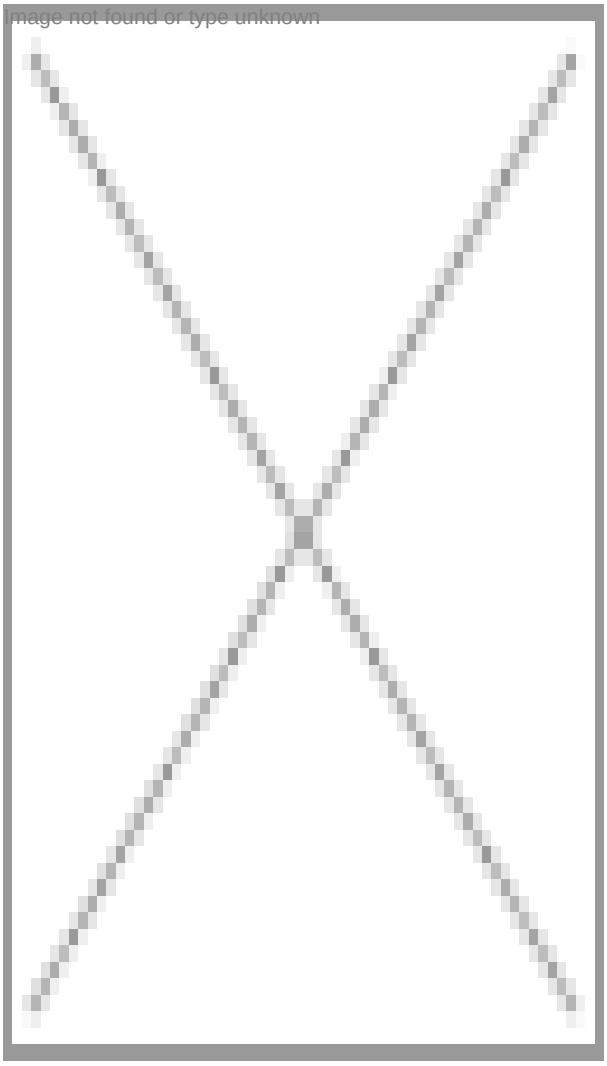


The famous line always has been that "Indian missed the bus for manufacturing destination". This may be true for other sectors, but not in the biotech sector. Walking into Hyderabad, one can see world class manufacturing centers in the campuses of Bharat Biotech, Biological E, Dr Reddy's Laboratories, Indian Immunologicals and Shantha Biotechnics to name a few. Moving into Bangalore, one would be fascinated with Biocon's plants. While Pune showcases world-class plants of Serum Institute, Delhi/Gurgaon houses impressive plants of Ranbaxy, Panacea Biotec etc.



Not just that. Contract manufacturing orders too are flowing. For instance, Biocon has a suppliers contract agreement with Bristol Myers Squibb for recombinant human insulin. Bharat Biotech has a contract with Wyeth. Surely, the opportunities in biotech product manufacturing are unfurling. The demand is on the rise. According to the Department of Biotechnology, the consumption of therapeutic recombinant proteins is going to increase significantly. The consumption of human insulin is estimated to increase from 95 kg in 1997 to 270 kg in 2005. Similarly the consumption for erythropoietin, interferons and streptokinase is estimated to increase to 4 kg by 2005 from 1.5 kg in 1997 and 2 million doses by 2005 from 0.2 million doses in 1997 and 3 million doses in 2005 from just 0.5 million doses in 1997, respectively.

Even the industry estimates that the market for biogenerics in India is expected to see a 43 percent jump from Rs 308.50 crore in 2001 to Rs 1,305.7 crore in 2005 and projected to reach Rs 1,864.3 crore by 2007 registering a growth of 19 percent.

Recognizing this huge potential, many companies are investing significantly in their R&D activities to reap the benefits by developing indigenous biotechnology products. While some companies are entering into marketing tie-ups and signing memorandum of understandings, some are going for in-licensing agreements to market the products in India.

There is no concrete data available on the investments made by the biotech companies on the manufacturing facilities. It is, therefore, not possible to give an accurate estimate of the investments made in biotech manufacturing. "However, based on the knowledge we have of the facilities built by biotech companies manufacturing biologicals and based on our knowledge of the cost of such vaccines, a very approximate estimate of the investments made would be of the order of Rs 1,000 crore," said Varaprasad Reddy, managing director, Shantha Biotechnics. This estimate does not include investments made in facilities for manufacturing fermentation based small molecule drugs such as statins, vitamins, anti-cancer agents and antibiotics.

India's strengths

Any manufacturing pharmaceuticals and biopharmaceuticals company would cite the following points as India's key strengths.

- Availability of educated and skilled manpower
- Proficiency in English
- Low capital and operational costs
- Proven track record in meeting international standards of quality.

Added Reddy, "Many Indian pharmaceutical companies have built manufacturing facilities approved by US FDA and EMEA. Companies like Ranbaxy, Dr Reddy's Laboratories are selling generic products in a big way in the US and Europe. In the biotech sector too, the scene is similar. Serum Institute has many of its products qualified by WHO. Shantha's Hepatitis B vaccine has been qualified by WHO. In contrast, few Chinese companies sell their pharmaceutical products in the US or Europe in a big way and none of the vaccines made in China, even though there are plenty of them sold in China, are qualified by WHO. The use of English as a means of communication probably helps Indian companies follow international standards of GMP, particularly with respect to documentation and may explain, at least partly, why Indian pharma and biotech companies are ahead of their Chinese counterparts in meeting global standards."

It is also no more a matter of cost arbitrage. Indian biopharmaceutical industry is going up the value chain. From being a pure reverse engineering industry focused on the domestic market, the industry is moving towards basic research driven, export oriented global presence, providing wide range of value added quality products and services. The companies, which are having business exposure to regulated markets and whose R&D activities are aligned to products going off patent are the favorites of the stock market too like Biocon.

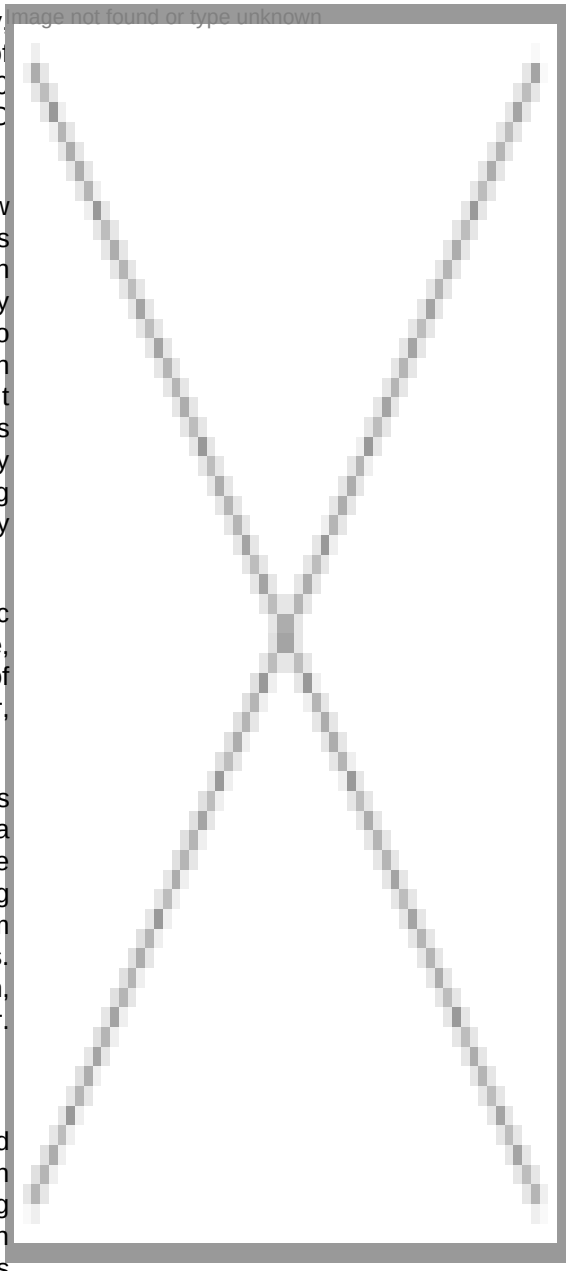
According to Dr Dhananjay Patankar, head, biotechnology, Intas Pharmaceuticals, which has recently launched a GCSF product, Nekine, in India, "There are two kinds of companies. Those specifically committed to biotechnology. Such companies will look at developing indigenous biopharmaceutical drugs. The second set of companies is that where biotechnology is not the core sector. But they want to enter this segment. Such companies will import and produce through tie-ups, in-licensing agreements, etc. Besides many multinationals sell the biopharmaceutical/recombinant products through the subsidiaries in India."

As of now only few Indian pharmaceutical companies like Wockhardt, Intas Pharmaceuticals, Cadila Pharmaceuticals and Cadila Healthcare have established capabilities to develop and manufacture recombinant products. Others like Shantha Biotechnics, Bharat Biotech International have already established their footholds in manufacturing of recombinant drugs in India.

Committed to Global Norms

There is ample proof that the Indian companies are committed to global standards. In fact Indian companies are understood to have received the maximum number of US Food and Drug Administration (USFDA) approvals. According to some reports, outside of the US, India ranks highest with 61 USFDA-approved plants. (Italy a close second with 60, Spain 25, China 22, Taiwan 9, Israel 7 and Hungary 5). India has the largest number of annual bulk drug filings (77) with USFDA. India is home to the largest number of pharma plants approved by USFDA outside the US. Indian pharma companies have also got certification from the European and Australian drug authorities.

Other international approvals include European Certificate of Suitability, MCA-UK (United Kingdom's medicine control agency), Irish Board of Medicines, TGA, Australia, completely environment friendly (ISO 14000 certified), WHO cGMP and ISO-9001 certified manufacturing facility, EC FDA, Novartis, USA and MCC of South Africa apart from local FDA.



Considering the flow of applications from Indian companies, USFDA is now looking at opening its office in India. The industry sources say that soon this could become a reality. Commenting on the approvals from the certification or the approving agency from the developed nations, Dr Dhananjay Patankar said they would give the approvals for manufacturing facility or to the product. About the amount of investments a company has to make on setting up a manufacturing facility of international standard, he said, "It depends on the scale of manufacturing/products. As far as Indian companies are concerned they can meet the GMP standards. Intas has already received the approval from TGA, Australia and MHRA, UK for bulk drug production. We know the system. It won't be a problem when a company comes out with a new drug."

"Cost involved in getting the product approval for the therapeutic recombinant drugs will vary as it involves three key issues-infrastructure, quality system and licensing," said Dr SD Ravetkar of Serum Institute of India. For renewal Kiran Majumdar Shaw, chairman and managing director, Biocon Ltd said, "Cost will be less."

If companies are not meeting the standards set by the international agencies then it may loose the contract. Haffkine Biopharmaceuticals Corporation, a government of Maharashtra undertaking is one such example. Haffkine Biopharmaceuticals, a manufacturer and exporter of vaccines to developing countries through UN Agencies, has lost a Rs 50 crore order last year from the UN agencies due to lack of certification from international agencies. Medha Gadgil, managing director, Haffkine Biopharmaceuticals Corporation, said, "We are working on upgrading our systems so as to get back the order. Gadgil is confident about getting the next year's order.

Growing Facilities

With the blockbuster drugs going off patent/turning generic in the regulated markets of the US and Europe, the generic markets are on a roll. Indian companies are filing Abbreviated New Drug Application (ANDAs)/Drug Master Files to serve these markets in terms of selling formulation drugs/sourcing bulk drugs to the generic companies respectively; this is being backed by getting their facilities approved by the regulatory agencies of regulated markets namely USFDA, UKMCA etc.

For example, Shantha has acquired competencies over the years to build and operate manufacturing facilities for biopharmaceuticals to international standards. Shantha has proven track record in meeting international standards of quality as its hepatitis B vaccine has been qualified by WHO.

"Shantha's capabilities in R&D, QC, QA and engineering would complement much to its strengths in manufacturing. Availability of competence in biotech process development, for example, would help troubleshoot in manufacturing. Similarly competency in testing biologicals would be of help in process control and finished product testing. Built in quality standards help the company in meeting international standards of GMP," informed Reddy.

Shantha now has four production suites, each about 16,000 sq.ft. in area, having class 100,000 and class 10,000 areas suitable for manufacturing biologicals. These facilities are equipped with sophisticated computer controlled fermentors (ranging from 500 Lâ€“1500 L), and downstream process equipment.

One of the production suits built in 1995 is being used mainly for manufacturing hepatitis B vaccine qualified by WHO. It has a capacity to 100 million doses of hepatitis B vaccine. The other three suits built recently are for manufacturing bacterial vaccines and other microbial cell culture based products have been designed to meet USFDA and EMEA standards. These manufacturing facilities are supported by other facilities including engineering services and utilities such as captive power

supply, water for injection, steam, compressed air, chilled water and oxygen supply lines, stores (8,000 sq.ft.) meeting GMP standards, QC laboratories (8,000 sq.ft.) and animal house (17,000 sq.ft.) meeting GLP requirements and an effluent treatment plant.

Tulip group currently has approximately 100,000 sq.ft. of GMP approved area with around 700 manufacturing, research and quality control personnel. By the year-end, the manufacturing space would be enhanced by about 15 percent along with appropriate investments in production hardware and manpower. "With this increase, we would be comfortable to double our turnover in terms of manufacturing traffic if the market requires so. In any case, with our current capacity, we would be able to fulfill our next year's objectives of Rs 100 crore by 2004-05," said DG Tripathi, director, Tulip group of companies.

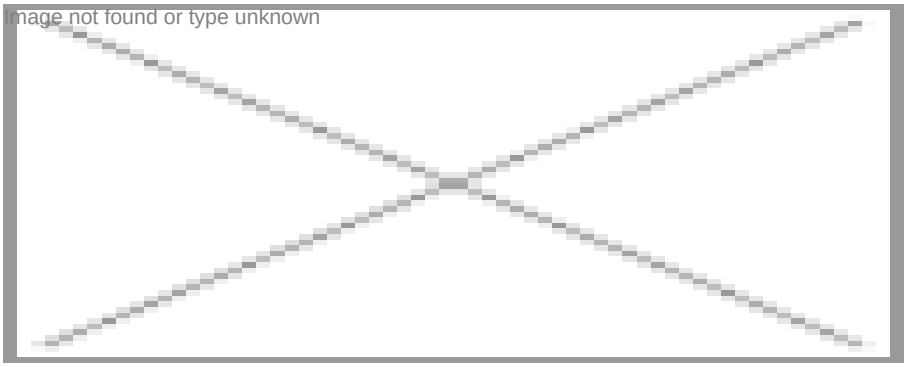
Serum Institute of India, a leading biopharmaceutical company in India with a turn over of Rs 491 crore is increasing its manufacturing capacity to meet the domestic as well as international demand. Dr SD Ravetkar, senior director, Serum Institute of India said, "We are in the process of completion of doubling our manufacturing capacity. Simultaneously we are increasing our investment on R&D, human resources and infrastructure. We are investing to tune of 7-8 percent of total sales into R&D."

With the acquisition of German Remedies Ltd and Banyan Chemicals, Zydus Cadila's manufacturing premises now comprise seven plants including its existing plants at Moraiya in Ahmedabad and Ankleshwar. The formulations plant at Moraiya is spread over 40 acres with a built up area of 53,000 sq.mt. This has the anti-rabies vaccine plant set up in technical collaboration with Swiss Serum and Vaccine Institute of Switzerland. It has commenced operations and the vaccines are ready for launch. The plant employs 660 people and houses warehouse facilities, quality control laboratory, formulation development and engineering departments.

Bharat Biotech International Ltd has set up a state-of-the-art manufacturing plant considered to be the largest in Asia-Pacific. It sprawls over a picturesque campus at Genome Valley, Hyderabad and is built with an investment of over Rs 100 crore.

According to Rajesh Jain, joint managing director, Panacea Biotec, "The manufacturing facilities are situated at New Delhi and Lalru (Punjab). A new pharmaceutical formulation plant is being set up at Baddi (Himachal Pradesh) which will comply with regulatory requirements of USFDA, MHRA, MCC-South Africa, WHO and other regulatory agencies of the world and also allow the company to avail fiscal incentives provided by the Government."

In the past year, auditors and representatives of WHO visited its formulations manufacturing facility and included Panacea in the list of preferred suppliers for the global program to eliminate Lymphatic Filariasis. Panacea Biotec continued making necessary investments in upgradation of the facility to meet the requirements of natural products like ThankGod Pain and Itch Relief Cream, Toff and Awayke.



Also it has invested in its existing facilities for vaccines formulation to obtain cGMP certification as per WHO guidelines. It initiated steps for setting up of new vaccine filling facility in compliance with cGMP requirements for filling of various biotechnology based injectable vaccines like Enivac HB (Hepatitis B), Trustworthy (Anthrax) and other combination vaccines including Easy Five [Pentavalent Vaccine (DTwP-HepB-Hib)] and Ecovac Tetravalent Easy Four (DTwP-Hib). Also, a new filling line separate area is being provided for pre-filled injection device in the new facility. The new facility was commissioned this year with an installed capacity of 3.25 million vials per annum.

In the case of Biocon, in December 2003, its submerged fermentation facility, its second extraction and synthetic conversion facility were inspected by USFDA for production of lovastatin, simvastatin and pravastatin. It has started developing several new facilities over approximately 5 Sq.km of area. In order to meet the demand for statins, it is augmenting its fermentation, extraction, and synthetic conversions capacities. It plans to spend Rs 120 crore in the next three years for the same. Besides, it has built a new facility for recombinant human insulin production. The company is expected to spend close to Rs 300-350 crore on the manufacturing facilities in the next three years.

Embracing New Patent Regime

With 2005 global patent agreement round the corner smaller biotechnology companies are being driven to do innovative

research and are picking niches where there is little competition.

The director of Tulip group of companies, DG Tulip said, "The group would continue to consolidate its strategy of manufacturing and marketing diagnostic products and platforms to address the needs of the laboratorians both nationally and internationally. Towards this goal, Tulip continues to address its product policies, R&D and product development requirements and indigenous efforts of import substitution with locally produced raw materials. The group will continue to access international markets much more vigorously than ever before."

Dr S D Ravetkar, senior director, Serum Institute of India Ltd, said, "With the product patent regime round the corner the companies should look at utilizing each other's strengths. (Just like Cipla entering into a tie up with Avesthagen for contract research). Contract manufacturing and contract research will grow with bio manufacturing trends in India."

Besides indigenous manufacturing Indian companies may also look for containerization, filling contract i.e., importing in small quantity and then manufacturing in bulk. The multinationals may also take the help of contract research organizations to work on new products, entities and molecules. They also prefer to market the products in India instead of putting money on manufacturing facilities for recombinant products.

However, Dr Ravetkar noted, "India should look at developing indigenous products, as it will help easy availability of the products at lesser cost. The indigenously developed recombinant drugs developed by Shantha Biotechnics and Bharat Biotech helped the consumers to avail the drugs at one-tenth the cost. It will also support the company to look at exports. That is the advantage of developing the products in house."

Kiran Majumdar Shaw, chairman and managing director, Biocon Ltd informed, "Definitely the focus will be on indigenous manufacturing of recombinant drugs. In the next few years, the growth will be on account of both indigenous manufacturing and filling contract. A lot of activities are taking place on this front and many more companies will shift to bio manufacturing in the next five years. Export is also a focus area the companies are looking at."

Bio manufacturing is emerging in India and the market for recombinant drugs has become fiercely competitive and price wars are common after a product launch. Along with the growth of the biomanufacturing, the allied sectors like contract manufacturing /contract research will also get a boost in India.

Narayan Kulkarni with Ch. Srinivas Rao and Faiz Askari