HEALTHCARE BIOTECHNOLOGY IN INDIA

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The production and commercialization of the first therapeutic recombinant human protein humulin (human insulin) in 1982 by Eli Lilly marked the dawn of a new era of unprecedented economic opportunities - the era of biotechnology hitherto unrecognized. The impact of biotechnology revolution was so strong in the U.S. that by late eighties all the 15 to 20 top multibillion pharmaceutical companies were into it and several entrepreneurial new biotechnology firms were established (Gibbons, 1984). For the most part they have been founded since 1976 - the same year the U.S. firm Genentech was founded. The peak year for the formation of biotechnology start-ups in the U.S. was 1982; in the UK. it was 1987. Start-ups in Japan were only few probably that the Japanese environment is more suited to the commercialization of bioproducts licensed from elsewhere.

The enormous economic potential of biotechnology was soon recognized by India as well which created the National Biotechnology Board (NBB) under the Ministry of Science and Technology in 1982 for the planning, promotion and coordination of biotechnology in the country. NBB was upgraded in 1986 to the Department of Biotechnology (DBT) also headed by a technocrat. In the last 20 years, DBT has spent billions of rupees on biotechnology covering development of infrastructure, manpower and almost the entire, spectrum of its research, development and applications (Table 1). DBT has nearly sponsored 48, post-graduate teaching courses which are undertaken by about 840 students per year. It has also established eight advanced autonomous institutions engaged in

world class research in biotechnology and two public sector industries (Table 2). Besides these establishments, DBT also awards a large number of research grants to investigators working in different areas of biotechnology and fellowships to work in Indian and foreign laboratories. Public investment in biotechnology has resulted in more than 5000 research, publications and a huge reservoir of trained manpower and 46 technologies which have been transferred to industries for further development and commercialization (DBT Annual Report 2002-2003). A few of these technologies have been launched and a few have been commercialized (Table 3). However, most of the commercialized products are not visible on the market and sales are insignificant. Two public sector undertakings, the Indian Vaccines Corporation Ltd. (IVCOL) and the Bharat Immunologicals & Biologicals Corporation Ltd. (BIBCOL) incorporated in mid nineties by DBT have not ,yet started full production. Since, 1996, BIBCOL has only formulated imported bulk into about 700 million doses oral polio vaccine which have been supplied to National, Immunization Programme (DBT Annual Report 2002-2003). IVCOL is a sick unit and , may never function.

Indian industry being very conservative looks only for the opportunities to get fast returns on their investments. They prefer to concentrate on trade and to create market for biotechnology products developed by US. and other companies. Biotechnology start-ups were formed in only a few of the top Indian pharmaceutical companies in the late eighties. Although, venture capital was available from banks and public sector establishments as soft loan and the Government of India also provided significant tax concessions on R & D expenditure, yet only few Indian pharmaceutical companies took advantage and most of them depended on internal funds perhaps because they were not willing to share profits with financiers.

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Table I. Programmes and R & D Projects undertaken by the DBT (1).

S.No.	Programmes	S.No.	Programmes
1	Human Resource Development		<ul style="list-style-type: none"> - Biofuels - Medicinal and aromatic - Plants <p>Medical Biotechnology</p> <ul style="list-style-type: none"> - Vaccines - Diagnostics - Drug Development <p>Human Genetics and Genome analysis</p> <p>Seri Biotechnology</p> <p>Stem Cell</p> <p>Food Biotechnology</p> <p>Environmental Biotechnology</p>
2	Bioinformatics Biogrid India	5	Biotech Product and Process Development
3	Infrastructure Facilities Biotech Facilities Programme support and Centre for Excellence	6	Societal Development Programme for Rural Areas Women Biotechnology SC/ST Population
4	Areas of Research Basic Research Agriculture <ul style="list-style-type: none"> - Crop Biotechnology - Biofertilizers - Biopesticides and Crop management - Animal Biotechnology - Aquaculture <p>Plant Biotechnology</p> <ul style="list-style-type: none"> - Plant Tissue Culture - Bioprospecting and Molecular Taxonomy 	7 8	International Cooperation Jai Vigyan National S & T Missions
		9	Patent Facilitating Cell

Table 2. Autonomous Institutes and public sector undertakings established by the Department of Biotechnology, Ministry of Science & Technology, Government of India.

S.No.	Autonomous Institution	Location
1	Centre for DNA Fingerprinting and Diagnosis	Hyderabad
2	Institute of Bioresources and Sustainable Development	Imphal (Manipur)
3	Institute of Life Sciences	Bhubaneswar
4	National Institute of Immunology	New Delhi
5	National Centre for Plant Genome Research, JNU	New Delhi
6	National Bioresource Development Board	New Delhi
7	National Brain Research Centre	Gurgaon
8	National Centre for Cell Sciences	Pune
Public Sector Undertakings		
1	Bharat Immunologicals & Biologicals Corporation Ltd.	Bulandsahr (U.P.)
2	Indian Vaccines Corporation Ltd.	Gurgaon

.Biotechnology being cost intensive requires whole huge funds to create adequate R & D. and manufacturing facilities. Indian industry obviously, focused initially on the development of diagnostic kits and reagents because it is faster and relatively cheaper to bring such products onto the market which ensures quick returns on the investments.

Achievements and rewards

Indian public sector has created sufficient technical manpower, world class R & D facilities, working models, easily available funds, awareness and a couple of industries. Indian technical manpower is produced at very high cost in terms of private and public money and time which is serving more the developed than their own country. Private sector has established strategic early leads and came out with important in-house developed diagnostic kits, reagents and other products which were at that time completely imported (Table 3). Many technologies were transferred to Indian industries and a few to other countries from Research Laboratories and Universities in India (Table 4). This success is phenomenal but economic achievements have been insignificant of that expected or that happened in the developed countries.

Economic developments of healthcare industry depend on the healthcare system, public awareness and cost versus benefits of the product and marketing strategies. India virtually has no healthcare system like in the U.S. or other developed countries. Sometimes back, health insurance was not even heard of in India. It has come to existence now but it is still available to a very small fragment of the society. In the absence of health

insurance to all; the cost of hospitalization, diagnosis, treatment and surgical procedures is borne by the patient and only some employees in the public and private sectors get the costs reimbursed. As a result of its high cost and scarce availability, majority of patients use and have access to only the minimum medical facility. Diagnosis in most cases is done by the physician/surgeon without the support of the laboratory tests to reduce the overall cost of treatment by eliminating payments to diagnostic laboratory. This certainly reduces cost of the treatment initially but often results in wrong diagnosis and wrong and lengthy treatment ultimately costing more in time and discomfort and sometimes even life. As required and expected by patients, a physician especially a private practitioner prefers to initiate treatment immediately. In the case of an infectious disease, a combination of antibiotics or broad spectrum antibiotics of different specificities is usually prescribed rather than recommending a diagnostic procedure which is often costlier than the treatment. This practice is routine which not only restricts the use of proper diagnosis but also the development of diagnostic industry. Strategically, Indian industry concentrated first on

the development of diagnostics and diagnostic reagents and both of these categories of products failed to generate business because of a total lack of a system, 'awareness and inexperienced marketing personnels having little knowledge about the product. Diagnostic industry made no efforts to develop awareness and marketing strategies and concepts to stress the 'need for diagnosis for correct and efficient treatment and failed in the creation of this market. The

Table 3. Some of the diagnostic test kits, reagents and other products indigenously manufactured and commercialized by Indian industry.

S.No.	Product	S.No.	Product
1	Reagents: Total about 350 reagents including antigens, monoclonal and polyclonal antibodies, antibody-enzyme conjugates.	7	Liposomal agglutination test for syphilis.
2	Rapid colour card test for pregnancy.	8	Recombinant Hepatitis B Vaccines
3	Latex agglutination test for pregnancy.	9	DPT vaccine
4	HIV ELISA	10	Polio vaccines
5	Monoclonal antibodies for blood grouping.	11	Rabies vaccines
6	Rapid colour card test for foecal occult blood.	12	Tetanus vaccine

Table 4. Some of the technologies developed by National and International Research Laboratories which were further developed and commercialized by Indian Industries.

S.No.	Products	S.No.	Products
1	Pregnancy tests	6	Hepatitis C tests
2	Filariasis test	7	Recombinant Hepatitis B vaccines
3	Typhoid test	8	Leprosy Immunomodulator/Vaccine
4	HIV 1/2 tests	9	Streptokinase/Thrombolyte
5	Hepatitis B tests	10	Hyaluronate sodium injections

total world diagnostic market is about US. \$ 26 billion out of which 43% is North America alone followed by Western Europe (27%), Japan (11%), Latin America (4%), India, China and Eastern Europe 1% each and 12% others (Theta Reports, April, 2002). Diagnostics for pregnancy, blood glucose and foecal occult blood (for colorectal cancer) have a market of more than a billion \$ in US. alone. All these products were developed by Indian industry and launched in the early nineties.

Subsequently, diagnostics for typhoid (simultaneous detection of Vi and O9 antigens of *S. typhi* using a pair of monoclonal antibodies), hepatitis B, syphilis (liposomal agglutination colour test), HIV, filariasis, etc. were developed and launched. Many of these tests particularly for *S. typhi*, syphilis, and filariasis were specific and first of the kind ever developed in the world yet all commercially failed. Therapeutic leprosy immunomodulator also first of its kind ever developed in the world did not pick-up at all and hyaluronic acid based ophthalmic surgical device and an injection for the treatment of the osteoarthritic pain of the knee joint

also performed miserably in the market.. India has developed and commercialized recombinant hepatitis B vaccines which were produced earlier by only SmithKline Beechum (now GlaxoSmithKline and Merck). The combined worldwide sale of hepatitis B vaccine was more than \$1.7 billion. Indian market for hepatitis B vaccine is estimated to be around Rs 60 crore. Indian hepatitis B vaccines offered low cost advantage over the imported vaccine yet it did not generate appreciable revenues to make companies. It is surprising to find that a major Indian pharma company after marketing indigenously produced diagnostic for colorectal cancer and several clinical chemistry kits and immunodiagnostics for pregnancy, typhoid, syphilis, HIV, blood grouping monoclonal antibodies and developing in-house technology for pilot plant scale manufacture of human chorionic gonadotropin closed its biotech operations. Another Indian pharma major also decided to close biotech R & D and productions but continued trading of diagnostics. Two other Indian pharma majors perhaps first to enter biotech R & D and some more also closed their R & D facilities. At present, about fifty products based on the technologies

Table 5. Sales of some of the biotechnology drugs (Source: Earnst & Young data from Med. Ad. News, July 2000 and May 2001).

Drug	Company	Chemical	Indication	Sales (\$ Millions)
Procrit	Johnson & Johnson	Epoetin- α	Anaemia	2,709
Epogen	Amgen	Epoetin- α	Anaemia	1,960
Intron A and Rebetron	Schering-Plough	Interferon- α/β and ribavirin	Hairy cell leukemia, warts, hepatitis B, hepatitis C. etc.	1,360
Neupogen	Amgen	Filgrastim	Neutropenia, etc.	1,220
Humulin	Eli Lilly	Human insulin	Diabetes	1,137
Avonex	Biogen	Interferon β/α	Multiple sclerosis	761
Engerix-B	Glaxo SmithKline	Hepatitis -B vaccine	Hepatitis B	700
Cerezyme	Genzyme	Imiglucerase	Type 1 Gaucher disease	537

transferred from DBT as well as from national and international research laboratories to some of these companies are supposed to be in the pipeline and continuing in pipeline for the last several years. Most of these products may never come out.

Analysis

Biotechnology has made phenomenal success in India in almost all the sectors including the healthcare. Excellent infrastructure and highly trained manpower have resulted in the development and commercialization of several monoclonal antibodies based diagnostics, recombinant and traditional therapeutic and prophylactic vaccines, biotherapeutics and biodevices. These technical successes have so far eluded economic success. A technology cannot be called successful until it achieves economic excellence more so about biotechnology because from the commercial perspective it is compared with cars and computers and has potential to influence global economy. Biotechnology in India started with a boom but did not go up to the end in the race. Each of the top four biotechnology products in the US. enjoyed sales exceeding \$ 1 billion in 2000. The combined sales of Epoetin (Epogen and Procrit) were more than \$ 4.6 billion (Table 5). A single biotech product can build companies worth \$ 10 billion as in the case of IDEC Pharmaceuticals in June 2001. Two products built Amgen, which is valued at \$ 68 billion. Biotech products can even move mountains. A positive phase III study for a protein used to treat sepsis added \$ 25 billion to

Eli Lilly's market value in the summer of 2000. Celera Genomics' piece of the genome landscape gained as much as \$14 billion in market value in two and a half years (Bird, 2001). In India, biotech products did not make biotech companies but inversely several pharma majors have closed their biotech operations. There are but few non- pharma start-ups in biotechnology which began with R & D and 'developed and commercialized recombinant vaccines, diagnostics and industrial enzymes. They have achieved some success and started making profits.

Biocon an enzyme producing company established in 1978 has made significant industrial contributions. It produced initially by traditional extraction processes a number of industrial enzymes and commercialized them. The company has transformed into a drug firm and also manufactures statins and immunosuppressants. It has planned to set-up large scale cell culture facility to produce monoclonal antibodies and therapeutic proteins. Biocon's value at present exceeds \$1.1 billion (Times of India, Ahmedabad, page 13, April, 08, 2004). Large scale cell culture facilities since long exists at Cadila (both Zydus and Healthcare groups), Shantha Biotechniques, Wockhardt and Bharat Biotech' and some of them are technically successful and produce therapeutic enzymes and 'vaccines and a few also produce recombinant vaccines, and therapeutic and diagnostic proteins.. All figures available through press, industry, expert Annual Reports or technical

Table 6. Prices of some of the imported and indigenously produced vaccines and devices (Indian Drug Review, Nov.-Dec. 2003).

Product	Indication	Manufacturer	Dose	Cost (Rs)
Biovac	Hepatitis B vaccine	Wockhard	10 µg/ 0.5 ml	140.00
			20 µg/ 1.0 ml	190.00
Shanvac	Hepatitis B vaccine	Shanta Biotechnic	10 µg/ 0.5 ml	150.00
			20 µg/ 1.0 ml	223.23
Engerix B	Hepatitis B vaccine	GlaxoSmithKline	10 µg/ 0.5 ml	181.00
			20 µg/ 1.0 ml	323.50
Visial	Eye surgery	Cadila Pharma	0.80 ml of 1.0%	700.00
Healon	Eye surgery	Parmacia, Sweden	0.55 ml of 1.0%	1936.00

departments speak primarily on what may happen in future in biotechnology in India but nobody has looked back to ascertain what really was achieved of golden dreams and forecasts made earlier. Actually, only little economic success has been achieved.

Some of the important reasons for economic failure of biotechnology has been lack of industrial wisdom, strategy and experience to launch and commercialize new products.

Indian pharma industry has hardly launched a new product. Most of the products manufactured by Indian pharma industry have been "me too type" which have already been produced and marketed elsewhere. It is well known that when first time more than 300 biological reagents, rapid colour card test for pregnancy, dipstick dot ELISA for S. typhi, hygienic occult foecal blood test, liposomal colour agglutination test for syphilis and HIV ELISA were marketed in the late eighties and early nineties, there was practically no competition in the market. Marketing manager responsible for these products having long experience of marketing drugs in a major pharma company 'frankly asked for "me too type products" for doing business and not the new products. Interestingly, when "me too type products" were developed in another major pharma company, the marketing manager wanted original products and not "me too type". It was true for not only diagnostics but for biotherapeutics, vaccines/immunomodulator, biodevices and other products as well. An absolutely original product for which the country should feel proud, the immunomodulator for use with multiple drug therapy for the treatment of leprosy which could be of assistance to eradicate leprosy from the face of the Earth was marketed by an Indian pharma major but did not succeed and the product is not even visible in the market at present. This indicates that while entering into biotechnology, India did consider everything but not marketing which still lacks in proper manpower trained to handle new products. Since new products

are not "me too type", awareness and interest have to be generated in the field for their use. Those scientists who developed the products could help in developing the missing marketing knowledge but they were kept away from marketing except for supporting the marketing team in resolving problems arising by the use of product in the market place. It shows that R&D, manufacturing and marketing lack adequate coordination and team spirit. Other important reasons include Government willingness and cost of the product. In order to establish a new industry, Governments' promotion is essential. GOI has established biotechnology in the public sector including establishment of two companies, the BIBCOLD and IVCOLD. Non-economic activities such as R & D, teaching and , development of trained manpower, working capital, establishment of highly specialized National Research Laboratories, etc., have all met with great successes. Public sector undertaking BIBCOLD functions only partially and IVCOLD is a failure. Private sector industry entered with indigenous products into the market saturated with imported products mainly from the U.S.. In spite of the fact that Indian products not only meet 'the approval criteria of the Drugs Controller General of India (DCGI) but compared well with the imported bests, 'the leader products' when tested by outside laboratories recognized and approved for the purpose by the DCGI. Neither the Indian market nor the GOI promotes such products. Many of such products were developed in the country's most prestigious National Research Laboratories with public funds and a few took more than 20 years of research and during their development their progress has been regularly monitored by special Task Forces and Expert Committees set by the GOI. Not accepting such a product developed with public funds in a National Research Laboratories and approved by Nations' Approval Authority, in the National Disease Control Programme to Control the Disease suggests

Government's unwillingness to promote such a product. The "imported crazy" Indian market sells anything with the label "imported" and the users proudly speak that we use only imported products in our clinic/ laboratory/hospital. However, little or no attention has been paid to understand whether clinical evaluation results and specifications of the imported product are applicable to Indian conditions and population that is genetically different from the population in which clinical testing was done. Some products such as HIV and, other ELISAs of national health importance are exempt from customs duty but an indigenous HIV ELISA manufacturer who imports ELISA plate and some reagents has to pay customs duty because only complete ELISA test kit is duty free and not its constituent plate and other reagents. Hence, an indigenous HIV and other ELISA test kits can not be cheaper than the imported ELISAs. As a result of this; HIV ELISA tests, which are continuously developed and marketed by Indian industries since the early nineties would not stand in competition against the imported kits. Therefore, hardly any of the 'indigenously manufactured ELISAs is available in the market and the production of many of them have been discontinued. Price does not seem to be an exclusive factor because in spite of the fact that non-ELISA type diagnostics, biotherapeutics, vaccines and other products have been offered by the Indian Industry at much cheaper prices than the imported identical products (Table 6), the products are not economically successful.

SUMMARY

Biotechnology in India has made great progress in the development of infrastructure, manpower, research and development and manufacturing of biological reagents, biodiagnostics, biotherapeutics, therapeutic and prophylactic vaccines and biodevices. Many of these indigenous biological reagents, biodiagnostics, therapeutic and prophylactic vaccines and biodevices have been commercialized. Commercially when biotechnology revenue has reached \$25 billions in the U.S. alone in 2000 excluding the revenues of biotech companies that were acquired by pharmaceutical companies, India has yet to register a measurable success. The conservative nature and craze of the Indian Industry for marketing imported biotechnology products, lack of Government support, almost non-existing national healthcare system and lack of trained managers for marketing biological and new products seem to be the important factors responsible for poor economic development of biotechnology in India. With the liberalization of Indian economy, more and more imported biotechnology products will enter into the Indian market. The conditions of internal development of biotechnology are not likely to improve in the near future and it is destined to grow only very slowly. Even today biotechnology in India may be called to be in its infancy.