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# Indian Efforts for Developing Biotechnology

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***Abstract***: Indian government shall remain in the forefront of developing a sound biotech base. A strong industry shall emerge in conventional biotech products. The local consumption shall also substantially rise. The patent expired products shall be the mainstay of modern product-portfolios. There would be more exploitation of GM-plants and the commercial introduction process shall be hastened. Large quantities of enzymes produced from GM organisms shall be in the market. Sizable sum has been spent in the public institutions. The industry is setting up robust facilities. More money shall therefore be channeled for applications, for which the basic research has to move up. Policy reorientation towards basic research in all areas of Indian needs shall benefit the country.

***Key words***: Biotechnology, health care, agriculture, recombinant therapeutics, Bt-cotton, Indian, biotech industry, manpower, biotech parks, GMOs

## Introduction

Biotechnology is a set of techniques developed through basic and applied research, using biological materials or their analogues. The techniques are applied to organisms or their parts to produce, identify or design substances or to modify organisms. The applications are to meet human needs.[1, 2]

## Indian Government Efforts

Indian government is in the forefront of developing a sound biotech base in the country. This situation emerges out of compulsions and social commitments to minimize foreign dependence, especially in the high-tech areas.

Indian foresight at the government level to benefit from modern biotechnology was much focused. It dates back to 1982, when a small

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division was created in the Department of Science and Technology of the Central Ministry of Science and Technology. Later on, in February 1986 a full-fledged Department of Biotechnology (DBT) was created[3] that was independent and , which could independently pilot singularly the multifaceted development in biotechnology in the country. Besides DBT, several other government departments also allocated funds for the development of biotechnology in the country.

The annual allocations[4] of funds over a decade during 1990-91 and 2000-01 (Table 1) by different departments are summarized below:

**Table 1: Allocation of Funds by Different Funding Agencies for Promoting Biotechnology in India**

Unit: million Rupees

| Funding Agencies | 1990/91 | | 2000/01 | | % Growth over 10 years | |
|---|---|---|---|---|---|---|
| | Total | Biotech | Total | Biotech | Total | Biotech |
| DBT | 655 | 655 | 1391 | 1391 | 212 | 212 |
| CSIR | 2351 | 24 | 9120 | 182 | 388 | 758 |
| DST | 2589 | 26 | 7798 | 234 | 301 | 900 |
| DSIR | 131 | 1 | 584 | 6 | 446 | 600 |
| ICAR | 3236 | 3 | 13990 | 280 | 432 | 9333 |
| ICMR | 396 | 15 | 1470 | 15 | 371 | 100 |
| UGC | 3495 | 35 | 14070 | 704 | 403 | 2011 |
| **TOTAL** | **12853** | **759** | **48423** | **2812** | | |

While DBT remained the main department from the government to promote biotechnology, with the passage of time several other scientific departments also started taking more interest in developing this area. However, the quantum of money allocated by major departments like ICAR for agricultural research in biotechnology, ICMR for medical research in biotechnology and other departments like the Ministry of Human Resource Development, University Grants Commission (UGC), and All India Council for Technical Education (AICTE) for engineering research in biotechnology had been lower. Up to the present time, this trend continues and DBT remains the main funding organ of biotechnology development in the country. The combined expenditure in biotechnology from all the funding agencies of the government up to the end of 2006 is considered to be around Rs. 28000 million (US $650 million). While the efforts made thus far are praise worthy, time has come to allocate more funds, especially to promote innovative application; novel biotech applications based on local technology are not yet adequate. To enable this to happen, basic understanding in new biology has to be more profound. Concomitantly, basic science has to be put to fast applications.

## Indian Commitments to Globalization in All Aspects of Biotechnology

India is a signatory to the World Trade Organization (WTO) and the country has enacted the provision of WTO in letters and spirit. The industrial licensing policy has been liberalized. Import duties have been rationalized. An equal label playing ground has been created for all the entrepreneurs, irrespective of whether they are Indian or foreigners. All steps have been taken in manners that do not create an imbalance in the core competence of the country. The Indian Intellectual Property Rights (IPR) laws have also been modified which are consistent with the Trade Related Intellectual Property Rights (TRIPS) of WTO. TRIPS require the member countries to comply with other aspects of IPR; these include protection of plant varieties, protection of trademarks and geographical indications. These have bearings in biotechnology. Indian Plant Variety Protection Act, enacted to comply with the provisions of TRIPS of WTO allows farmers to grow and retain the purchased and cultivated planting materials including seeds under farmers' rights. This process enables the use of F2 hybrids and varieties for cultivation, which assists and augments the needs of poor farmers for planting materials. In practice, this process has contributed to increased agricultural output from poor farmers, who were used to cultivate saved seeds of lower productivity.

Being also a signatory to the Convention on Biological Diversity (CBD), India is committed to protect its genetic biodiversity; concurrently it would have to consent to enabling access to people or parties to its genetic biodiversity. India has enacted its Biodiversity Law and has constituted its designated authority for accessing Indian Genetic Biodiversity by the CBD member countries.

India is making rapid progress after the initiation of liberalization in 1991.The decision to liberalize was not linked with political uncertainties that prevailed over the years, which continue to exist. The fast progress is linked with enhancement of productive abilities to manufacture and to export in various countries, especially in USA. Biotechnology shall make rapid progress as the abilities to export also enhances.

## Indian Regulations for Genetically Modified Organisms and Substances[5]

Use of all genetically modified (GM) substances is regulated under the Environment (Protection) Act 1986 (EPA) and the Rules 1989 (Rules). Guidelines have been issued from time to time (1990, 1994, 1998, 1999 and 2008) to ease the application process. The genetically modified organisms (GMOs) can be living as in the case of microorganisms, plants and animals (GM edible yeast or lactobacillus or a host of agricultural produces such GM corn, potato, tomato, soybean, wheat, rice, mustard/ rape seed, etc); they can also be substances derived from GMOs that are non-living like inactivated GMOs, or substances derived from GMOs like proteins, nucleic acids, carbohydrates, lipids etc., which are produced from GMOs. The Rules require that all GM organisms and products thereof be introduced only after they are found to be safe; safe to the natural environment as well as safe for the health of human and animals. The law is based on precautionary principle.

India is a signatory to the Treaty on Cartagena Protocol, which is a Treaty for regulating the trans-boundary movement of GMOs; GMOs are designated as Living Modified Organisms (LMOs) in the Protocol. The Protocol is consistent with the Indian Rules on GMOs; Indian Rules also cover the products produced from GMOs and is thus wider in its scope.

The Department of Biotechnology (DBT) of the Government of India is considering setting up of a National Biotechnology Regulatory Authority (NBRA) as an independent, autonomous and professionally-led body to provide a single window mechanism for bio-safety clearance of genetically modified products and processes. The clearance process may become more versatile as the NBRA gets enacted and becomes operational. The creation of NBRA shall include defining its linkage with EPA and Rules, besides defined administrative authority.

While a rational regulatory structure is in place, there is an urgent need to invest for creating more competence for testing and assessing the safety of GMOs in public funded institutions. Public-private partnership overseen by the government could be other alternative structures. GMOs shall be utilized in several fields of human needs from drugs to food and drinks to agriculture (including animal husbandry, poultry, fisheries and aquatic life), industry-applications and environment management. But capacity to assess GMO technology in several facets such as risk assessment, risk management, unique identification and quantification when in the open environment especially in situations of advantageous presence, and long term impact of GMOs on human health and environment are areas where there are inadequacies. The areas of public education, public participation and public confidence building are also weak, which need strengthening. The existing infrastructure for handling GMOs need also be strengthened. Inadequate national capacity and skills to handle this technology would promote implementation of restrictive policies, which would be counter-productive to national benefits. Government efforts are to be strongly coupled with public and private organizations to handle such a highly science-based technology. Considering the potential benefits from GMO technologies especially in agriculture, the need for a priority to enhancing capacity building cannot be belittled.

Humankind has been exposed to GMOs for more than one decade. The horizon of knowledge has expanded. The perception of risks from certain GMOs has changed. The GM organisms used in contained environment for producing bioactive pharmaceutical substances have benefited millions; there is no report about adversities created by such organisms. In agriculture, GM crops have been produced more economically; they have benefited people. There is yet no proven report of irreversible damage to environment or human. Use of GM organisms has significantly contributed to production of certain biological substances like the enzymes, which have contributed to the emergence of better detergents, textiles, leather, poultry feed, etc. Indian biotechnology can make strong contributions in the international market in generic therapeutic biomedicines; at home, in agriculture the use of GMOs can contribute to significant gains in efficiency and productivity. In other areas like innovative diagnostic devices and pollution remediation, the GMO technology can perform more efficiently. India does not have major innovation round the corner. Therefore, available technologies should be used to the maximum extent to benefit the country; the regulations should not hinder the fast use of genetically modified substances in commerce, where products have proven safe elsewhere over a period of time. The Bt-cotton technology was approved in early 2002; there is yet no new GM plant approved for Indian agriculture. Is there is a need to introspect how the commercial introduction in India of elsewhere found safe GMOs can be made faster?"

Several new materials are evolving in the biotech horizon. Humanized monoclonal antibodies; si-RNAs; therapeutic human proteins made in plants or animals or viruses; modified cells; stem cells; and the like would use recombinant DNA technology at some stages of their manufacture and application. Many other substances would be designed, based on knowledge of cell biology and cellular regulations. The existing law does not clearly define if these substances are covered in all situations of their use. In their use, there are potential risks to the recipients. Should their safety be evaluated under the laws, regulating GMOs?

## Biotechnology Parks: Government Efforts[6]

The government of India through the department of biotechnology has been instrumental to promoting the setting up of small and medium industries in biotechnology in different parts of the country. Towards these efforts the government with the assistance of the state governments has earmarked land and such zones have been designated as Biotechnology Parks. Such parks have been planned to provide financial and other logistical support to the young entrepreneurs who are not in a position to incur high capital expenditure in the biotech industry but have the intellectual capabilities to develop, design and perfect new biotech products and processes by utilizing such facilities.

Up to the present time, Biotech Parks have been created or planned/proposed in a number of states in India including Tamilnadu, Andhra Pradesh, Kerala, Karnataka, Uttar Pradesh, Punjab, Maharashtra, Gujarat, Uttaranchal, Rajasthan, Delhi, Orissa, Madhya Pradesh etc. The total investment contemplated in such facilities is estimated at approximately 15 billion rupees.

Biotech Parks are facilities created mainly to promote tiny, small and medium biotech entrepreneurs. Such entrepreneurs may find the parks attractive. Tiny and small entrepreneurs can initiate modern biotech products if they come from academia with proof of concepts with them. Such possessions require a backup of basic research with potentials of applications. The Indian academia is not biased upon the application-oriented research; there may not be many who are ready to come forward to take a business risk. Development of conventional biotech industries in the parks would tantamount to providing subsidized facilities. Can such industries pay back? Is there a need to review how the parks could promote modern biotech industries in preference to the conventional biotech industries?

## Manpower Development in Biotechnology: National and Private Efforts[1]

One of the few countries to initiate an integrated programme of human resource development in biotechnology was India. The courses comprised post-graduate teaching programmes, short term training courses in India and abroad as also long term overseas courses to develop better faculties. The postgraduate courses were initiated in 1985 in collaboration with UGC, ICAR and the Department of Ocean Development. The curriculum contained most of the areas and elements in different institutions. The teaching programme is continuously monitored by the government to ensure minimum and uniform teaching standards. Currently the DBT is supporting seventy institutions for teaching general biotechnology, seven in agricultural biotechnology, one each in medical and marine biotechnology besides certain diploma courses in biochemical technology and molecular biology. The total student output annually is around 1000 numbers. The Indian Institute of Science (IISc), Bangalore has also been involved in selecting quality students for certain areas through written examination. All the students qualifying the DBT sponsored programmes are provided fellowships to ease the entry of meritorious but economically backward classes.

To upgrade the knowledge and research areas of interest, the Indian scientists are exposed to newer cutting-edge areas in biotechnology R&D by the DBT by offering overseas associates as well as short-term training courses. Full-fledged departments of biotechnology are being set up in various institutes all over India. Besides the efforts of DBT, the AICTE has approved B. Tech programmes in biotechnology in several public colleges/institutions. Other than higher educational institutions, expansion of biotechnology as a subject has been planned at school level also by the AICTE and UGC with the introduction of a specific module on biotechnology. The Ministry of Human Resource Development is also promoting biotechnology programs through its instruments in various institutions. The total output of post-graduate students in biotechnology from the government endeavor is about 1500 numbers annually.

Besides government efforts, great interest has been taken by several private entrepreneurs to set up institutions to teach biotechnology at graduate and post-graduate levels. Some private engineering colleges are also offering graduate degrees (B. Tech) in biotechnology. Private entrepreneurs running teaching institutions have taken advantage of the over promotion of biotechnology by the society. The private institutes turn out nearly 5000 additional students.

The total number of biotech students turned out by the country from various institutions is around 6500, which is a sizeable number. Such students belong to the average age group of 21-25 years and they possess degrees as B. Tech or M. Sc or M. Tech or MBA in biotechnology. These students compete with several thousands other life sciences students for jobs; competition is thus becoming tough.

Although biotechnology has grown in multiple facets of human activities creating career opportunities, at present, the students passing out face stiff competition for obtaining a job. A large number works in research projects, some pursuing their PhD. They often accept under paid jobs. Many of them leave the country for better opportunities; maximum opportunity exists in U.S.A., Canada and certain European countries including UK. This situation needs serious attention. The Indian industrial sector opportunities are application oriented, requiring special skills for high paid jobs. Specialized jobs are not many; these include scale up and process development, manufacture, quality control, preclinical and clinical research, regulatory affairs, documentation and project management. Process development skills require sound knowledge in chemical and biochemical engineering. In manufacture, specialized equipment is deployed in crafted facilities; experience in handling such equipment is necessary. Quality control activities call for hands-on experience in specialized techniques and instruments handling. Clinical research is about dosage finding, dosage fixing, generating information on safety and efficacy in human subjects in specialized hospitals. Documentation for product registration is a specialized training, requiring skill in scientific writing and presentation, in accordance with legal compliance of existing rules and acts. Project managers build manufacturing facilities for biotech projects; they lead an entire project. Their expertise requires leadership for inspiring the team to accomplish the goal. They identify action items, organize meetings, coordinate and track the progress, quality and cost. Project managers should have excellent communication skills and should be able to coordinate among various departments. Project managers are not specialists but they should possess multidisciplinary skills with sound knowledge in biotechnology. In all the above areas, the presently graduated biotech students do not receive adequate skills from their institutions. The biotech industry has to spend considerable resources to in-breed the required skills. Modern biotech industry is yet at the developmental stage in India. As the industry develops, there would be more growth in trade, transport, manufacture, project management, information management, finance management and communication. Sound development of modern biotech industry shall create avenues for more jobs in India in the coming years. In the meantime, if the turnouts remain at the current rate then there may be the emergence of situations of noticeable unemployment for the biotechnology pass outs.

## Scenario of Modern Biotech Products in India

India has been practicing conventional biotechnology for several decades. Products manufactured by the use of genetic engineering, immunological techniques, cell culture methods and hybridoma technology are increasingly being used during the last 15 years and local research in these areas has been intensified. The following Table 2 gives[7] the local production, imports and exports of biotech products during 2007 and the estimate for 2012.

**Table 2: Local Production, Import, Export and Import as % of Local Consumption**

| | Sub Sectors of Biotech Products (Rs. In billion) | | | | Total | |
|---|---|---|---|---|---|---|
| Product Availability Mode | Health Care Products | Agricul-ture | Indus-trial Products | Other Biotech Products | Billion Rs. | Billion US $ |
| **2007** | | | | | | |
| Local Production | 53.85 | 40.60 | 38.50 | 2.70 | 135.65 | 3.16 |
| Imports | 12.65 | 1.00 | 4.10 | 1.15 | 18.90 | 0.44 |
| Exports | 15.95 | 1.10 | 2.10 | 1.30 | 20.45 | 0.48 |
| Imports as % of Local consumption | 25% | 2.5% | 10% | 45% | | |
| **2012 (Estimate)** | | | | | | |
| Local Production | 120.50 | 69.30 | 55.20 | 8.20 | 253.20 | 5.89 |
| Imports | 10.90 | 2.00 | 5.00 | 1.30 | 19.20 | 0.45 |
| Exports | 47.00 | 4.00 | 3.50 | 2.70 | 57.20 | 1.33 |
| Imports as % of local consumption | 12.9% | 3% | 8.8% | 19.1% | | |

Health care products include vaccines, diagnostics, recombinant products and fermentation based substances. Agriculture includes traded seeds (hybrids and varieties), bio-fertilizers & pesticides, plant tissue culture and other industries. Industrial and other products include enzymes, bioinformatics, alcohol & fermented beverages as well as research chemicals used in biotechnology work.

The main indicators from the above table are the trend of increase in local consumption and decrease in imports over the years. Local consumption, which is the total of local production and imports minus exports, shall be on significant rise; the quantum of imports as the percentage of local consumption shall decrease over the years. These are indicators of brisk industrialization in biotechnology.

In agriculture, insect-resistant Bt-cotton was approved for cultivation in the country in early 2002; this wise decision contributed significantly to increase in the cotton lint production and improved its quality. This had also contributed to sizable reduction in the use of chemical pesticides. The crucial transgenic components of the technology were imported from three countries, namely USA, China and Japan; the insect –resistant trans-genetic trait was introduced in several Indian hybrids that made the difference. During 2007-08, nearly 14 million acres of land were brought under the cultivation of Bt cotton using locally produced seeds worth 10200 million rupees[8]; cotton lint production registered 31.5 million bales.[9]

Modern biotechnology is rather new to India. There is little doubt however, that the applications of modern biotechnology would increase very fast, as the products or processes hold great potential for providing much better solutions to improve the health of people or the quality of life, improve agricultural productivity significantly along with supplying more nutritious food, produce industrial bio-products at much cheaper prices and improve the quality of environment more effectively on a sustainable basis.

## Indian Capabilities in Modern Biotechnology

Coming back to Indian developments, while by the end of 2007 there existed over 900 companies operating in all sectors of biotechnology, there were only about 60 companies that were working in modern biotechnology.

None of the Indian companies have introduced any significant biotech product of original research in Indian market that could be considered as unique, introduced for the first time in the world. But some have introduced known products that tantamount to effective imports substitution. Some others have teamed up with foreign companies for sourcing technologies and are experimenting with new products produced by foreign technologies with a view to introduce them into the Indian market within the framework of Indian laws. Certain companies are also introducing novel and effective but non-IPR protected genes in to Indian germplasms to increase agricultural productivity or to reduce production costs. All these conditions and situations are satisfactory to begin with, but the country has to go a long way to come up with innovative products that would be original and that would have cutting edge impact in the global context. The existing scenario depicts considerable lack in basic research and inadequate long term planning in the industry. Why is such a scenario emerging?

Ideas and innovations surface from insights and observations of individuals imagining novel possibilities and making challenging conjectures. Such situations are encountered, among other reasons, under conditions of extreme stress, where sustainability and survival conditions are at stake. This is not yet the condition in the biotech R&D sector of the industry in India in the global context.

Indian biotech industry with significant turnover has to inculcate talented individuals to prepare for harnessing opportunities, for which the key persons have to be knowledgeable and well informed about the innovative platforms with profound acquaintance of global developments. Concomitantly, the industry cannot be shy of investing heavily in potential areas of basic research, where possibilities exist for applications. It is futile for the industry to pursue basic R&D where applications are not in sight; the team leaders have, therefore, to be carefully chosen who have a knack for applications. For becoming an innovative company, the individual industry has to have patience and would have to distinguish between intangible assets and R&D costs.

Production: The modern biotech products are only a few, which are being produced currently in the country. They include the following in various biotech sectors [1, 2, 10, 11and 12] (Table 3).

Up to the October 2008, twenty-two recombinant drugs (Table 4) have been approved [7, 12] for marketing in India, of which only eleven are being manufactured as indicated in Table 3.

**Table 3: Modern Biotech Products Currently (2006-07) being Produced in the Country**

| Sector | Major Industries Producing with Remarks |
|---|---|
| **Health** | |
| **Hepatitis B surface antigen based Vaccine** | Transgene Biotech, Hyderabad conducted first experiments in the country using recombinant *Hansenula polymorpha*. Technology belonged to Rhein Biotech, Germany. |
| | Shantha Biotechnics, Hyderabad used recombinant *Pichia pastoris* for this. Osmania University and CCMB both at Hyderabad and other assistance taken by co. |
| | Wockhardt Ltd. Aurangabad used recombinant yeast strain of *Hansenula polymorpha*. Technology belonged to Rhein Biotech, Germany. |
| | Bharat Biotech International Ltd., Hyderabad produced in *Pichia pastoris*. Assistance from IISc, Bangalore. |
| | Panacea Biotech Ltd., Delhi used recombinant *Pichia pastoris*. The technology belonged to CIGB of Cuba. |
| | Serum Institute of India Ltd., Pune used recombinant *Hansenula polymorpha*. Technology from Transgene Biotech, Hyderabad. |
| | Biological E Ltd., Hyderabad produced the substance using recombinant *Pichia pastoris*. The technology was obtained from the IISc, Bangalore. |
| **Granulocyte Colony Stimulating Factor (G-CSF)** | Dr. Reddy's Laboratory developed the technology using transformed *E. coli*. The technology was developed in-house. |
| | Intas Ltd. Ahmedabad also developed the technology in *E. coli*. The technology was developed in-house. |
| | Several other companies are developing the technology while many are importing & selling. Biocon also producing. |
| **Recombinant Erythropoietin** | Wockhardt Ltd. Aurangabad producing using modified CHO cell line. It was an Italian technology. |
| | Intas India Ltd. Ahmedabad is also producing it. The strain was procured and technology perfected in-house. |
| | Efforts being made by several others. Also, there are direct importers. Many are formulating product by importing bulk. |
| **Interferon alpha 2B & pegylated product** | Shantha Biotehcnics Ltd. Hyderabad developed the products in *E. coli* strain. The technology was developed in-house. |
| | Efforts by several other newcomers as well as introduction of the product by direct importers. Several companies are trying to develop the pegylated form of the product. |
| **Epidermal Growth Factor** | Bharat Biotech Ltd. Hyderabad developed the product in E. coli. The technology was developed in-house with assistance from IGIB scientists. |

*Table 3 continued*

*Table 3 continued*

| | |
|---|---|
| **Streptokinase** | Shantha Biotechnics, Hyderabad; Bharat Biotech, Hyderabad & Biocon, Banglore developed this technology in *E. coli*. The recombinant product is inherently unstable and stabilization is tricky. |
| **Recombinant Human Insulin** | The product was developed in *Hansenula polymorpha* by Wockhardt India Ltd. The basic technology was procured from Rhein Biotech, Germany.<br><br>The product was developed in *Pichia pastoris* by Biocon India Ltd. The strain was procured from Shantha Biotechnics, Hyderabad.<br><br>Efforts by several other newcomers as well as introduction of the product by direct importers. Several Indian companies are trying to develop the basic technology. |
| **NIMOTUZUMAB** | Biocon Ltd. Bangalore has launched a monoclonal antibody produced by genetic engineering method, which works to block certain receptors of epidermal growth factor that are responsible for proliferation of cancer cells. The technology belongs to Cuban Centre of Molecular Immunology. Biocon received the rights for the product in India. |
| **RITUXIMAB** | Dr. Reddy's Laboratory, Hyderabad has introduced the product based on local production and purification. The product is indicated for treating Non-Hodgkin's Lymphoma and Rheumatoid Arthritis. The technology and the recombinant cell line were procured from U.S.A. |
| **Several New Products & Bio-Generics** | Many companies are working on different compounds with/without collaborations to develop the generic products and to market them. |
| **Agriculture** | |
| **Bt Cotton** | **Private Sector** |
| | Mahyco-Monsanto (MM), a sister concern of Monsanto Inc., USA and Maharastra Hybrid Seeds Company Ltd., (Mahyco) Jalna obtained approval for producing Bt cotton seeds containing *Cry1Ac* gene (MON 531 event) in March 2002 and started selling. Later, they introduced seeds containing two genes namely *Cry1Ac* & *Cry2Ab* from event MON 15985. Company also working to generate herbicide resistant plants using CP4 EPSPS gene of Monsanto USA. Hybrid Bt-cotton seeds were introduced through Mahyco.<br><br>MM sub-licensed several companies namely Rasi Seeds Company Ltd., Nuziveedu Seeds Co. Ltd., Hyderabad, Tamilnadu, Nath Seeds Ltd. Aurangabad, Ankur Seeds Ltd., Nagpur, Krishidhan Seeds Ltd., Jalna, Ajeet Seeds Ltd., Aurangabad, Ganga Kaveri Seeds Pvt. Ltd. Hyderabad, Tulasi Seeds Pvt. Ltd., Guntur, Prabhat Seeds |

*Table 3 continued*

*Table 3 continued*

| | |
|---|---|
| | Ltd. Hyderabad, Emergent Genetics, Hyderabad, Vikram Seeds Pvt. Ltd., Ahmedabad, Pravardhan Seeds Ltd., Hyderabad, Vikki Agrotech Pvt. Ltd., Hyderabad, Prabhat Agri biotech Ltd. Hyderabad, Vibha Agrotech Ltd., Hyderabad, Nandi Seeds (P) Ltd., Ahmedabad, Pro Agro Seeds (P) Ltd., New Delhi, Namdhari Seeds (P) Ltd., Bangalore, Bio Seeds Research, Hyderabad, Vibha seeds (P) Ltd., Hyderabad, Proagro Seeds Co. (P) Ltd., Gurgaon, Amar Biotech Ltd., Hyderabad, Bayer Bioscience Pvt. Limited, Hyderabad, Seed Works India Pvt. Ltd, Hyderabad and Solar Agrotech Pvt. Ltd., Rajkot to use Bt-C*ry1Ac* (MON531 event) in their non-Bt cotton lines. MM also licensed several companies to produce Bt-cotton hybrids containing two genes namely *Cry1Ac* & *Cry2Ab* from event MON 15985 to Mahyco, Krishidhan, Ajeet, Nuziveedu, Rasi, Amar Biotech, Anjur, Bayer, Bioseeds, Ganga Kaveri, Kaveri, Monsanto Genetics Pvt. Ltd., Mumbai, Nandi, Prabhat, Tulasi, Vibha, Vikarm and Namdhari. |
| | Nath Seeds Ltd. Aurangabad obtained cotton seeds containing insect resistant genes named as " GFM *Cry1A*" containing a fusion of Bt-*Cry1Ab* & *Cry-1Ac,*. The stable hybrids are being sold. The technology was procured from Biocentury Transgene Company, China. Nath also sold the technology to Navkar Hybrid seeds Pvt. Ltd. Ahmedabad, Uniphos Enterprises, Vapi, Yashoda Hybrid Seeds Pvt. Ltd., Hinganghat, Zuari Seeds Ltd., Bangalore, Green Gold Pvt. Ltd., Aurangabad and Safal seeds & Biotech Ltd., Mumbai for producing Bt-hybrids. |
| | Syngenta India Ltd., Pune has introduced insect resistant cotton seeds containing Vip-3 gene. The stable hybrids are being sold. Syngenta India obtained the original technology from its parent company. |
| | JK Agri Genetics Seeds Ltd., Secunderabad, purchased transgenic seeds containing Bt-*Cry1Ac* gene (event 1) from BREF-Bioteck, IIT, Kharagpur & UDSC New Delhi to produce Bt-hybrids, which are being marketed. The technology was developed at IIT Kharagpur by BREF-Biotek & UDSC New Delhi. |
| | **Public Sector Institutions** |
| | Central Institute for Cotton Research, Nagpur has developed plants resistant to lepidopteran pests using Bt. *cry* genes. Transformed cotton Bt BN Variety has been introduced. |

Several companies are also importing the above products besides supply through the local manufacturers. The solely imported eleven products were approved for sale, based on data on clinical trials generated out side India.

**Table 4: Recombinant Therapeutic Drugs Approved for Marketing in India**

| S. No. | Molecules | Therapeutic applications |
|---|---|---|
| 1. | Hepatitis B vaccine (r- HBsAg based) | Immunization against Hepatitis B virus |
| 2. | Granulocyte Colony Stimulating Factor | Treatment of neutropenia |
| 3. | Erythropoietin | Treatment of anaemia |
| 4. | Interferon alpha 2B | Treatment of leukemia, Hepatitis B and Hepatitis C |
| 5. | Epidermal Growth factor (EGF) | Organ morphogenesis and mitogenesis |
| 6. | Streptokinase | Dissolution of clot in acute myocardial infarction |
| 7. | Human insulin | Treatment of diabetes |
| 8. | GM-CSF | Chemotherapy induced neutropenia |
| 9. | Interferon alpha 2A | Chronic myeloid leukemia |
| 10. | Human growth hormone | Treatment of dwarfism in children |
| 11. | Nimotuzumab | Treatment of breast cancer |
| 12. | Rituximab | Treating non-Hodgkin's lymphoma & arthritis. |
| 13. | Tissue Plasminogen Activator | Dissolution of clot in acute myocardial infarction |
| 14. | Blood factor VIII | Treatment of haemophilia type A |
| 15. | Follicle stimulating hormone | Treatment of reproductive disorders |
| 16. | Teriparatide (Forteo) | Parathyroid hormone for treating osteoporosis |
| 17. | Drerecogin alpha (Xigris) | Burns and severe sepsis |
| 18. | Platelet Derived Growth Factor (PDGF) | Receptor antagonist in certain types of cancer |
| 19. | Interleukin 2 | Treatment of renal cell carcinoma |
| 20. | Blood factor VII (Eptacogalpha) | To control bleeding in hemophilia patients |
| 21. | Interferon gamma | To treat chronic granulomatous disease & osteopetrosis |
| 22. | Interleukin 11 | To treat thrombocytopenia (Platelet reduction) |

Research & Development: Basic research in modern biotechnology is mainly in public funded institutions. Industry is substantively in areas of applications. In healthcare, some institutes are trying to develop generic biopharmaceuticals and novel methods of delivering them; a few are engaged in drug designing and software development, utilizing techniques of bioinformatics. In agriculture [5, 10 & 11], research is pursued for the development of genetically modified rice, potato, tomato, corn/ maize, brinjal/eggplant, mustard, pigeon pea, cauliflower, cabbage, chickpea, groundnut, black-gram, wheat, banana, coffee, muskmelon and tobacco. Both private and public institutes are in research. Different kinds of transgenic nucleic acid constructs are being handled. The genes are mainly out sourced. Some analogues have been constructed based on available literature and individual skills to derive economic advantage in cultivation. Several institutes are working to produce enzymes from recombinant organisms; the products and processes being developed are for xylanase, different kinds of proteases, lipases, cellulases, amylases, phytase and rennin (for cheese making); certain enzymes for molecular biology research are also being worked upon. The efforts certainly need more spread and dispersion. Besides pursuing more avenues for applications, basic investigations to tackle serious problems in health and agriculture should be undertaken in a focused manner.

The global picture of production and use of modern biotech products is very wide. The major health care products already approved globally[13] with their annual sales turnover is placed below in Table 5.

**Table 5: The Global Major Biotech Products Market by Class 2001, 2002, 2005 and Projections for 2010**

| Class | Sales 2001 ($m) | Sales 2002 ($m) | Sales 2005 ($m) | Estimated Sales 2010 ($m) |
|---|---|---|---|---|
| Erythropoetins | 6,702 | 8,426 | 12,815 | 17,350 |
| Interferons | 3,923 | 5,731 | 6,635 | 8,470 |
| Insulin | 3,949 | 4,400 | 5,800 | 10,340 |
| Monoclonal antibodies | 2,997 | 4,150 | 9,120 | 18,200 |
| Blood factors | 3,188 | 3,565 | 4,985 | 6,360 |
| Colony stimulating factors | 2,059 | 2,739 | 4,630 | 5,910 |
| Growth hormones | 1,652 | 1,703 | 1,860 | 2,050 |
| Interleukins | 173 | 213 | 390 | 630 |
| Growth factors | 108 | 123 | 180 | 360 |
| Therapeutic vaccines | 50 | 68 | 170 | 340 |
| Others (calcitonins, enzymes, TNF, etc.) | 2,080 | 2,222 | 2,600 | 7,000 |
| Total | 26,881 | 33,340 | 49,185 | 77,010 |

The actual sale of top 25 biotech companies in the world for the year 2005 was reported to be US $ 40 billion[1], which is about 82 per cent of the global sales for the year 2005. This indicates that the biotech products are monopolized within a very small number of players and would remain so for some time in the future till there is adequate global development and dispersal.

The global monopolistic situation needs to be studied and understood in order to improve the local situation in India. Monopoly comes mainly from IPR; IPR-protected products are the gifts of intense research.

In order to understand the dynamics of research across the world, it is necessary to analyze what research work is presently going on across the globe. The developments taking place globally in terms of progress of emergence of new products in various areas in the health care products arena is described below[14] in Table 6.

**Table 6: Number of Biotechnology Drugs in Development**

**Biotechnology Medicines Under Development by Therapeutic Category (Upto Dec. 2006)**

| Therapeutic Category | No of Drugs |
|---|---|
| AIDS/HIV/Infection/Related Conditions | 22 |
| Autoimmune Disorders | 44 |
| Blood Disorders | 10 |
| Cancer/Related Conditions | 210 |
| Cardiovascular Diseases | 22 |
| Diabetes/Related Conditions | 15 |
| Digestive Disorders | 14 |
| Eye Conditions | 6 |
| Genetic Disorders | 9 |
| Growth Disorders | 4 |
| Infectious Diseases | 50 |
| Neurological Disorders | 17 |
| Respiratory Disorders | 13 |
| Skin Disorders | 7 |
| Transplantation | 4 |
| Other | 18 |
| **Total** | **465** |

In 2007, more than 100 new biotech drugs have been marketed globally. Wide ranges of biotech drugs are under development as shown above; major R&D work is being carried out in U.S.A. In India no new R& D stage product has yet emerged that would qualify to be rated as unique that has potential for making significant impact globally.

In agriculture, efforts to develop GM plants and planting materials are being made in India as has been indicated earlier. The global development is moving much faster and several types of genetically modified plants are being invented that are safe to the environment as also the food products produced from them are safe to consume. Such developmental work is a continuous process and if India wishes to take advantage from them, extensive alliance[15] may have to be created till the local capabilities are sharpened. The strength of India lies in its genetic biodiversity as well as several parental lines developed in agriculture that are proven to be more efficacious in productivity and resistance to stressful conditions. Therefore, incorporation of more favourable transgenic traits in them would benefit Indian agriculture considerably. The question is why Indian development is not matching the global competition.

It would be evident from the above that in all the sub-sectors of modern biotechnology India has to make more progress in basic research as well as in applications in new biology, to catch up.

## Future Trend and Interventions in Biotechnology

India already has developed competence in selected areas that provide the entrepreneurs an edge over other developing countries to set up viable and competitive biotech industry in certain areas. Indian Government continues to play a significant role in the promotion of biotechnology in all its facets. The efforts of DBT during the initial years in transferring institutionally developed technologies to the industry have been summarized.[16, 17] These efforts have been instrumental to developing competence mainly in the conventional biotech products.

Existing and new entrepreneurs shall be expanding their activities and entering in to the bio-similar or bio-generic products in health care area and in genetically modified plants, (using available genes and constructs) in agriculture. Indian productive parental lines for hybrids and varieties (for self-pollinated crops) shall be extensively utilized in producing GM plants using borrowed genes, in agriculture. Expansion shall also be taking place in conventional biotech activities in all sectors of biotechnology. The deployment of the existing mindset in a background of almost non-existing basic research infrastructure at sites of the existing industrial premises would not enable or encourage them to put efforts to invent or discover such new products that would have sales of jackpot kind (annual sale more than 1billion US dollars). With sound expertise already existing in the deployment of microbial fermentation processes and with modest capabilities in downstream processes for recovering milligram or microgram quantities of metabolites from liter quantities of fermented broth using, especially standardized micro-filtration and chromatographic techniques as well as membrane filtration methods, where for products or processes deployment very little basic research inputs are contemplated and where complex product characterization services requiring inputs from sophisticated instruments such as RP-HPLC, MALDI-TOF, DNA sequencing, capillary gel electrophoresis, etc. are available on hire, many entrepreneurs shall invest in several value added bio-pharmaceuticals, which are expected to be produced in sizeable quantities locally. Concerted efforts would be made especially for products where the selling prices are several times higher than their manufacturing costs and the availabilities are still in the hands of a few foreign companies that are yet monopolizing the world market, while the product patents have expired on them or are on the verge of expiry. There would be crowding of several companies in such endeavour and once in into the business endeavour, several of such entrants shall invest in R&D in order to become more productive. It is anticipated that the market competitiveness and the compulsions to remain efficient shall drive sizeable investment in creating R&D capabilities in biotechnology in the industry sector. This situation shall be fuelled and stimulated by several government departments and institutions by extending assistance by providing seed capital to certain classes of activities and entrepreneurs. It is not yet clear if such strategies are adequate.

India has to have more healthy people to face the global competition. Several neglected diseases of the poor including tuberculosis, malaria, diarrhea, trypanosomiasis, dengue, leishmaniasis and lymphatic filariasis are responsible for many man-day losses in productivity. Indian biotech R&D has to address these problems in public funded institutions and come out with robust solutions. In other major areas that contribute to significant loss of man-days such as diabetes, cardiovascular diseases, cancer and mental health disorders, efforts should be made through policy interventions to have access to current biotech drugs to treat these disorders. Transgenic substances have potentials for raising the efficiency in agriculture and food availability. Basic research in public funded institutions needs to be stepped up in strategic areas; these include development of novel genes, promoters, selectable markers, protocols for plants and animals transformation & regeneration, field testing & performance evaluation, environmental and food-safety evaluation, etc. General public has to be made aware and knowledgeable by the government regarding crops and foods improved by the application of genetic engineering. Regulations have to be coupled with sound science and societal interest factors to speed up the decision making process for the commercial use of GMOs on a precautionary principle.

## Concluding Remarks

India may emerge as a strong industry in biotech products in the coming years. The scenario shall manifest dominance in the conventional biotech products. The local consumption shall also rise substantially. The patent expired biotech products shall be the mainstay of modern product portfolios. In agriculture, many stress tolerant genes shall be inserted into Indian plants to produce, say pest-resistant plants. Large quantities of enzymes produced from GM organisms shall be in the market.

Conventional biotech industry shall grow fast and sizably in the present business environment. Such products shall meet the local demand and a portion shall get exported too. Recombinant DNA products shall be exported from among the generic biotech segment, where product patents have expired. But the markets in the developed world would not be easily accessible; the industry and the government may have to closely work to ease the process.

There are indications that productivity in agriculture is required to be raised fast; use of GMOs can contribute to the process. Trans-genes may be IPR-protected elsewhere. But India has strong foothold to negotiate for authorizing the use of its genetic parental materials, where trans-genes would be inserted. In the background of increasing food prices and large subsidy in agriculture, the exploitation of GM-plants and seeds may be examined on a case-by-case basis, and the commercial introduction process be hastened.

Large sum has been spent in the public institutions. The industry is setting up more basic facilities for biotechnology. More money shall, therefore, be channeled towards industrial R&D for which the basic research has to move up. Innovation is the creative ability of transforming basic understanding into applications. India needs more of innovations in that sense of the term both in its institutions and in industry. The country shall have expectations from such innovations to have some star products emerging. Wisdom lies in taking more proactive steps to develop a globally competitive local industry that stands on solid foundation of basic research. Facilitation of biotech industries no doubt makes economic gain; but modern new products should also emerge. Otherwise, the achievements would continue to look small before the world developments where companies are moving ahead skillfully with more concerted efforts, after the human genome sequence was unveiled in 2002 to read the "Book of life" chapter by chapter to bring in better solutions in several facets of modern biotechnology. Forging strong alliance among the Indian industry and the public institutions should make a difference for the country in the global context.

## Endnotes

1 Ghosh (2008).
2 Ghosh (1998).
3 Website homepage of Department of Biotechnology, Government of India. http://www.dbtindia.gov.in/
4 Ministry of Finance, Govt. of India, Budgetary Papers of Relevant Years.
5 Ghosh and Ramanaiah (2000).
6 DBT (2006).
7 Author's study & estimate
8 Compiled by the authors by interviewing major companies and government departments
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10 Ghosh (1999).
11 Sharma, Charak and Ramanaiah (2003).
12 Indian GMO Research Information system; www.igmoris.nic.in.
13 Estimate for 2010 is based on basic information from Patent Scan Vol. 8, No. 7, Jan 2007, pp 3-4
14 Medicines in Development, Biotechnology 2006 Report. Pharmaceutical Research and Manufacturers of America (PhRMA). Website: www.phrma.org
15 Ghosh (2004).
16 Ghosh (1996).
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