ORIGIN, EVOLUTION AND STATUS OF THE MEDICAL BIOTECHNOLOGY INDUSTRY: PERSPECTIVES AND PROBLEMS FOR INDIA

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SANGEETA TYAGI

Centre for Studies in Science Policy
School of Social Sciences
Jawaharlal Nehru University
New Delhi-110067
India
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CENTRE FOR STUDIES IN SCIENCE POLICY
SCHOOL OF SOCIAL SCIENCES
JAWAHARLAL NEHRU UNIVERSITY
NEW DELHI-110067

Gram: JAYENU
Phone: 6107676
Extn: 2461

Date: 31st July 2003

Certificate

This is to certify that the dissertation entitled **Origin, Evolution and Status of the Medical Biotechnology Industry: Perspectives and Problems for India,** submitted by **Sangeeta Tyagi** in partial fulfillment of the requirements for the award of the degree of **Master of Philosophy** of Jawaharlal Nehru University is original work according to the best of our knowledge and may be placed before the examiners for evaluation.

Chairperson **Supervisor** **Co supervisor**

DEDICATED TO MY PARENTS

AND MY TEACHERS

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Sangeeta Tyagi

Sangeeta Tyagi
Centre for Studies in Science Policy
School Of Social Sciences
Jawaharlal Nehru University
New Delhi, PIN 110067.

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INTRODUCTION

The term 'biotechnology' encompasses many activities, which have in common the fact that they all harness the fundamental abilities of living organisms.[1]

Biotechnology is the most recent phase in a historical continuum of the use of biological organisms for practical purposes.[2] The practical use of biotechnology in high yielding crop varieties and for medical purposes is universally acknowledged. Biotechnology encompasses techniques applied to living organisms or parts thereof to identify or design substances or to produce or to modify organisms for specific applications.

Biotechnology is not new.[3] It has been practiced in ancient fermentation and wine industries. Selective breeding of animal and plant varieties was of common practice during ancient time. Biotechnology applications were common among earlier human civilizations but utilizing the understanding of the genes in the laboratory with better precision is comparatively a recent phenomenon.

A notable feature of the living organisms is the diversity of biological processes they undergo. These processes may serve as biological factories, designed to convert specific raw materials into specific products. Modern biotechnology draws its strength from these biological processes, which have been developed over billions of years of evolution.[4]

Biotechnology is broadly classified as traditional biotechnology and modern biotechnology. Traditional biotechnology techniques were in practice before the discovery of DNA (deoxyribose nucleic acid) and mainly related with utilization of biochemical and

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[1] Steve Prentis, *Biotechnology: A New Industrial Revolution*, London: London Orbis Publishing, 1984, p. no.18.

[2] P.K. Ghosh, " Biotechnology in India- Current status and future challenges", *Invention Intelligence*, July-August, 1999 pp. 149-161.

[3] Ann Murphy and Judi Perrella, 1993, "Overview and Brief History of Biotechnology" Woodrow Wilson Biology Institute, available at http://www.woodrow.org/teachers/bi/1993/intro.html.

[4] Above no.1, p. no.20

physiological processes of the organisms. The techniques developed afterwards, such as cell fusion techniques, recombinant DNA technology, protein engineering and structure-based molecular designs, are considered modern biotechnology and are mainly concerned with genetic engineering.[5]

From development point of view biotechnology has seen three phases. First phase included the ancient biotechnology techniques prevalent in the ancient civilizations. It was related with the fermentation and wine industry as well as selective breeding of plant and animal varieties. The second phase started with the advent of antibiotics. This phase is characterized by the fact that it acknowledged the participation of microorganisms in curing certain diseases through the manufacturing of antibiotics. The third phase is occasionally termed as the modern biotechnology phase and includes the manipulation of genetic information through techniques like genetic engineering that allow exchange of genetic information between two non-interbreeding species, which was not possible earlier. Thus, the biotechnology practices came under laboratory control from the field trials.

The discovery of the recombinant deoxyribose nucleic acid technique (r-DNA technique)[6] and polymerase chain reaction technique (PCR)[7] proved to be landmark in the history of biotechnology. These techniques brought the manipulation of natural genetic information under control, within the limits of laboratory. Exchange of genetic information between two non-interbreeding species could be realized only with the help of various modern biotechnology techniques such as r-DNA technique, e.g. expression of human gene in bacterial cell. This phase is still continuing to develop with the development of more advanced techniques to utilize the information coded in the genetic

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[5] Ghosh, above no. 2, 1999, p. no.149.

[6] Recombinant DNA is a technique, which produce hybrid DNA molecule in the laboratory by joining pieces of DNA from different sources (species), available at http://www.plpa.agri.umn.edu/scag1500/definitions.html.

[7] Polymerase Chain Reaction (PCR) is a technique to enlarge a specific DNA sequence *in vitro* (outside living cell) using a DNA replicating enzyme and repeated cycles of heating and cooling. PCR often amplifies the starting material many thousands or millions of times, For details please visit http://www.plpa.agri.umn.edu/scag1500/definitions.html

expression[8] of living beings (human, plants, animals and micro-organisms) for various purposes in the field of medical sciences, agriculture, energy, food and industry.

Biotechnology is an interdisciplinary activity. It cuts across various disciplines such as molecular biology, biochemistry, microbiology and information sciences. In other words, biotechnology is an applied science utilizing biological organisms, systems or processes in manufacturing and service industries.[9] Microbiology deals with the study of microorganisms. According to W.T. Astbury, who is one of the founders of the discipline of molecular biology, it is concerned with the study of biological molecules. In the current context molecular biology deals with structural (specific structure of a molecule under a specific condition), functional (function of the molecule in that condition) and informational (three-dimensional structure of the molecule and its behavior) aspects of these molecules (such as proteins, lipids and nucleic acids).

The study of molecular nature of genetic material gave birth to molecular genetics. Only in the 19th century, study of the chemical and physical nature of genetically important molecules such as nucleic acids brought biochemistry and biophysics in molecular biology to study the details of genetic material.[10]

Biotechnology Integration in Heath Care

The morbidity and mortality patterns are different between developing and developed countries. Besides that, differences are found in health care facilities and access to effective medical treatment in the context of globalization because the per capita income

[8] In molecular genetics, this usually means the eventual appearance of the polypeptide encoded by the gene. A gene is a unit of heredity, usually a stretch of DNA with well-defined function, such as one coding for a protein or one that promotes transcription of other proteins. Genetic code is the language in which DNA's instructions are written. The code consists of triplets of nucleotides (codons), with each triplet corresponding to one amino acid in a protein structure or to a signal to start or stop protein production. For details please visit http://www.plpa.agri.umn.edu/scag1500/definitions.html.

[9] Vimal Kumar and Preeti Sharma, "Biotechnology In India-Vision for 2020"; *Invention Intelligence*, July-August, 1999, pp.169- 175.

[10] Allen Garland, "The Origin and Development of Molecular Biology" in *Life Sciences in the Twentieth Century,* 1978, Cambridge University Press.

is highly variable among developed and developing countries.[11] In Asia, Africa and Central and South America, infectious and parasitic diseases are rampant. In developed countries high society life style drugs (e.g. cardio vascular and central nervous system disorders and diseases) are more in demand than the drugs required for treatment of diseases such as malaria, which are common among developing countries.[12] This fact indicates that the focus of research areas in these countries will be different and hence acknowledges the participation of developing countries in research and utilization of biotechnology according to their own priorities.

It is important to look at the integration of biotechnology in the medical sector because of the re-emergence of drug resistant strains of disease causing microorganisms, for example, as in the case of tuberculosis (TB). Secondly, there are more than 3500 diseases caused by single gene defect for which no cure is available, for example, thalassaemia, sickle cell anemia, inherited blood clotting disorders. In the third category of diseases such as HIV, AIDS and cancer, for which no permanent treatment is available, biotechnology also seems to provide an answer. The most important aspect of biotechnology drugs and vaccines is the better efficacy and efficiency of such drugs in targeting a particular disease.

Medical biotechnology offers three categories of products. First are biotechnology therapeutic drugs to cure an existing disease. Second category is of biotechnology vaccines to induce immunity against a disease before the disease affects a healthy person. In third category are the diagnostic kits, which are based upon biotechnology techniques and detect the presence of a particular disease or disorder in a patient.[13]

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[11] As an effect of globalization foreign companies are free to come and compete with the local companies making use of the local skills, raw materials and making profits. But it is necessary to cross check such operations, to see if they are bringing some technology to the host country to boost the biotechnology industry.

[12] Above no.1, Steve Prentis, 1984. For example the funds allocated for cancer research and cardiovascular diseases in the 1980s in developed countries, were 100-200% higher as compared to malaria.

[13] Diagnostic Kits are medical devices used to detect a particular disease or symptoms of a disease, based on the presence of an antibody or antigen.

Genetic engineering or genetic manipulation is a widely used technique in medical biotechnology. This specific technique allows modification of the natural genetic expression of an organism, through altering, substituting, eliminating or adding genetic information.[14] It may be utilized for curing a genetic disorder through gene therapy,[15] for producing a recombined genetic material for the production of therapeutic proteins through rDNA technique[16] or for utilizing certain properties of a biological organism to detect a particular disease or disorder through diagnostic kits.

With the emergence of biotechnology, the drug discovery process has undergone a change. Emergence of new biotechnology tools such as proteomics (study of proteins), genomics (study of genes), biosensors (study of biological sensors) and new drug delivery systems (NDDS) allow production of drugs easily and effectively. Biotechnology drugs could be either extracted from a living source (plant, animal, microorganism) through biotechnology techniques or produced through a biotechnological process or technique.[17] Biotechnology drugs are seen as better alternatives than the chemical drugs in terms of

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[14] Anna C. Pai, *Foundations of Genetics: A Science for Society,* London: Mc Graw Hill Publication1985, p. no.221.

[15] Mae-Wan Ho, *Genetic Engineering: Dream Or Nightmare. The brave new world of Bad Science and Big Business,* Third World Network: Penang Malaysia, 1998.

Treating diseases by replacing the defective gene, either by incorporating a normal copy of the gene in the germ cells (egg or sperm) or in the embryo (germ line gene replacement therapy), or by supplying copies of the normal gene to be taken up and incorporated into the cells of adult (somatic cell gene replacement therapy).

[16]e.g. Vaccine, which is a preparation of killed or living attenuated microorganisms or part thereof, which are administered to a person or animal to produce artificial immunity to a particular disease and antibiotics, which is a chemical substance that can kill or inhibit the growth of a microorganism.
For details visit http://www.plpa.agri.umn.edu/scag1500/definitions.html.

[17] For example a biopharmaceutical drug is a therapeutic biological compound derived from or related with the use of a living organism or their components. This category includes monoclonal and polyclonal antibodies, recombinant or DNA vaccines, antisense oligonucleotides and therapeutic gene. On the other hand biologics are derived from living organisms but are complex mixtures that are manufactured by using biotechnology techniques. For details visit http://www.tufts.edu/med/cssd/images/otlk2001.pdf and http://www.aphis.usda.gov/vs/cvb/.

quality.[18] The efficacy and efficiency of a new biotechnology drug or compound (to cure a particular disease) is tested through clinical trials.

Medical Biotechnology in India

Although quite a few parallels are drawn between the Information Technology (IT) industry and the Biotechnology (BT) industry, there are differences between the two.[19] The biotechnology sector in India is strongly linked with the pharmaceutical or agriculture industry. A larger part of the research in biotechnology is done in publicly funded research institutes.[20] Institutions like National Research Development Corporation (NRDC) and Biotechnology Consortium India Limited (BCIL) facilitate links between research institutes and industry. The role of private funding or venture capital is not very popular in India.[21]

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[18] Sylvester E. J. and Klotz Lynn C., *The Gene Age. Genetic Engineering and the Next Industrial Revolution,* New York, US: Charles Scribner's Sons 1983.

[19] Table: Differences between BT and IT

Attribute	Biotechnology	IT
Capital investment	low	high
Product development Time	less than 1yr	3-10 yrs
Product development cost	low	high
Regulatory controls	few	many
Failure Risks	low	high
Entry barrier	low	high
IPR costs &values	low	high
Market size	medium to large	small to medium
VentureCapital's understanding	good	poor
Market size of services	~1 bn	$10 bn (CRO)
Cross licensing	high	medium to high
Public acceptance	high	low (sensitive)

Source: Kiran Mazumdar, Biotech India, 2003 available at http://www.biotech-india.com/exhibition_cov..htm.

[20] Nagesh Kumar, " Role of government intervention in the commercialization of the biotechnology. A case study of Filariasis test kit in India", *ELISA- As Diagnostic Tool–Prospects and Implications*, (eds.) S.Visalakshi and S. Mohan, India: Wiley Eastern Limited, 1992.

[21] Report by ICICI Bank "Funding Innovations In Biotechnology" at Biotech India 2003, Feb. 5-8, 2003 New Delhi, available at http://www.biotech-india.com/exhibition_cov..htm.
and also see Sanjay Sardana, "Adequate policy framework required to boost biotech industry", *Financial Express,* 11 August, 2001.

Owing to the process patenting systems, Indian pharmaceutical companies have developed strong process development skills.[22] Transnational pharmaceutical companies are having alliances with Indian pharmaceutical companies in order to accelerate their research and development (R and D) activity as well as to explore new marketing opportunities.[23]

Disease and poverty are the main problems of a developing country like India. On the one hand, morbidity and mortality rate is high; on the other, per capita expenditure on health care is far less as compared to developed countries. It means that not only the drug or health product quality but also the affordability of the drug is important in the Indian context. This gives an important role to a health care company or institution operating here in India.

In India major healthcare problems are vector borne (caused by insects or other third carriers, which carry the disease from the main pathogen to the host). Malaria, leishmaniasis, filariasis, leprosy and influenza are of common occurrence and occur due to lack of proper preventive measures. Most of these diseases can be prevented through appropriate use of vaccines and diagnostic kits. This acknowledges the necessity of prioritization of preventive healthcare methods over treatment. The Government of India (GOI) had also acknowledged priority of primary healthcare methods through many national health programmes, e.g. the immunization programme. Biotechnology therapeutics are important but so far in India these are marketed through licenses from foreign companies and not manufactured indigenously[24].

Biotechnology vaccines are better in terms of risk associated with them, as they use only parts of viruses or bacteria rather than the whole live or dead microorganism as in case of traditional vaccines. The need of new biotechnology-based vaccines is growing

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[22] *PHARMA EXPO 2001*, 53rd Indian Pharmaceutical Congress 2001 published by Saket House, Ahmedabad, India,2002 and
"The Biotechnology Market in India" available at http://www.infoexport.gc.ca/in

[23] For e.g.Wockhardt with Rhein Biotech (Germany), Nicholas Piramal and Cytran (USA), Torrent and Sanofi (France), UB Group and Sante (France)

[24] Ghosh, above no.2.

because of the unavailability of any cure based on existing vaccines or the anti- resistance behavior of the viruses to existing vaccines.

Biotechnology seems to offer a hope to provide an answer for the demand of high quality vaccines at an affordable price to cover a large portion of the population. However, except for human insulin and hepatitis B vaccine, which are manufactured indigenously, majority of other biotechnology products meet particular medical needs and are generally imported.

Issues

Biotechnology in the current context seems to provide an answer to the problems of food, disease, energy and the environment without much harm to the existing ecological system. In the medical field, biotechnology techniques and processes offer a better understanding and cure (treatment) of the diseases.

Most of the biotechnology drugs have been resulted from the research of biotechnology companies or biopharmaceutical companies. Biopharmaceutical companies are those diversified pharmaceutical companies which have integrated biotechnology skills within themselves. Generally biotechnology companies find a suitable molecule or drug that could be used against a disease and license it to a pharmaceutical company for development, manufacture and clinical trials. On the other hand, biopharmaceutical companies utilize internal or external biotechnology skills and resources to develop and manufacture biotechnology drugs. Both kinds of companies are active in the medical field. This implies that medical biotechnology is a result of the combination of the capabilities of both pharmaceuticals and biotechnology.

In India also the medical biotechnology sector is strongly related with the pharmaceutical sector. Many established pharmaceutical companies such as Ranbaxy, Wockhardt and Nicholas Piramal are diversifying into biotechnology. Backed up by the 1970 Patent Act, which recognizes process patent, backward engineering or process development skills have been strongly developed among Indian pharmaceutical companies. Many Indian biotechnology and biopharmaceutical companies are active in medical

biotechnology research and development. A description of these companies can provide insights into the focus of research and development activities in India.

The nature and focus of foreign collaborations in the field of medical biotechnology provides insights into the future scope and direction of the medical biotechnology industry in India. This study is important in terms of understanding the present availability of the biotechnology healthcare products in India as compared to the requirements.

The present study on the "Origin, Evolution and Status of Medical Biotechnology Industry: Perspectives and Problems for India" gives a description of the growth and development of the Indian medical biotechnology sector in human healthcare. It has been divided into 6 chapters.

Chapter 1 includes a review of secondary literature. The ideas of various authors have been reviewed to highlight the important issues related to the integration of biotechnology in the medical sector.

Chapter 2 deals with the evolution of biotechnology. It concentrates on the scientific and social aspects related with, and responsible for, the evolution of modern biotechnology from ancient biotechnology.

Chapter 3 examines the structure of biotechnology industry in the United States (US). It focuses on the structure, development, and commercialization influencing the development of biotechnology industry in the US.

Chapter 4 deals with the structure and status of the medical biotechnology industry and products in India.

Chapter 5 presents a summary of fieldwork undertaken during the course of the present study. The fieldwork is based on secondary as well as primary sources. A set of medical biotechnology companies operating in Delhi is taken for case study. The selection of companies is based upon the latest Directory of Biotechnology Companies in India, published by Biotechnology Consortium of India Limited (BCIL).

Chapter 6 includes conclusions and perspectives drawn on the basis of the study.

The first objective of the study is to explore what the research and development focus of the medical biotechnology industry in India is, and the second whether the availability of medical biotechnology products in India are in alignment with their requirements.

Limitations of the study

The study has some limitations in terms of covering various related issues. The following issues are not included in the study:

1) Medicinal plants and derived products;
2) Over the counter products (OTC) and nutraceuticals;
3) The question of patents in the biotechnology industry.

CHAPTER 1

REVIEW OF SECONDARY LITERATURE

Introduction

Biotechnology is an interdisciplinary activity. It is not a single technology, but a general term encompassing a variety of novel techniques (e.g. genetic engineering and monoclonal antibody technology as well as an array of new technologies) derived from the understanding of biosciences (here the term "biosciences" refers to biological sciences, biophysics and biochemistry).[1] In the field of healthcare, scientists use technology to understand the disease process with higher specificity, and design therapies that will either block the disease process at a specific point or destroy the cause of disease with higher precision. The true nature of biotechnology and its impact on society can be better understood under three main aspects. First, the peculiar nature of biotechnology industry and its development; second, the commercialization of biotechnology products, which are different from other contemporary technologies like information and communication technology (ICT), and third, the impact of biotechnology and its products on society. The present chapter provides a review of secondary literature relating to all these aspects.

1.1. Biotechnology Industry

In the United States, the biotechnology industry has emerged from the interaction among new biotechnology firms (NBFs), large corporations and universities. In other countries the development of biotechnology has been based on the research activities of large integrated companies, often in collaboration with domestic or foreign universities and public research centers (Barbanti et al. 1999). NBFs possess the knowledge, research capabilities and linkages but lack capital, assets and skills in downstream activities (e.g. manufacturing, clinical trials, regulatory processes). On the other hand, large established companies lack scientific

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[1] Jacquline Estades and Shyama V. Ramani, "Technological Competence and the influence of Networks: A Comparative Analysis of New Biotechnology Firms In France and Britain", *Technology Analysis and Strategic Management*, 1998, Vol.10, No.4, p. no. 483.

skills but have assets and competencies required for commercialization of biotechnology products.

Bijman (1995) gives an account of the biotechnology industry in the US and argues that strong but flexible relationship between the academia and industry in the US resulted in the formation of NBFs. This collaboration and commercialization of academic assets resulted in alliances or joint ventures between academicians and entrepreneurs. Kenny and Davis (1997) stress that biotechnology developed as an industry only in the US, where it is comprised of independent enterprises. In other developed countries biotechnology has been subsumed under the traditional pharmaceutical or chemical or food companies. Hence the character of the biotechnology sector is more of an 'enabling technology' in these countries.

At the level of firms and industry the development of biotechnology requires the interaction of several agents, characterized by specific capabilities in different technological fields or specialized in distinct phases of the innovative process. In other words, collaboration is a prominent feature of the biotechnology industry. This has allowed different agents, characterized by different but complimentary or supplementary competencies, to merge their capabilities to come out with a product.

According to some interpretations, collaborative arrangements in the biotechnology industry could be considered a transient phenomenon, which is bound to decrease in scale and scope as the technology matures, and as higher degrees of vertical integration are established in the industry (Teece 1986, Mowery 1988). Here networking is seen as a weaker and temporary phenomenon, which tends to become stable only after acquiring a 'constellation' or quasivertical integration structure, i.e. a constellation of firms exists around a central or large company that entertains and directs a number of other sub-ordinate companies. But these subordinate companies have little or no interaction among themselves.

In other interpretations, collaboration represents a new form of organization of innovative activities that is emerging as a response to the increasingly complex and abstract nature of the knowledge base. In this view, collaboration is likely to expand over time generating an intricate network of firms, each of them specialized in particular technological areas or stages of the innovative process. In this perspective,

the agent of innovation is not an individual firm but the network itself (Teece 1986, Pisano and Shan 1988, Cohen and Levinthal 1989, Pisano 1991, Arora and Gambardella 1992). Here a large number of companies interact with each other in the network and each company has an equally important position in the network. This interpretation suggests that firms or companies continue to grow and enlarge their network subsequently.

Weisenfield et al. (2001) discuss the collaboration profile of biotechnology companies in order to understand various forms of networks present in the biotechnology industry and the purposes they achieve. The authors hold the view that biotechnology companies in the current context exist either as a 'virtual company' or as an industrial platform' for networking among themselves as well as with outsiders. As Freeman (1987) points out that external collaboration plays a vital role for successful innovation. A purely technology-oriented horizontal (at equal levels) collaboration focuses on information exchange and know-how generation, whereas the vertical (at unequal levels) integration stresses upon internalizing the external activities. Virtual companies are temporary project-based cooperations, whereas an industrial platform is a research-oriented extended network, which is seen as a means of technology transfer and access to latest information among the members. The purpose of a virtual company as a project-based collaboration is to bring the product to the market and gain profits. The industrial platform on the other hand focuses on sharing the knowledge generated in the network and improving links between fundamental research and commercial applications (i.e. a long-term cooperation).

Various motives have been suggested to explain the nature of collaborations (Barbanti et al. 1999). First, collaborations allow reduction and sharing of risks. Second, they allow firms to get access to resources that would otherwise be impossible or too costly to obtain. Thirdly, they allow the exploitation of the advantages stemming from the specialization of various agents in different technological areas or in different phases of the innovative process.

From a theoretical perspective, the most diffused interpretation is based on the consideration of the transaction costs involved in the exchange of technical knowledge. Sometimes this explanation is supplemented by a consideration relating

to the nature of the learning process involved. In this context, collaboration represents a valid alternative to pure market transactions (Mowery1988). It is widely recognized that the transfer of knowledge involves transaction costs of various sorts linked to the specific and tacit nature of technical knowledge and to appropriability problems. Thus technical information cannot be exchanged in anonymous transactions, given the need to develop complimentary tacit knowledge, skills and assets. On the other hand, collaboration might avoid the inefficiencies linked with complete integration. This is particularly the case whenever innovation requires high R and D expenditures, technical change is rapid, and the underlying knowledge pool is highly complex and multidisciplinary. To sum up, collaboration is more likely to arise when:

a) innovation rests on costly and risky R and D activities.
b) multidisciplinary scientific knowledge is an important input in the innovative process.
c) when such knowledge is generic and codified, so that could be easily absorbed in the current routines.
d) when degree of cumulativeness of the innovative activities is either low (so that the learning processes of different entities do not diverge too much and their coordination is relatively easy) or very high (so that firms necessarily specialize in some specific activity) but generate convergent and or colliding trajectories.

To explain how two firms of the same financial and knowledge portfolio might acquire different levels of technological competence, the 'resource-based theory of firms' is presented. It explains the role of resources and capabilities in a firm. The theory suggests that the performance of a firm depend not only on its financial resources but also on its specific assets and competencies. Here technological competence represents the ability of a firm to exploit its resources to create particular technologies relevant to its requirements (Wernerfelt 1984; Hamel and Prahalad 1990) and can be represented by the R and D and product portfolios of the firm. This could be possible either through internal R and D activities or through external networks.

Diffusion of networks amongst firms rests upon the assumption that industrial research is making a systematic use of relatively general and abstract knowledge (Teece, 1986). In this perspective innovative activities cannot be reduced to the process of acquisition of information.[2] Rather, innovation is the result of learning processes, which involve the development of highly specific cognitive frames (i.e. models for solving the problem) and generate competencies which are highly specific and are synthesized and stored in routines (Holland et al. 1986; Marengo 1992). Such learning processes create and store specific competencies for firms. Acquisition of knowledge from external sources and coordination of learning processes promote diversity in industry (Teece et al. 1990; Dosi, Teece and Winter 1992; Malerba and Orsenigo 1993).

Collaboration has served the primary function to link resources and competencies that were fragmented among different agents. The development and commercialization of biotechnology created the need to devise organizational structures suited for bringing together all the capabilities required and coordinate differentiated learning processes. It has resulted in complex linkages across different organizations to facilitate specialization and division of labour.

From the perspective of biotechnology firms, it is difficult to duplicate or substitute these capabilities. These capabilities should be viewed as a function of internal learning, external learning and proprietary processes developed by the firm (Pisano 1991; Schroeder, Bates and Junttila 2002). Internal learning is a result of learning by experience. External learning is gained either by acquiring external skills through collaborations or through backward or forward linkages (Tsang, 2002). Based on the process of learning, firms build or accumulate assets, which are not easy to duplicate or substitute (Thomke and Kummerale, 2002; Ruet, 2002). On the other hand the agency business activity is negatively related to the product innovation efforts (Li and Gima, 2000).

[2] Innovation could be of various kinds. Radical innovations brings out a design change in a core component or at the top of design hierarchy. Modular innovation entails changes in the materials and fundamental principles used to design components but involves functions farther from the apex of the design hierarchy. Incremental innovations are made to maximize the performance potential inherent in a given approach to component design.

The resource-based theory maintains that a firm's performance advantage is based on its unique resources. Biotechnology is a knowledge-oriented activity; and complexity, tacitness and specificity (CTS) of a firm's technological knowledge act as a barrier, leading to slow knowledge diffusion and prevent imitation. Complexity is usually defined according to the dimensions that increase the difficulty of comprehending a system (organization, device), function or products. Specificity of the technological knowledge for a firm arises from two sources: resource specificity and design or product specificity. Tacitness of knowledge is the particular nature of knowledge, which arises from the inability to articulate the principles that affect the level of performance. It implies that knowledge cannot be communicated easily to enable others to reproduce a firm's performance. In other words it could be concluded that technological knowledge and product performance are linked together (McEvily, 2002).

The assets and skills accumulated over the years gain competitive advantage for a firm (Thomke and Kuemmrle, 2002). These assets and skills are not easy to replicate or transfer because of the following:

(1) difficulty of imitating a particular asset (affected by interdependencies with other assets).

(2) difficulty of trading assets (difficulty in absorption of assets when these are accessed through external alliances).

(3) role of rapidly changing technological environment (difficulty of fully specifying all factors imitation or adoption 'ex-ante').

In sum, the biotechnology industry is unique in terms of the resources and skills utilized there. These skills cannot be easily imitated or acquired. Certain level of knowledge and skills are required to assimilate and absorb the acquired knowledge. Collaboration and vertical integration are considered to be the prominent features of the biotechnology industry. Some of the diversifying pharmaceutical firms in the biotechnology field are trying to integrate external scientific skills (backward integration) whereas biotechnology firms are integrating the manufacturing skills (forward integration) in order to become independent. But collaboration is still

considered important, as either all the skills could not easily be integrated or the process of integration is too expensive to be undertaken (Pisano, 1990).

1.2. Commercialization of Biotechnology Products

Results of research activities become visible through the commercialization process, which enables manufacturing of a product from the results of research work. The contemporary biotechnology industry largely arises from the university-based research. The technology, techniques and even the products of biotechnology were pioneered in university laboratories. The pattern of the biotechnology industry was different as there were no developed skills in the field initially. Students and faculty in university research were placed in industry, and specialized scientific and managerial skills were developed later (Arora, Landau and Rosenberg, 1999; Henderson et al, 1999).

Biotechnology as an industry arises out of the interaction of scientific practices in molecular biology, bioprocesing techniques and biochemical engineering (Kenny, 1986). The new biotechnology industry is based on the knowledge in the fermentation and biological materials processing, which was developed (and utilized) in the pharmaceutical and food processing industries (Bud, 1989).

In the commercialization process, innovation and the requirement of the customer are both equally important. Technological innovation may be described as the process by which the knowledge to produce a product, improve the performance of an existing product or reduce its cost or market the product more efficiently is made possible, which otherwise not possibly available in the market (Parthasarthy 1987). Each firm has certain specific technological resources (skills, designs or methods) to produce products. Customer value often rests on more than technological capabilities; it also depends on complimentary assets (Teece, 1986). Complimentary assets such as reputation, marketing and distribution channels enhance a customer's perception of a firm's performance. A firm's capabilities judged, through customer value, bring comparative advantage for the firm (Afuah, 2002). In other words, the extent of competitive or comparative advantage of a firm could derive in a particular product segment and that also depends on how the core competencies of the firm

could also be deployed in other product segments and their performance. By examining consumers' evaluation of a particular technology, as its performance improves, one can have insights into the impact of demand on competitive dynamics (Ander, 2002). This concept is useful in the current context to understand the convergent behaviour of the biotechnology industry.

Zahra and Nielsen (2001) examined the effect of internal and external sources on successful technology commercialization. According to them successful technology commercialization refers to a firm's ability to develop, produce, market new products and create new knowledge. The resource-based view of firms suggests that internal or external sources, derived from human or technical assets or resources, provide new knowledge to the firm whose appropriate integration in the existing system determines the success of technology commercialization.

The most widespread effect of the commercialization of biotechnology is seen in transnational pharmaceutical companies (TNCs). The transnational pharmaceutical industry has been in the forefront of gaining advantage from biotechnological research advances. Biotechnology companies were initially created to supplement research for these transnational pharmaceutical companies (Whittakar and Bower, 1994; Sapienza, 1995; Ramani, 1999).

Kenny (1989) argued that the World Wars and consequently the need of better medication led the pharmaceutical industry to explore new horizons for filling their product pipelines. The contemporary developments in molecular biology, microbiology and biochemistry led to genetic engineering and a new hope in form of biotechnological techniques and commercial applications of biotechnology for production.

The biotechnology industry from the beginning has been related to the pharmaceutical sector. In fact in the US the biotechnology industry arose to meet the needs of the pharmaceutical industry (Sheldon Krimsky, 1982). The advent of NBFs (New Biotechnology Firms) initiated a more scientific approach in the pharmaceutical industry. Collaboration with NBFs provides better tools for research, process development and manufacturing for the pharmaceutical industry (Arora, Landau and Rosenberg 1999; Henderson et al. 1999; Malerba and Orsenigo 2002).

Biotechnology could be used either as a production technique or search tool in the pharmaceutical industry. The use of biotechnology as a production technique had created changes in the basic skills of the existing firms, particularly those related with the process development and manufacturing. These tools led to an advance in the scientific knowledge of the pharmaceutical industry. Depending on the knowledge required for utilizing these tools, the firm could either build in-house capabilities or find an external source having these skills to do the job. This led to the commercialization of R and D activity in the pharmaceutical industry (Henderson et al. 1999; Malerba and Orsenigo, 2002).

Transnational pharmaceutical companies (TNCs) pursue biotechnology capabilities through collaborations, mergers and acquisitions, or contracts in a particular product segment. Through these collaborations, TNCs aim to gain profit from the biotechnological innovations and NBFs aim to become big and established. Although these two segments of the industry are said to exist in a symbiotic relationship, an alliance with large pharmaceutical firms may lead to the loss of control of biotechnology startups over production and research choice (Tapon et al. 2001; Lock and Greuel 2001). This suggests that somewhere the balance is unequal between the two and the relation is rather supplementary than complementary.

Whittaker and Bower (1994) conducted a study of the dependence of pharmaceutical companies upon external sources (biotechnology companies) for novel technology and products, to understand whether this is a long term, industry wide trend or merely a temporary or local response to acquire capabilities of the biotechnology field. They concluded that this resort to external sources of technology in the pharmaceutical industry follows the trends of wider industrial world towards functional specialization. Hence they argued that biotechnology companies are increasingly taking on the role of suppliers of innovation for pharmaceutical companies. It may be added that biotechnology skills focused in the appropriate research areas only, can benefit a pharmaceutical company, and the research choices depend upon the magnitude and direction of R and D of the firm (Sapienza, 1995).

Larger mature pharmaceutical firms use inter-sector technology cooperation and knowledge transfer to build competencies in non-core technology area, whereas smaller firms focus upon such relationship for problem solving in core technology areas (Desai 1980, Geisler 2000, Santoro and Chakrabarti, 2002).

Product diversification affects the competitive advantage of a firm. A firm can enter a new product segment through a new product line, which could be possible either through in-house R and D capability building or entering an international joint venture. In the context of an international joint venture (IJV) in a new product segment, the relatedness of an IJV's products with that of its foreign and local parents is positively associated with its performance (Luo 2002, Ramaswamy et al. 2002). It implies that the related product diversification creates an opportunity for a firm to improve its ability to integrate and synthesize internal resources and external learning, and to apply both to gain competitive advantage.

The biotechnology industry in India is still in its infancy and is strongly related mainly with the agriculture or pharmaceutical sector. This implies that biotechnology is playing the role of an enabling technology in these sectors. In the pharmaceuticals sector, the means of primary health care such as diagnostic kits and vaccines are the most required product segments in India. The therapeutic protein products are not manufactured but marketed in India through licenses from TNCs (Ramani 1999; Ghosh 1999).

India has a strong process development background in the pharmaceutical sector and some of the leading pharmaceutical companies are trying to integrate biotechnology. These biopharmaceutical companies are the best examples in India to understand the extent and scope of biotechnology integration in the pharmaceutical industry. However, the integration of biotechnology in pharmaceutical firms has not been studied extensively so the availability of data is limited (Ramani and Venkataramani 1999, Ramani and Visalakshi 2001).

The R and D expenditure of Indian pharmaceutical firms is very low as compared to their Western counterparts (Bowonder, 2001; Visalakshi, 1995, 2000; Ramani 1999). Besides this the Indian pharmaceutical companies are generally

concentrating on low-risk research areas. Most of the pharmaceutical companies are concentrating on biogenerics (Ghosh 1999, Ramani 1999, Nagappa et al. 2001).

The Department of Biotechnology (DBT) of the Government of India, through some research institutions and university departments, undertakes the majority of biotechnology-related research and development programmes. The strategy of the Indian government is focused on the creation of scientific competence and certain infrastructural facilities but not on the creation of industrial competence per se (Ramani and Visalakshi, 2001). According to the directory 'Research Profile of Biotechnology Activities in India', published by DBT there are 19 CSIR units, 34 ICAR units, 10 ICMR units, 42 universities supported by the state and 61 independent research or teaching institutions that are active in the field of biotechnology. In India, about 14% of the human resources generated in the country in the biotechnology sector are absorbed in the industry, 67% in research and about 17% go abroad (DBT, Annual Report 1995-96, p. no. 74).

The research quality of the Indian biotechnology sector is said to be more or less equivalent to the international standards but the commercialization part is poor comparatively (Visalakshi, 1992, 1995; Kumar 1992). The industry does not appear to be interested in buying the technology from public R and D institutions and rather opts for foreign products for marketing, which brings immediate profits. The reasons vary from poor efficiency of the technology, lack of engineering skills in the R and D institutes to help set up large commercial plants and availability of cheaper foreign alternatives in the market (Parthasarthy 1987, Kumar 1995).

A comparative analysis of information technology (IT) and biotechnology (BT) firms in India in terms of their assets specificity, partnership and global strategies suggests that biotechnology is a high-investment industry with high risk in terms of return. The foreign biotechnology companies with mature technology are not interested in technology transfer and there is no precise global strategy to follow up for the BT sector in India (Ruet, 2002). Hence it could be concluded that the foreign collaborations could not be seen as the appropriate vehicle to bring (bio)technology to India as the foreign companies collaborate generally for marketing their products (Ghosh, 1992, 1999; Ramani and Venkataramani, 1999).

TNCs, dealing in new technologies like biotechnology, have started performing some of their R and D in developing countries. The main motive for this is both technology related (i.e. gaining access to foreign science and technology resources, skilled manpower and infrastructural facilities) and cost related (the cost of developing and manufacturing a product is lesser). It implies that TNCs use R and D strategies to complement their existing capabilities and reduce risks and costs (Reddy and Sigurdson, 1994; Sandhya and Visalakshi 2000).

1.3. Biotechnology and Society

Historians and social scientists strongly suggest that technology is a social process (Ziman 1999). The evolution and development of every technology in a particular society is a mixture of the joint result of the inherent (self-developing) logic of the technology itself, and of the response towards the technology by different actors in the society. In other words, the evolution is the result of the impact of the selected ramification of the technology on society and the response of society to that impact. The preparedness of a society to accept the changes that had been brought to the existing technology system through a new technology influences the direction of growth and evaluation of that particular technology in that context.

E. Russels Eggers, President of DNA Science, said in an interview that the transfer of technology does not come when science or new technologies or the industry is ready but when the factors that underpin the old technology begin to change.[3] New discoveries and technologies accelerate synergies in the existing system but the so-called reshaping of society is brought in through society's own choices of technology.

Society recognizes the results of human activities in a particular business area as commodities. Unless the results of human productive activity came to be considered as a saleable commodity, private capital will not be invested. In other words, the pioneers of industrial biotechnology not only have developed the product

[3] Edward J Sylvester. and Lynn C. Klotz., *The Gene Age: Genetic Engineering and the Next Industrial Revolution*, New York, US: Charles Scribner's Sons, 1983.

but also the social, legal and economic institutions within which the product is embedded.

According to Sager (2001) there are two fundamental drivers that explain the impact of biotechnology on society. First, the extent to which biotechnological integration proceeds in society may strongly impact the perception and use of biotechnology in society. This means that if the technological integration and cross-field convergence remains low, biotechnology products may remain relatively rare. On the other hand if the technological integration and convergence of biotechnology is high, biotechnology products will be in surplus for a variety of applications. Second, the degrees to which the public eventually accepts biotechnologically derived products and processes as legitimate and reliable alternatives in comparison to contemporary products affect and shape both product demand and public policy. This implies that high public acceptance of biotechnology might lead to substantial enthusiasm for the use of biotechnology products and processes, which in turn will lead to strong educational and legislative efforts for the appropriate use of biotechnology.

In a broader view these two drivers suggest four discrete alternative scenarios for the future of biotechnology in a particular society. The present day situation could be said to be that of low public acceptance and low technology integration, which has resulted in public confusion and uncertainty regarding the use of biotechnology products and processes. The second situation could be that of high public acceptance and high technology integration (or techno-utopia), which would result in enthusiastic acceptance and increased demand of biotechnology products and processe in the society. The third situation might be that where public acceptance is high but technology integration is low (or grass roots). This may result in a strong public support for the expansion of biotechnology products, processes and ancillary industries. The fourth hypothetical situation could be that where public acceptance is low but technology integration is high (or authoritarian state). In this situation public might reject and suspect the true nature of biotechnology products and processes provided.

The notion of biotechnology movement in the public sphere can be seen as a triangular response of public perception (which is generally informal in nature), mass mediation (formal activity) and regulatory system (seen through policy initiatives taken by the state). Public perception is an informal activity, which results from the various interactions among the public groups, communities (scientific or non scientific) and information generated through the media. It generates public pressure either to support or to oppose any activity affecting public life. Materialization of such pressure through policy framing is another aspect.

Public perception and mass mediation make public opinion, whereas regulation is the State's activity. Public policy framework ideally should consider public opinion in the first place. But it is not the case always. Framing a policy for a technology to take a desired shape in a particular society is decided by the priorities chosen and is influenced by a variety of socio-economic and political factors. State's funding priorities establish the path for future research and development of the technology, which in turn influence the society and culture.

In the current context, the media plays an important role in framing public opinion. Kohring and Matthes (2002) discussed the role of the media in framing perception of modern biotechnology in Germany during 1992-1999. They found that the media selectively choose a frame to interpret an idea or theme to the general public. Frame here should be considered a particular way to interpret an idea. To frame is to select some aspects of a perceived reality and make them more salient in a communicating context in such a way that promote a particular problem definition and causal interpretation of the problem. These frames are used to mould or make the audience think according to a definite line, which might be a pre-conceived notion. It works on the principle of selection (of an idea or issue), emphasis (on a pre-conceived aspect) and presentation accordingly to develop an audience to perceive the issue in the desired way. It gives a picture that the media influences the readers. However, the extent of influence could not be clearly determined.

Dahiden (2002) affirms the argument of Kohring and Matthes that the media influences readers although he denies the fact that public could be completely naïve. The argument implies that although the media uses a frame to interpret an issue, the

media creates awareness and highlights that generates concern among public. This concern in turn generates a logical push from the public, which might take shape in the form of framing a public policy by the state.

The role of public organizations and non-governmental organizations is also important in generating public awareness. The programmes and campaigns generated through these organizations help develop a platform for interaction of public and scientific knowledge. Such efforts create better understanding at the social level and help realize the possible impact of a related issue (Makeig, 2002).

Baur (2002) analyzed the biotechnology debate in the United Kingdom during 1973-1999. He found that green biotechnology (agricultural biotechnology) has received more media attention than red biotechnology (medical biotechnology). On the other hand, red biotechnology is evaluated positively and has been influential in the development of a new regulatory framework. Baur stresses that the framing of issues raised by biotechnology take place through a process of social construction and are not natural.

The plurality of theoretical approaches indicates the complexity of the issue. However, there is no general theory to explain formulation of explicitly cause-effect relations among biotechnology policy, media coverage and public perception. However, the economic relevance of the national biotechnology industry, the extent of technology diffusion in the society and the relative age of a technology are influential. One thing that is not extensively looked at is the role of industry-led public relations as an input for the media.

Gutleling (2002) addresses the relational balance between controversy and consensus in the field of biotechnology in Holland. According to his empirical findings the Dutch find biotechnology as a positive technology for their national development and the country is characterized by the participatory role of non-governmental organizations in policy making. Gutleling relates the development of biotechnology with the perceived economic importance of the technology that was constituted by the media presenting a favourable view of the technology. In short the context of technological application is important in a society.

Working Hypothesis

From the above discussion it is clear that the development of medical biotechnology in different countries would take different shapes and routes. There is no single model of development of the biotechnology industry even among developed countries.

The United States presents one model where biotechnology is accepted and developed as an industry. In the US, collaborations among academic scientists, pharmaceutical industry and venture capitalists brought the biotechnology industry into existence. The choice of biotechnology research and development in the US is related with the requirements of the existing industry, which also sponsors a substantial portion of the research, whereas in other developed countries the biotechnology research mainly proceeds through the interaction of established firms with research institutes of national or foreign origin.

In spite of a strong tradition in molecular biology, Europe has not witnessed the same level of acceptance and growth of the biotechnology industry and is characterized by skepticism and confusion, about biotechnology products and processes, in public perception and policy interpretations. European biotechnology companies find the European regulatory system ambiguous enough to follow. Besides, the lack of public confidence in the European food safety regulatory system has had a negative impact on commercialization of biotechnology products (Thumm, 2002 and US-EU Biotechnology Cooperation Agreement). This ambiguity leads to absence of a large-scale participation of the industrial sector in the biotechnology field and low acceptance of biotechnology products in Europe.

The biotechnology industry has developed in Switzerland and Britain with the help of TNCs. Leading Swiss and British pharmaceutical companies (like Ciba-Geigy and Roche) have attempted to build strong biotechnology capabilities through a combination of internal capability development and external acquisition. These companies do not have internal capabilities in biotechnology but they have collaborated with biotechnology companies in order to acquire biotechnology skills (Whittaker and Bower, 1994).

Developing countries on the other hand face a different situation. Obviously, it is not easy for them to compete with developed countries. Developing countries are characterized by scarcity of financial resources, knowledge of the latest advancements in the field of biotechnology and sophisticated infrastructure to imitate a developed nation's model to develop the latest technologies. However, Cuba and China can be taken as examples to understand the development of the biotechnology industry in the developing world. Cuba had set up the Center for Genetic Engineering and Biotechnology in 1986, with the assistance of UNIDO. There was hardly any indigenous research and development and with the help of turnkey technology brought in, primarily from the US, including the needed microorganisms and clones, the Cuban Government set up major production facilities.

The Chinese Government has sponsored research and development that aimed to develop biotechnology products on priority. The Chinese National Center for Biotechnology Development administers the funds and the Chinese Academy of Sciences organizes and implements the key projects. The responsibility for funding and delivering the goods more or less remains with the same body.[4] It shows that in China research and development projects and production centers are fully integrated. These two models mentioned above have one crucial element in common. The production units were set up as fully integrated units along with research and development programmes and are sponsored by the Governments in those countries.

In India, from the production point of view, the Department of Biotechnology initiated two projects in the field of vaccines production, i.e. Bharat Immunologicals and Biologicals Corporation Limited (BIBCOL) and Indian Vaccines Corporation Limited (IVCOL). The former has not yet started production, but manages to import components of polio vaccine and reconstitute the oral polio vaccine for the Indian market. After several years of major efforts in a joint venture project with the leading French Vaccine Company, Pasteur Merieux, the venture, IVCOL was aborted owing to various factors (non-availability of markets and non-viability of the vaccine being

[4] *The Economist*, "Biotech's yin and yang", Dec.2002, pp. 75-77. China claims to produce human insulin, streptokinase and interferons and interleukin-2, erythropoeitin, G-CSF, GM CSF and EGF which are in last phase of clinical trials there.

two of the major ones). The project was too capital-intensive and in view of the low value of the products the private sector has hesitated to invest in this area.[5]

The final objective of the present study is to assess the nature of medical biotechnology sector in India and find whether the developments in the field are in alignment with the social requirements.

[5] Why has the Indian industry not come forward to set up multi-purpose biotechnology production centres? There are several reasons for the current status of biotechnology in the country. Some of them are worth mentioning here. Inability to obtain 'state-of-the-art' strains of microorganisms and clones with competitive expression levels and lack of faith in indigenous R and D programmes and products. The domestic market, however large it may seem, is not large enough to warrant heavy investments in the production of biotechnology products, from industrial point of view. Due to strong patent protection, exports would be difficult because of lack of experience and facilities for scale-up and downstream processing of therapeutic proteins The regulatory guidelines are still not clear whether products produced using biotechnology would be cleared by the regulatory agencies, without new pre-clinical and clinical data.

CHAPTER 2

EVOLUTION OF BIOTECHNOLOGY

Introduction

The term 'biotechnology' appeared first in 1920 in a bulletin of the Bureau of Biotechnology that was published from Yorkshire.[1] In Encyclopedia Britannica Supplement of 1926, Thomson had attributed the coinage of the term to Patrick Geddes, a Scottish biologist and sociologist. Thomson explained that the term meant use of biological organisms for the benefit of humankind. In 1919 Karl Ereky, a Hungarian engineer, defined the term biotechnology as all lines of work, which with the aid of living organisms produce products from raw materials. Ereky envisioned a biochemical age similar to the stone and iron ages.

The process of evolution of ancient biotechnology techniques into today's modern technologies used in the biotechnology industry to create new products is of great historical importance.[2] The history of biotechnology began when human beings became domesticated enough to breed plants and animals; gather and process herbs for medicine; make bread, wine and beer; create many fermented food products, including yogurt, cheese; create septic systems to deal with their digestive and excretory waste products; and create vaccines to immunize themselves against diseases. Examples of such processes go back to 5000 to 10,000 BC.

The development of modern biotechnology from the ancient biotechnology became possible through better understanding and development of biological sciences. It includes the isolation of DNA in 1869 by Friederich Miescher, the discovery of penicillin by Alexander Fleming in 1928, the discovery of the structure of DNA in 1953 by James

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[1] Purohit S.S. and Mathur S.K., *Biotechnology-Fundamental and Applications* Agro Botanical Publishers, India, 1996, cf. Kumar V. and Sharma P. "Biotechnology in India-Vision for 2020"; *Invention Intelligence*, July-Aug., 1999,pp.169-175. Also see http://biotech.tec.nh.us/BT210/Intro1.html

[2] Through several years of careful seed selection, farmers could maintain and strengthen such desirable traits. The possibilities for improving plants expanded as a result of Gregor Mendel's investigations in the mid-1860s of hereditary traits in peas. Once the genetic basis of heredity was understood, the benefits of crossbreeding, or hybridization, became apparent: plants with different desirable traits could be used to cultivate a later generation that combined these characteristics.

Watson, Francis Crick and Rosalind Franklin, the deciphering of the genetic code in 1961 by Marshall Nirenberg and H. Gobind Khorana, the first recombinant DNA experiments in 1973 by Walter Gilbert, the creation of the first hybridomas in 1975, the start of first successful biotechnology company Genentech in 1976, the production of the first monoclonal antibodies for diagnostics in 1982, and the production of the first human therapeutic protein (humulin) in 1982.

2.1. Three Phases in Development of Biotechnology

From the development point of view, biotechnology can be divided into three phases. The first is the phase of ancient biotechnology, which includes biotechniques prevalent in the ancient Indian, Egyptian and other societies. This phase of biotechnology in one form or another has flourished since prehistoric times. When the first human beings realized that they could plant their own crops and breed animals of their choice, they learned to use biotechnology. These involved the discovery that fruit juices could be fermented into wine, milk could be converted into cheese or yogurt, beer could be made by fermenting solutions of malt or a way found to make soft, spongy bread. Simultaneously, as animal breeders realized that different physical traits could be either magnified or lost by mating appropriate pairs of animals, they too engaged in the manipulations of biochemical or genetic characteristics of organisms.[3] This phase roughly lasted until the discovery of antibiotics in 1928. Biotechnology techniques used during this phase were mainly related to utilization of fermentation, together with trial and error techniques used for growing hybrid crops as well as animal varieties.

One important point to be noted here is that the ancient techniques that brought about the exchange of genetic material between different crop varieties or animal breeds were based upon the experimental choice of the farmer or the owner of the animal herd, and were not chosen scientifically. But this fact in no way lessens the importance of those

[3] Manufacture of industrial chemicals such as glycerol, acetone, and butanol using bacteria became possible after German scientist Buchner in 1897 discovered that enzymes extracted from yeast are effective in converting sugar into alcohol. Besides this large-scale sewage purification systems based on microbial activity were also introduced in many cities.
See Ann Murphy and Judi Perrella, 1993, "Overview and Brief History of Biotechnology" Woodrow Wilson Biology Institute, available at http://www.woodrow.org/teachers/bi/1993/intro.html and
"What is Biotechnology" on http://www.accessexcellence.org/AB/BC/Overview_and_Brief_History.html.

trials. Repeated selection and trial had given a general idea about the characteristics of the resultant hybrid crop or animal variety. There was no scientific support to get the exact desired results and it was more learning by doing. For generations, seeds were produced and selectively preserved for future use.[4] Thus three points of difference could be easily seen between ancient biotechnology and modern biotechnology. First, the crossing of species was different from genetic engineering. The former allowed crossing only between natural interbreeding species unlike the latter, which also allowed exchange and expression of genetic information between non-interbreeding species. Second, the speed of expression was much slower in ancient biotechnology and took years to show up. Third, ancient biotechnology included a smaller number of plant and animal species and negligible knowledge about the utilization of microorganisms.[5]

The second phase roughly started with the advent of penicillin, the first antibiotic product, discovered by Alexander Fleming in 1928.[6] This phase was characterized by the involvement of biotechnology techniques utilizing microorganisms for medical purposes. The basic area of scientific activity during this phase was microbiology. Microbiology is that area of biological science, which studies the nature and characteristics of various microorganisms. The search for antibiotics began in the early 19th century following the acceptance of germ theory.[7] Germ theory propounded that various microorganisms (such

4 Michael J. Reiss and Roger Straughan, *"Improving Nature? The science and ethics of genetic engineering"*, Cambridge University Press: 1996.

The domestication of animals and plants started during 10000 to 8000 BC. Dog was the first animal to be domesticated in Mesopotamia and Canaan, followed by goats and sheep in 8000- 7000BC. For more than 10000 years farmers selected animals and plants to utilize their capabilities according to their requirements, it shows that genetics is probably a much older science than it is generally realized. Ancient biotechnology techniques had changed certain plant varieties altogether. For example, the modern wheat used in bread making is so different from native wheat found in Middle East that scientists are still uncertain about its precise ancestry. Present variety of wheat contains approximately three times the number of genes as wild wheat found in Middle East. It suggests that at least two interspecies crosses would have been performed at two separate occasions, in breeding one species (variety) of wheat with another species.

5 An understanding of the scientific principles behind crude techniques even without the help of sophisticated laboratories and equipment was a true practice of biotechnology.

6 Penicillin is an antibiotic, derived from the mold Penicillium. The understanding of the chemical basis of cell function intensified during the post-war emergence when a variety of diseases were rampant without any cure and penicillin and a variety of other antibiotics saved millions of lives.

7 During 1860s and 70s the work of two scientists Louis Pasteur in France and Robert Koch in Germany proved that a particular identifiable microbes cause certain diseases of humans and other animals including

as bacteria and fungi) are responsible for causing certain diseases in human and animals. The scientific advancements during this period later found that not all microorganisms were harmful. Certain microorganisms could be utilized in counteracting the disease causing behavior of other microorganisms without causing any harm to the host leading to the concept of selective toxicity. This concept led to the development of antibiotics and vaccines. Antibiotics are produced inside the cell through a chain of various bio-chemical reactions and each reaction is highly specific in terms of choice of the conditions required (e.g. selection of enzyme, catalyst and temperature conditions). Large-scale production of these antibiotics came much later because it required different skills to set up production units that also maintain the quality of the final product. This was achieved only in the 1940s. German scientist Gerhard Dogmagk investigated the effects of different chemical dyes on bacterial infections and found that dye 'prontosil' cured diseases caused by streptococcus. This result started a search for synthetic antibiotics. This period lasted from 1928 to 1975.

The third phase in biotechnology is the phase of modern biotechnology. It started with the discovery of the recombinant DNA technique and polymerase chain reaction technique (PCR).[8]These two prove to be landmarks in the history of biotechnology. These techniques brought the manipulation of natural genetic information under control within laboratory. Exchange and utilization of genetic information between two naturally interbreeding species was present during the earlier two phases of biotechnology, but the third phase is different in the sense that exchanges of genetic information between two non-interbreeding species could also be realized with the help of various techniques developed later (i.e. modern biotechnology techniques such as rDNA technique) as for example expression of human gene in bacterial cell. This phase is still continuing to develop with the development of more advanced techniques and tools to utilize the information coded in the genetic expression of living beings (human, plants, animals and

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tuberculosis, anthrax and cholera. Before the establishment of germ theory the cause of the disease was left to possible assumptions. Acceptance of germ theory induced a new era of diagnosis and treatment in the field of medicine.

[8] See Introduction, p. no.2 and also visit http://www.plpa.agri.umn.edu/scag1500/definitions.html.

micro-organisms) for various purposes in the field of medical sciences, agriculture, energy, food and manufacturing industry.[9]

2.2. Chronology of Scientific Advancements

There has been continuity in the content and form of biotechnology experienced by different generations. The potential of life had become the basis for biotechnology and has never been a discovery.

Socrates the Greek philosopher speculated (around 420 BC) on why children did not always resemble their parents. Hippocrates proposed that it is heredity, which is passed on to offspring from parents and sometimes skips expression in the immediately following generation.[10] In the 17th century William Harvey (1630) found that plants and animals alike reproduce in sexual manner, i.e. males contribute pollen or sperm; females contribute eggs and Francesco Redi for the first time used an experiment to disprove spontaneous generation[11]. Anton van Leuwenhoek was the first scientist to describe protozoa and bacteria and to recognize that such microorganisms might play a role in fermentation. In the early 18th century (1701) Giacomo Pylarini practiced inoculation, intentionally giving children smallpox to prevent a serious case later in life.

The late eighteenth century and the beginning of the nineteenth century saw the advent of vaccinations, crop rotation involving leguminous crops, and animal drawn machinery.[12] In 1798 Edward Jenner published his book comparing vaccination

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[9] In molecular genetics, genetic expression usually means the eventual appearance of the polypeptide encoded by the gene. A gene is a unit of heredity, usually a stretch of DNA with well-defined function, such as one coding for a protein or one that promotes transcription of other proteins. Genetic code is the language in which DNA's instructions are written. The code consists of triplets of nucleotides (codons), with each triplet corresponding to one amino acid in a protein structure or to a signal to start or stop protein production.

[10] Hippocrates (460 - 377 BC) determined that the male contribution to a child's heredity is carried in the semen. By analogy, he suggested that there is a similar fluid in women, since children clearly receive traits from each in approximately equal proportion.

[11] Spontaneous generation theory suggests that God has created all the animals and plants species on earth with in a span of ten days at the time of creation of the universe, through asexual reproduction; and all living species possesses the similar characteristics and physical appearance as at time of their creation.

[12] Farmers in Europe increased their cultivation of leguminous crops and began rotating crops to increase yield and land use.

(intentionally infecting humans with cowpox to induce resistance to smallpox) to inoculation (intentionally infecting humans with a putatively mild strain of smallpox to induce resistance to severe strain of the disease).[13] During 19th century Louis Pasteur (1822 – 1895) proved that fermentation is the result of activity of yeasts and bacteria and invented the process of pasteurization, heating wine sufficiently to inactivate microbes (that would otherwise turn the 'vin' to 'vin aigre' or sour wine) while at the same time not ruining the flavor of the wine. Germ theory was established during this time and Pasteur developed a rabies vaccine in 1884, which underwent first human trials in the following year. Wilhelm Kolle, a German bacteriologist, developed cholera and typhoid vaccines in 1896. Calmette and Guerin developed a vaccine against TB but this vaccine, called BCG, was not used until 1921. During this time E.B. Wilson elaborated August Weismann's chromosome theory of heredity.[14]

In 1897 Eduard Buchner demonstrated that fermentation could occur with an extract of yeast in the absence of intact yeast cells. This was a defining moment in the history of biochemistry and enzymology. Later Friedrich Loeffler and P. Frosch reported that the pathogen of the foot-and-mouth disease of cattle is so small that it passes through filters that trap the smallest bacteria; such pathogens came to be known as 'filterable viruses'. Ronald Ross discovered Plasmodium, the protozoan that causes malaria, in the Anopheles mosquito and showed that the mosquito transmits the disease from one person to another. In 1900 Walter Reed established that mosquitoes transmit yellow fever; it was the first human disease known to be caused by a virus.

Charles Darwin gave the theory of natural selection and Gregor Mendel presented the laws of heredity in the 19th century.[15] Mendel proposed that invisible internal units of

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[13] Vaccine comes from the Latin word 'vaccinus' - meaning 'from cows'.

[14] In living beings all homologous chromosomes show similar properties except one pair, this pair has got chromosomes with differ with each other and they determine the sex of that living being. Such chromosomes are called sex chromosomes while rests of the chromosomes are called Autosmes. For details please visit http:// www.genpromag.com/scripts/glossary.asp.

[15] In 1859 Darwin gave a hypothesis that animal populations adapt their forms over time to best exploit the environment, a process he referred to as "natural selection." As he traveled in the Galapagos Islands, he observed how the finch's beaks on each island were adapted to their food sources. He theorized that only the creatures best suited to their environment survive to reproduce. Darwin also inferred the process of adaptive radiation, wherein populations spread out into the environment to exploit specialized resources. Charles Darwin's "On the Origin of Species," was published in London.

information account for observable traits that are passed to the following generations.[16] Walter Stanborough Sutton suggested that Mendel's 'factors' are located on chromosomes and chromosomes are paired. After observing chromosomal movements (during meiosis), Sutton developed the chromosomal theory of heredity.

Thomas Hunt Morgan proved that genes are carried on chromosomes, establishing the basis of modern genetics.[17] Later, William Bateson and Reginald Crudell Punnett demonstrated that some genes modify the action of other genes. This was the first recognition of a role for genetics in biochemistry, but the idea remained unappreciated until the work of Beadle and Tatum in the 1940s.[18]

In 1937 Frederick Charles Bawden discovered that tobacco mosaic virus contains RNA. Later Joshua Lederberg and Norton Zinder showed that bacteria sometimes exchange genes by an indirect method called transduction, in which a virus mediates the exchange by sharing bits of DNA from one bacterial cell and transporting the bacterial genes into the next cell it infects. Later Arthur Kornberg (in1967) synthesized infectious viral DNA and Peter Duesberg and Peter Vogt (1969), discovered the first oncogene in a virus. William Hayes discovered that plasmids (circular strands of DNA in the cytoplasm of bacterial cell) could be used to transfer introduced genetic markers from one bacterium to another. In 1965 scientists found that the plasmids are responsible for the antibiotic resistance in bacteria. This observation led to the classification of the plasmids.

After Watson and Crick described the DNA structure in 1953, Francis Crick and George Gamov established the central dogma of molecular biology and suggested that genetic information flows only in one direction, from DNA to messenger RNA and from messenger RNA to ribosomes, to produce a protein.

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[16] Mendel's work remained unnoticed, until 1900, when Hugo de Vries, Erich Von Tschermak, and Carl Correns rediscovered Mendel's mechanism of heredity.

[17] In 1926 Thomas Hunt Morgan published 'gene theory' and Herbert M. Evans found (incorrectly) that human cells contain 48 chromosomes.

[18] 1941 George Beadle and Edward Tatum experimented with Neurospora, a mold that grows on bread in the tropics and developed the 'one-gene-one-enzyme' hypothesis i.e. each gene is translated into an enzyme to perform a particular task within an organism.

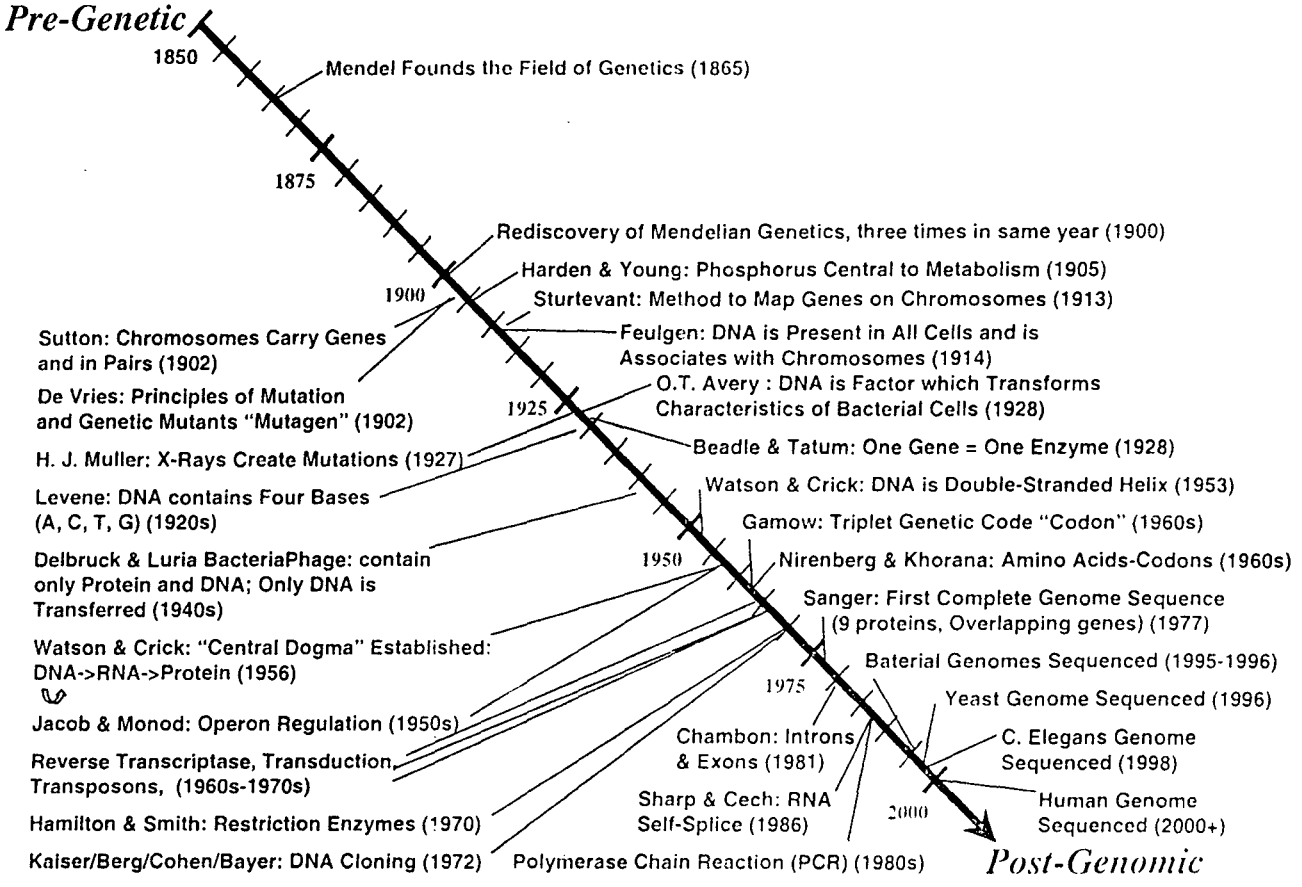

Fig. 1. A brief history of genetics and molecular biology.

Paul Berg in 1972 constructed the first recombinant DNA molecule by synthetically joining two different strands of DNA in the lab from different species.[19] Later Kohler and Milstein fused cells together to produce monoclonal antibodies. In 1980 Kary Mullis and others at Cetus Corporation in Berkeley, California, invented a technique for multiplying DNA sequences in vitro by the polymerase chain reaction (PCR).[20] New DNA techniques combines PCR, DNA chips, and computer programming providing a new tool in the search for disease-causing genes to be used for gene therapy. The recent completion of human genome sequencing (in April 2003) provides new hope in the field of diagnosis and treatment.

2.3. Convergence of Various Disciplines:

The convergence of disciplines witnessed in the 1920s and 1930s occurred primarily within two large areas. On the one hand, embryology, biochemistry, cytology, and genetics began to come together, and a unified approach that might explain all the biological processes at cellular and molecular level, was initiated. On the other, convergence of genetics, evolution and embryonic development began to re-emerge in a new unified theory of evolution of the living system.

Knowledge of chromosome movements during formation of egg and sperm or during embryonic cell division was the foundation of embryology and cytology. Knowledge of the structure of chromosomes and their relation to the factors of 'Mendelian' hereditary resulted in the form of genetics. Knowledge of the nature of individual adaptations and their changes in frequency within a population over time was the contribution of evolutionary theory.

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[19] In 1975 a moratorium on recombinant DNA experiments was called for at an international meeting at Asilomar, California, where scientists urged the Government to adopt guidelines regulating recombinant DNA experimentation. The scientists insisted on the development and use of "safe" bacteria and plasmids. In 1977 Genentech, Inc., reports the production of the first human protein manufactured in a bacterium i.e., somatostatin. For the first time, a synthetic, recombinant gene was used to clone a protein. Many consider this to be the advent of the 'age of biotechnology'.

[20] For details see Introduction p. no. 2. PCR has been called the most revolutionary new technique in molecular biology in the 1980s. Cetus patented the process, and in the summer of 1991 sold the patent to Hoffman-La Roche, Inc. for $300 million. In 1981 Genentech, Inc. cloned interferon gamma and in 1990 the first gene therapy took place, on a four-year-old girl with an immune-system disorder called ADA deficiency. The therapy appeared to work but initiated a discussion on ethical values.

In the early twentieth century, scientists tried to answer a number of unresolved questions centered on the problem of embryonic differentiation leading to the formation of various embryonic tissues and organ systems. Because of lack of the precise tools for studying these problems at the molecular and biochemical level, embryologists had to focus on the level of organization.[21] Later information available from biochemistry (pathways of protein synthesis), molecular structure (X-ray crystallography) and studies on the genetic nature (process of carrying information into the next generation) of an animal made the bio-chemical pathways clearer, by which these processes operate and hence made it possible to synthesize complete proteins in test tubes.

Molecular biology and its sub discipline molecular genetics concern both the structure and function of biologically important molecules. Molecular genetics grew out of the attempt to understand the nature and working of gene.[22] It was different from genetics, which until the late 1930s was concerned primarily with the mechanism of gene function. It differs from biochemistry, which until 1950s was concerned primarily with the function of molecules and concerned with the three-dimensional molecular structure only.[23] This suggests that biochemistry as well as other areas of biology began to enter into molecular genetics and the central dogma of biology was extended as far as evolutionary theory, suggesting that even the mechanism of evolution could be taken down to the molecular level and understood in terms of the process of genetic transmission, transcription, translation and embryonic differentiation.

Biochemical genetics provided an explicit connection between the genes and the proteins made. The direct product of gene action is a polypeptide chain, which forms almost a whole protein molecule. These findings suggested possible links between the

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[21] Allen Garland, "The Convergence of Disciplines: Embryology, Genetics and Evolution, 1915-1960", *Life Science in the twentieth Century,* Cambridge University Press: 1978, pp. 99-114.

[22] Molecular genetics grew out of the attempt to apply the integrated knowledge of the function, structure and three-dimensional linkages of a genetic molecule to understand the classical chromosome theory that states chromosomes as the carrier of genetic information from parents to offspring.

[23] Before 1950s there were three separate lines of thinking in molecular biology. First, was the structural approach, concerned with the structure of biological molecules. Second, was biochemical approach that concerned with the interaction of biological molecules in the cell metabolism and hereditary. Third, was the informational approach and was rather a recent development, concerned with the flow of genetic information from one generation to the next and the mechanism responsible for the translation of this information into biological molecules. The fusion of these approaches became unified and then only molecular biology achieved a pre- eminent position in the 20th century.

sequence of information in the gene and the sequence of amino acids in its product, the protein. But gene replication and guidance of protein synthesis are distinctly biochemical problems; they are dependent upon a variety of precursors present in the cell and are intimately connected to various metabolic pathways. In other words, every structural feature had to be consistent with the biological demands placed (or coded) on the DNA molecule. Relating structural and biochemical knowledge with biological function allowed the understanding of the link between chromosome structure and mechanism of transmission through genes.

Hence in the late 19th century growth of molecular biology has shown the union of evolutionary, hereditary, embryological, biochemical and anatomical concepts. It offered a new unified approach to study the life in which all biological phenomenons could be explained as intricately related. Embryonic development was to be explained in terms of hereditary, embryology and cell physiology. All biological phenomenons could be understood in terms of chromosomes and genes on the one hand and molecules and atoms on the other.

Biotechnology seems to be leading a sudden new biological revolution. It has brought a world of engineered products. Biotechnology has been described as 'Janus-faced.'[24] This implies that there are two sides. On the one side, biotechnology techniques allow DNA to be manipulated to move genes from one organism to another. On the other, biotechnology involves relatively new technologies whose consequences are untested and should be met with caution.

2.4. Impact of Biotechnology at the end of the 20th Century

Biotechnology at the beginning of the twentieth century began to bring industry and agriculture together. Work in the 1930s was geared towards using surplus agricultural products to supply industrial requirements. During World War I, fermentation processes were developed that produced acetone from starch and paint solvents for the rapidly growing automobile industry. The advent of World War II

[24] Robert Bud used this term. For details please see "Overview and History of Biotechnology" available at http://www.accessexcellence.org/AB/BC/Overview_and_Brief_History.html.

brought the manufacture of penicillin. The bio-technical focus moved to pharmaceuticals. The Cold War years were dominated by work with microorganisms in preparation for biological warfare, as well as antibiotics and fermentation processes.

Today's biotechnology has its roots in chemistry, physics, and biology and is used in many areas. The marked increase in our understanding of living organisms and their cell products grants us the ability to control many functions of various cells and organisms. New biotechnological techniques have permitted scientists to manipulate desired traits. The development of techniques has resulted in three major branches of biotechnology: genetic engineering, diagnostic techniques, and cell or tissue culture techniques.

Nowadays, the techniques of DNA fingerprinting is a common practice in forensics, and gene splicing and recombinant DNA technology actually combine the genetic elements of two or more living cells. Immunoassays are used not only in medicine for drug level and pregnancy testing but also by farmers in detection of unsafe levels of pesticides, herbicides, and toxins on crops and in animal products.[25] Functioning lengths of DNA can be taken from one organism and incorporated into another for production of a specific protein, for example, we can cause bacterial cells to produce human proteins and it is possible to synthesize therapeutic molecules that have never before existed.[26]

Modern biotechnology based on recombinant DNA technology uses recombinant organisms to serve in the production of food, medicines, industrial purposes and to solve environmental problems. This leads to the division of biotechnology into four areas agricultural biotechnology, pharmaceutical biotechnology, industrial biotechnology and environmental biotechnology. Pharmaceutical biotechnology products include human therapeutic, vaccine and diagnostic proteins and industrial proteins.

The evolution of medical biotechnology as an industry has precedents in terms of scientific and applied research. The history of modern biotechnology could provide some insights into the socio-economic requirements of society as well as pattern of

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[25] These assays also provide rapid field tests for industrial chemicals in ground water, sediment, and soil.

[26]For example, production of insulin and other medicines is accomplished through cloning of designed vectors that carries the chosen gene.

development of medical biotechnology industry. A model, appropriate for the development of the biotechnology industry in a country must suit its socio-economic conditions. However, it is not possible to assess and evaluate the qualities of all models available for the development of biotechnology industry, so United States is taken up as a model to understand the peculiar nature and major components of the medical biotechnology industry.

CHAPTER 3

BIOTECHNOLOGY INDUSTRY IN THE UNITED STATES

Introduction

The growing knowledge of biological sciences and continuous desire of humanity to harness the world around led several biologists and businessmen in the late 1970s to come together. They considered the possibility of leveraging the knowledge of molecular and cellular biology into products that could be sold in an open market and this idea gave birth to the biotechnology industry.

Claims had been made since the beginning of 21st century that the era of biotechnology was near at hand. This early optimism could be explained in two ways: first, the evolutionary significance of a new industrial age; and second, the belief that biology would furnish the requirements of a new industry.[1] Henri Bergson, a French philosopher, biologist and sociologist, for the first time had argued that life is special with infinite potential to be utilized for human interests and biological systems could be considered as machines with their special ability to reproduce and improve the quality of various products for human use.[2]

Biotechnology is defined as a technology utilizing the functions of living organisms (including plant, animal and micro-organisms) for human purposes, and the industries that utilize these biological functions for production of substances are termed as biotechnology industries. The present chapter deals with the development of these industries in the United States, which is said to have a well-developed biotechnology industry.

3.1. Development of Biotechnology Industry in United States

The term 'biotechnology industry' is a matter of debate. Kenny and Davis (1995) had argued that only in the United States had biotechnology become an industry that is composed of freestanding biotechnology firms. In other advanced

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[1] Robert Bud, "Biology and the Third Industrial Revolution: An Early Twentieth Century Vision", paper presented at SHOT, August 1992.

[2] Ibid.

industrial countries it has been subsumed under the traditional agricultural, pharmaceutical, chemical or food industries. This implies that as some of the biotechnology techniques became central to the research and development efforts in these industries, they started utilizing biotechnology as an enabling technology to improve their current line of work.

The development of the biotechnology industry in the US should be seen as a triangle of university science, industry (especially transnational pharmaceutical companies) and venture capital. Strong university–industry relationship is one of the important aspects in the development of the US biotechnology industry. In the 1970s most of the expertise in genetic engineering was found at the universities.[3] University faculties had also started many of the new biotechnology firms (NBFs), retaining simultaneously their professorship and participating in the development of a company.[4]

The advent of World War II and Cold War years were dominated by work on microorganisms and antibiotics. The biotechnological research focus during this period moved to pharmaceuticals and therapeutics, and it laid the foundations for the development of the medical biotechnology industry in the United States.

Venture capitalism arose after World War II and became involved with biotechnology research and development at an early stage. Venture capitalists took up a potential business idea or opportunity, assessed its potential growth and commercial aspects, and attracted investment from the industry to be invested into that idea. In other words, venture capitalists assisted the firms in investing into an area of high

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[3] In the early phase of the biotechnology industry the only source of technical expertise available were the postdoctoral students in the university. The start-up biotechnology firms have to create both managerial and scientific human resources as per to the requirements of the biotechnology industry. Genetech's first employees were postdoctoral students from Boyer's lab who work exclusively on company projects.

[4] Edward J. Sylvester & Lynn C. Klotz, *THE GENE AGE Genetic Engineering and the Next Industrial Revolution,* US Charles Scribners Sons, 1983. For example, Walter Gilbert, a professor at Harvard, was the chairman of the both the board of directors and the science advisory board in the biotechnology company Biogen. Genentech was also established with the help of Herbert Boyer a professor at University of San Francisco.

risk, which could bring high returns. Through these activities the venture capitalists lowered the entry barriers for entrepreneurs.[5]

The development of recombinant DNA technology offered the hope that cells could be transformed into 'factories' for the production of biological materials, which may also have business opportunities. At Stanford University, Paul Berg discovered a way to splice genes, i.e. obtain desired DNA fragments. Later Stanley Cohen and Herbert Boyer were successful in developing a technique to recombine two or more different DNA fragmented from different species and creating a recombined DNA (rDNA). This was the first recombinant DNA experiment, which had opened a new way for genetic engineering. Once a redesigned DNA is made, the only process left was to grow a whole colony from that redesigned single parent and this process is called 'cloning'.

At the University of California San Francisco, biochemists Bill Rutter and Howard Goodman, reported, the isolation of the gene for rat insulin in 1977. Later Genentech's (a biotechnology company) success at cloning a human insulin gene and licensing the marketing rights to Eli-Lilly (a pharmaceutical company) in 1978 created the possibility that the biotechnology industry could lead to new products. Afterwards a line of small biotechnology companies with basic skills in biotechnology R and D came into existence.

The lack of innovations in drug discovery techniques made the pharmaceutical industry look favourably to the development of new biological techniques that could be utilized in the drug discovery process. The large pharmaceutical firms with research laboratories and extensive marketing networks in the United States had tried to increase the entry barriers for interested competitors through research. To fulfill the need of research and development in biotechnology eventually resulted in the creation

[5] Before a dollar could be realized through 'genefacture' an array of new biotechnology companies had been set up with the help of university scientists and venture capitalists. Venture capital financing of biology professors was used to create commercial firms based on the research undertaken at the university. Genentech was the first successful example of university - venture capital collaboration, established in January 1976 by venture capitalist Kleiner Perkins and Robert Swanson and their scientist partner was Herbert Boyer a Professor at University of California, San Francisco (UCSF). The business offices of Perkins were the initial office for Genetech, which also made the initial investment of $ 1,00,000. Major drug houses and chemical companies had also started sponsoring (by some estimates $ 1 billion) into biotechnology industry for new research and development work.

of new research-based small biotechnology firms.[6] Most of these firms were established near universities such as Harvard, MIT, and Stanford.

It is clear from the above discussion that biotechnology developed in the United States via two routes: first, through the biotechnology research and development activities undertaken in the established transnational pharmaceutical companies (TNCs) and second, through the development of new biotechnology firms (NBFs).[7]

The growth of an industry can be traced through the development of its associations. During the earliest days the 'Pharmaceutical Manufacturers Association' was the de-facto voice of the biotechnology industry. In 1981 seven NBFs combined to create the 'Industrial Biotechnology Association' (IBA).[8] In 1984 eleven other companies joined hands to form the 'Association of Biotechnology Companies' (ABC) with the purpose of representing the smaller biotechnology firms. In 1993 these two organizations (the IBA with 150 members and the ABC with 340 members) merged to form the 'Biotechnology Industry Organization' (BIO).[9]

Another indicator of the growth of the biotechnology industry was the rise of trade journals that provided it a voice.[10] Before biotechnology was commercialized, scholarly journals such as *Science* and *Nature* constituted a communication medium for molecular biologists. Growth of biotechnology as an industry can be traced, for example, through 'Genetic Engineering News' (GEN) publication schedule. In 1981 GEN was bimonthly; by 1987 it was monthly; and in 1992 it became biweekly. Changes in the publication's subtitle also reflect the changing nature of the industry.

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[6] Franco Malerba and Luigi Orsenigo, "Innovation and Market Structure in the Dynamics of the Pharmaceutical Industry and Biotechnology: Towards a History Friendly Model", *Industrial and Corporate Change*, Vol.11, No.4, 1999, p. 669.

[7] In the US it spawned both the emergence of radically new actors in the biotechnology industry– the new specialized biotechnology startups as well as the gradual creation of biotechnology programmes within the established firms.

[8] P. German, "IBA Gels Underway"; *Genetic Engineering News*, Nov/Dec 1981, p.6.

[9] E. Chistensen "The Biotechnology Industry Organization: The sun is greater than the parts"; *Genetic Engineering News,* 1 April 1993, p. 17 c.f. Martin Kenny and U.C.Davis "Biotechnology and the Creation of a new Economic Space"; *Private Science: Biotechnology and the Rise of the Molecular Sciences*, ed. A. Thackray, Philadelphia: University Of Pennsylvania Press.

[10] ibid

In 1981 it was 'The Information Source of Biotechnology Industry'; in 1987 'The Source of Bioprocess or Biotechnology News'; and in 1992 it became 'Biotechnology, Bioregulation, Bioprocess and Bioresearch'. In effect GEN was supported by the industry using biotechnology, and represents commercial biotechnology.

3.2. Industrial production of Biotechnology Products

The industrial production of biotechnology products began in the United States when recombinant human insulin was first developed and marketed there in 1982.[11] The efforts leading up to this landmark event began in the early 1970s when research scientists developed and constructed vectors by cutting out and pasting pieces of DNA together to create a new piece of DNA (recombinant DNA), which could be inserted into the bacterium *Escherichia coli* (transformation) with the help of vectors. This method is utilized to produce human insulin through bacterial cells.[12]

The next step in the development of biotechnology products is related with the process development and up-scaling. During process development the best growth conditions are identified that produce the maximum amount of a protein as efficiently as possible.[13] From process development, one proceeds to large-scale manufacture.

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[11] In 1970 Eli Lilly, the largest US Producer of insulin licensed the cloned microorganism from Genentech. This transaction validated biotechnology as an endeavor that could produce commercially viable results.

[12] A piece of recombinant DNA was constructed that could also confer resistance to a particular antibiotic. Then human gene responsible for making of insulin was added to the r DNA. If this recombinant DNA containing the human insulin gene was used to transform *Escherichia coli*, the bacteria that grew contained not only the antibiotic resistant gene but also the insulin gene. Additional new pieces of DNA were then added to promote the expression of the human insulin gene so that this new recombinant DNA (expression vector) could be used to transform *Escherichia coli*. Thus, large quantities of human insulin messenger RNA were formed, which in turn were translated into large quantities of the human insulin protein.

[13] Process development also includes the development of media, buffers, reagents, solutions, and assays and the choice of tools for the growth of recombinant cells. When these cells reach certain predetermined conditions, they are transferred into a larger volume of growth medium. This is called upstream processing. Following upstream processing, the cells are separated from the media in which they are growing and the protein is isolated from the cells or the media by a combination of techniques that include filtration, chromatography, and concentration. This process is termed downstream processing. Both these upstream and downstream processing proceed in a predictable manner and monitored through quality control.

The best process is scaled-up to produce large quantities of human protein for large-scale manufacture.

3.3. Biotechnology in Transnational Pharmaceutical Companies (TNCs)

The advent of biotechnology had a significant impact on both organizational and industrial structure of the pharmaceutical industry.[14] The growth of a pharmaceutical firm depends upon the number of drugs discovered in different therapeutic categories. Given the large number of therapeutic categories and different development processes, it is difficult for any firm to win the market, except in specific therapeutic categories for a limited period of time. The advent of biotechnology started to change this picture. First, it introduced rough approximations of the cognitive processes underlying drug discovery.[15] The unified improved approach of scientific knowledge allowed firms to focus their search into particular directions and design compounds that might have particular therapeutic effects. Second, a better understanding of the biological sciences also helps improve the quality of some drugs. On these bases, new science-based firms enter the market, trying to discover new drugs.

The drug discovery process has undergone a change with the emergence of biotechnology based-drug molecules.[16] It has been facilitated with the emergence of new biotechnology tools such as proteomics (study of proteins), genomics (study of genes), biosensors (study of biological sensors) and new drug delivery systems (NDDS). The efficacy and efficiency of a new biotechnology drug or compound (to

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[14] F. Malerba et al. 1999; Barabanti et al, 1999; Talveera A. and Perez E.M 2003.

[15] Barabanti et al. 1999; Bowonder et al. 1999 and Shayama V. Ramani 1999

[16] A drug that is made by using a biotechnology technique or extracted from a living source (plant, animal, microorganism) is called a biotechnology drug. For example a biopharmaceutical drug is a therapeutic biological compound derived from or related with the use of living organism or their components e.g. monoclonal and polyclonal antibodies, recombinant or DNA vaccines, antisense oligonucleotide and therapeutic genes. Biologics are derived from living organisms but are complex mixtures, which are manufactured by using biotechnology techniques.
For details please see
http://www.tufts.edu/med/cssd/images/otlk2001.pdf and http://www.aphis.usda.gov/vs/cvb

cure a particular disease) is tested through clinical trials.[17] Biotechnology companies license the molecules or compounds after discovery to a pharmaceutical partner to further develop, do the clinical trials and market the drug. This type of collaboration or alliance between the biotechnology companies and the pharmaceutical firms are most common. In the year 2000 there were more than 400 such alliances all over the world.[18]

The history of the pharmaceutical industry can be analyzed as an evolutionary process. The growth and development of the pharmaceutical industry has changed a lot with the availability of various biological tools.[19] The first period from 1850 to 1945 was one in which little new drug development occurred and research conducted was based on relatively primitive methods. During this period the industry relied largely on 'random screening' for finding new drugs. Under this approach, chemical compounds present in nature were randomly screened, in test-tube experiments on laboratory animals for their potential therapeutic activity.[20] Firms randomly explored molecules until they found one that might become a useful drug and they could later

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[17] There are two types of clinical trials i.e. pre-clinical and clinical. The pre- clinical trials are held on the animal subjects. The clinical trials are carried on human volunteers (patients as well as healthy people). Around 75-80% of the whole cost in these trials lies in the final large-scale phase III trial of the clinical trails, which include trial on 1000-3000 patients to evaluate the possible benefits and side effects of the drug on a long-term use. Such trials are expensive. Many biotechnology companies license out their products to big pharmaceutical groups, which complete the development of a potential molecule and market the drug later.

[18] Paul Abrahans and Victoria Griffith "Slow acting Medicine" *Financial Times* 5th April, 2001, FT.com.

[19] The pharmaceutical industry has been considered as a science based industry, which in turn has influenced the nature of industrial research over time and had undergone a series of radical technological and institutional changes. It had affected the nature of the processes of drug discovery. Malerba et al. 1999.

[20] Pharmaceutical companies maintained enormous libraries of chemical compounds by searching new compounds in swamps, streams and soil samples. Thousands of compounds have to be subjected to multiple screens before researchers honed in on a promising substance. Serendipity played a key role. Since in general the 'mechanism of action' of most of the drugs was not well understood. Researchers were generally forced to rely on the use of animal models as screens. The design of new compounds was a slow painstaking process that draws heavily on skills in analytical and medicinal chemistry. Many important classes of drug were discovered in this way, including most of the important diuretics, many of the most widely used psychoactive drugs and several powerful antibiotics. But little of this knowledge was codified, so new compound design was driven as much by the skills of individual chemists. Hence the role of science was modest.

patent it. The patent provides protection from imitation for a certain amount of time and over a given range of similar molecules. After discovery, firms engage in the development of the drug, regardless of the problems related with efficacy and marketability of the new drug. All this suggests that the degree of uncertainty related to the development of a new drug was quite high.

In the 1970s the industry began to utilize the scientific knowledge for guided drug discovery. Advances in physiology, pharmacology, enzymology and cell biology led to a better understanding of the biochemical and molecular roots of many diseases. All this made it possible to understand the natural history and the cause of a number of key diseases. It helped researchers screen more promising compounds that might have particular therapeutic effects. Thus techniques of guided search provided researchers more effective ways to screen compounds for possible therapeutic effects and hence influenced the process of discovery of new drugs.

The third epoch of the industry has its roots in the 1970s but did not come to full flower until quite recently. It is the use of genetic engineering tools in the production and discovery of new drugs. Biotechnology can be used either as a production technique for the production of proteins or other molecules whose therapeutic properties were already well understood, or it can be used as a search tool for finding new therapies and products.[21] These tools led to an advance in the scientific knowledge of the pharmaceutical industry.[22] The use of biotechnology as a production technique has created changes in the basic skills of the existing firms, particularly those related with process development and manufacturing.

3.4. Emergence of New Biotechnology Firms (NBFs)

Two discoveries really triggered the development of NBFs. First was the discovery of a technique to transfer specific genes from one organism to another, by American scientists Boyer and Cohen in 1973; and second was the invention of cell

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[21]Rebecca Henderson et al, " The pharmaceutical industry and the revolution in molecular biology: Interactions among scientific, institutional, and organizational change"; *The Sources Of Industrial Leadership* eds. D.C. Mowery and R.R. Nelson, Cambridge: Cambridge University Press, 1999.

[22] Such tools include genomics, proteomics and bioinformatics etc. which allow the scientists to study the properties and behaviour of a molecule under a particular condition.

fusion technique or 'hybridoma technique' by British scientists Milstein and Kohler in 1975.[23] Recognizing the commercial potential of these discoveries, many NBFs were founded by university scientists in collaboration with entrepreneurs and suppliers of venture capital. One more reason for the development of NBFs was the access to scope economies in basic biotechnology research and development. In other words the development of different commercial products based on similar basic technologies helped in developing more scope for these firms.[24]

The creation of NBFs and the increased spending through corporate research budgets help build the infrastructure for the biotechnology input industry. NBFs initially to a larger extent depend on venture capital and relationship with established companies, for their financing. Although venture capital was an important source of funds for NBFs, contract research for established firms has always been important.[25] Between 1985 and 1997 established enterprises, mostly in the pharmaceutical and chemical industry, provided 56% of the total funds invested in NBFs[26]. Apart from the need for capital, NBFs also benefited from their relationship with established firms to get access to downstream capabilities in manufacturing, clinical testing, regulatory processes and distribution.

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[23] Sally Smith Hughes, "Making dollars out of DNA. The first Major Patent in Biotechnology and commercialization of Molecular biology 1974-1980"; *Isis,* Vol. 92, No. 3 Sept 2001, pp 541-575

[24] Economies of scope occur when firms achieve cost savings by increasing the variety of goods and services that they produce. Such effects arise when it is possible to share components and to use the same facilities and personnel to produce several products. For example, a bank may sell retail insurance products in its local branches in order to spread the fixed costs (like the office rent) over a larger number of products. Economies of scale occur when firms achieve per unit cost savings by producing more of a good or service (i.e. when average costs decrease as output increases). Such effects arise when it is possible to spread fixed costs over a higher output. http://europa.eu.int/comm/competition/general_info/e_en.html

[25] Jos Bijman, "Strategies of US Biotechnology Companies"; *Biotechnology and Development Monitor,* No. 24, 1995, pp 12-16.

[26] *Ernst and Young 13 Annual Biotechnology Report;* ,Ernst and Young LLP, Palo alto, CA1999.

Biotechnology is a field of rapid change and innovation, associated with high levels of risk. The elements that characterize the biotechnology firms are the R and D focus and availability of networks.[27]

Table 1: US Biotechnology firms with highest R and D expenditures in 1999

Firm	Sales	US $	% of sale	% change 1998
Amgen	3340	822.8	24.6	24
Genentech	1421.4	367.3	25.8	-7
Chiron	762.6	303.4	39.8	6
Elan Pharmaceuticals	1014.4	233.1	23.2	56
Alza	795.9	183.6	23.1	0
Millenium Pharmaceuticals	183.7	159.9	87	40
Incyte Genomics	157	146.8	93.5	51
Immunex	541.7	126.7	23.4	6
Gilead Sciences	169	112.9	66.8	-12
IOCS	79.6	100.5	126.3	31

Source: *Micropatent Database*, 1995-2000, Micropatent: East Haven , CT, 2000. Cf. Bowonder, "The Emerging Technology Trajectory", *Chemical Innovation*, March 2001.

On the other hand, networking provides access to different markets as well as flexibility to the firms to perform R and D more quickly and less expensively than in the past.[28] It allows sharing of the latest information among the members of the network and minimizes probable risk of failure in process of drug development. Network refers to a set of relations that involve either a non-market exchange (of information, instruments, genetic material, personnel etc.), a market exchange (renting facilities, research contracts, production contracts, financing, licensing, consultancy, distribution contracts etc.) or a strategic alliance (which includes joint

[27] The nine largest biotechnology companies spent 23-93% of their sales on R and D.; Bowonder, 2001.

[28] Gilbert, R *"Survival of the Fittest: Emerging Pharmaceutical companies in the UK"* London: West LB. Panmure, 1999 and
Grandori A *'Interfirm Networks: Organization and Industrial competitiveness"*, Ed Grandori A, London: Routledge 1999, p 1-14

control of resources as well as monetary transfers). Networks act as both resource and constraint on the technological competence of the firm.

The stability of a network permits mobilization of the associated resources in the short run, but at the same time the stability of the network might create rigidity and irreversible constraints for the firm concerned in the long term. On the other hand, 'flexibility' of the network makes it possible to open the network to other agents and allow adaptation to change the environment. Firms manipulate networks in order to arrive at equilibrium between the 'stability' and 'flexibility' offered by a network.[29]

Biotechnology companies in the current context exist as either virtual companies or an industrial platform, for networking among themselves as well as with other pharmaceutical companies for market access. Weisenfield (2001) argued that virtual companies are temporary project-based cooperation networks, whereas industrial platform is a research-oriented extended network that is utilized for access to latest information.

3.5. Vertical Integration in the Biotechnology Industry

The US biotechnology industry developed in two phases.[30] The establishments of new biotechnology firms and a strong division of labour between the new NBFs and established firms characterized the first phase. During the second phase, started in the mid 1980s, NBFs and established firms were involved in an integration process.

In contemporary industries, joint ventures and other forms of inter-firm cooperation activities were increasingly becoming important for the development activities, commercialization and diffusion of the technical know-how. It implies that decisions about which type of activities in the innovation chain should be internalized

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[29] Estades J. and Ramani, Shyama V., "Technological Competence and the influence of Networks : A Comparative Analysis of New Biotechnology Firms in France and Britain", *Technology Analysis and Strategic Management,* Vol. 10, No. 4, 1998, pp.483-495. op. cit.Ref. no.15

[30] Jos Bijman, 1995, p.14

and which ones could be accessed through contractual arrangements were directly related to the technology strategy of the firm.[31]

The vertical division of labour between NBFs and the established firms that initially characterized the biotechnology industry had not been stable for long.[32] While NBFs and established firms continue to engage in collaborative arrangements, there has been a trend towards forward integration by NBFs into manufacturing, and backward integration by the established enterprises into biotechnology research and development activities. Vertical integration allows the accumulation of a firm's skills in a particular activity through repeated projects. Vertical integration of R and D and manufacturing may facilitate the requisite level of communication and co-ordination within a firm.[33]

The main reason for forward or backward movement in the integration process was the avoidance of excessive transaction costs between established firms and NBFs for research and development and manufacturing activities respectively. In biotechnology, transaction costs for manufacturing arise from the complexity of process development and scale up process and the problems of protecting intellectual property thus obtained.

There has been a close interaction between the scientists who develop a microbial process or a technique for the production of a specific protein and the bioengineers who design an industrial manufacturing process. Trial and error and learning by doing are still important activities in the scale up process

Another reason is that an intensive collaboration between product developers and process engineers of different firms generates highly proprietary information but

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[31] Sapienza, Alice M.; "Assessing the R and D capability of the Japanese Pharmanceutical Industry"; *R and D Management*, Vol.23, No.1, January 1993

[32] Pisano, 1991; Bijman, 1995

[33] Such experience represents creation of valuable assets, which allows new projects to proceed from a base of shared knowledge. This in turn provides a common frame for communication and problem solving with in a firm.

it could not be protected through patents only.[34] By the vertical integration of research and development and manufacturing, the protection problem is solved to some extent, and the boundaries, which might impede the flow of sensitive information, can be removed. For the established firms that sponsor research and development contracts, transaction costs increase as generic research projects result in concrete product development. With product development, much of the know-how generated becomes firm (NBF) specific and nearly impossible to transfer the contract next time to a new firm. Thus the sponsor becomes increasingly dependent on the R and D supplier. On the other hand NBFs could make profits by internalizing the manufacturing facilities rather than buying manufacturing services from contractors or turning over manufacturing responsibilities to their joint venture partners.

3.5.a. Forward Integration by NBFs

Products have emerged from the research and development programmes of biotechnology companies. To minimize the manufacturing cost and gain more profits out of their research, biotechnology companies have been integrating forward into manufacturing, rather than buying manufacturing services from contractors or turning over manufacturing responsibilities to joint venture partners. Many biotechnology companies continue to complement their internal manufacturing capabilities and data suggests that many of those companies are pursuing manufacturing.

In 1987 biotechnology companies in the US were fulfilling 80% of their manufacturing needs in-house[35] and two-third of biotechnology companies had their own manufacturing facilities.[36] While many firms have only pilot-scale manufacturing facilities in house, it must be remembered that most biotechnology

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[34] As the patent may lie with a firm but the knowledge is shared between the collaborators. It is not always easy to look for another partner, as all the skills, assets and experience is not easy to replicate. It creates increasing dependency on the partner for executing a particular part of the whole process. Hence the information has to be shared between the partners.
D. Teece, "Profiting from technological Innovation: Implications for Integration, collaboration, Licensing and Public Policy" in *Research Policy,* vol. 15 No.6, 1986, pp. 285-305

[35] Arthur Young International, "*Biotech 88*" p. 31, c.f. Pisano, 1991

[36] Ernst & Young *'Biotech 90: Into the Next Decade'*; Ann Liebert, Inc. New York 1989, p. 76

firms do not need large-scale manufacturing.[37] For example in vaccines and monoclonal-based diagnostics, the required volumes of antibodies are sufficiently low and serve a specific section for which small-scale manufacturing is sufficient.

Two other indicators of vertical integration by NBFs are the ratio of R and D revenues to product sales and the ratio of R and D expenditure to R and D revenues. R and D revenues are typically generated by contractual agreements with corporate partners who support specific R and D programmes in return for manufacturing and marketing rights. A decline in R and D revenues relative to either product sales or R and D expenditure would indicate that biotechnology firms are holding a greater share of the downstream activities. A possible alternative to either manufacturing in-house or selling manufacturing rights to a corporate partner is to use a contract manufacturer. The contract-manufacturing segment is still small in the biotechnology industry, reassuring the evidence of internal manufacturing by NBFs.[38]

While many biotechnology companies have become vertically integrated, the companies in therapeutic products segment do not appear to be increasing in integrative behavior. The difference in extent of vertical integration into manufacturing versus marketing is also suggested by the incidence of different types of collaborative arrangements. The findings of the Ernst and Young survey suggest that marketing and distribution of biotechnology-based diagnostics and pharmaceutical products are mostly held by partners.[39] The Ernst and Young survey found that marketing arrangements were the most common type of agreements being negotiated by biotechnology companies, while manufacturing agreements were least common.

3.5.b. Backward Integration by TNCs

Established enterprises from pharmaceutical industries are vertically integrating backward into biotechnology research and development. According to a

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[37] Pisano, 1991, p. 241

[38] ibid

[39] Ernst & Young '*Biotech 90: Into the Next Decade*';Ann Liebert, Inc. New York (1989) p. 83

survey by the Office of Technology Assessment (OTA), only a few large companies had in-house biotechnology research and development programmes before 1980.[40] In 1988 the OTA reported the results of a follow-up survey indicating that 96% of the 53 established companies it had surveyed, had in-house biotechnology R and D facilities. However, the survey also revealed that the external sources of R and D continue to be important and 83% of the sample reported to sponsor external biotechnology R and D. But there is evidence that more biotechnology-based therapeutics drugs emerge from the in-house R and D laboratories of the established companies. After examining the biotechnology R and D activities of 30 of the world's largest pharmaceutical companies, Pisano (1990) also supports the view that the majority of biotechnology projects are undertaken by transnational pharmaceutical companies.[41] These projects include both monoclonal antibody and rDNA based products and a wide range of therapeutic applications.

Table2: FDA Approved Biotechnology Products

Product	Date	Developer	Marketer
Human Insulin	1982	Genentech	Eli- Lilly
Human Growth Hormone	1985	Genentech	Genentech
Alpha Interferon	1986	Biogen	Schering- Plough
Alpha Interferon	1986	Genentech	Hoffmann La Roche
OKT3 Mab	1986	J&J	J&J
Hepatitis B Vaccine	1986	Chiron	Merk
T- PA	1987	Genentech	Genentech
Human Growth Hormone	1987	Eli- Lilly	Eli- Lilly
Erythropoetin (EPO)	1989	Amgen	Amgen
Hepatitis B Vaccine	1989	Biogen	Smithkline Beecham

Source: D. Mayank, "*Biotechnology-Industry Report*", Merril -Lynch, Dec. 12, 1989

[40] Office of Technology Assessment, *Commercial Biotechnology: An International Analysis*, US Government Printing Office Congress of United States, Washington D.C., 1984.

[41] G. Pisano, "The R and D Boundaries of the firm: An Empirical Analysis", *Administrative science quarterly*, Vol. 35No.1, 1990, pp. 153-176.
Also see Ernst & Young 'Biotech 90: Into the New decade', New York 1989.

The table shows:
Number of total cases = 10
NBF developer and marketer = 3
NBF developer-established firm marketer =5
Established firm developer and marketer = 2

This analysis suggests that the established enterprises have a good share of in-house R and D projects in the medical products segment and also hold developing and marketing rights of new biotechnology products. Generally, these firms are less willing to limit themselves to the distribution of biotechnology products only. Hence vertical integration does increase a firm's share of value-added products. However, such a strategy could be detrimental if a firm is less capable of adding value in a particular activity in comparison to a NBF.

3.6. Current Status of the Industry

The established TNCs and NBFs are two sets of firms participating in the establishment of the biotechnology industry in the United States. Biotechnology has brought new tools that can be utilized in the pharmaceutical sector to offer new products and processes. The nature of the tools may be different as some:

1) Tools lead to increased understanding of biology, e.g. 'proteomics'.[42]
2) Tools create new approaches to develop therapeutic compounds, e.g. combinatorial chemistry and computer based molecular designing.
3) Tools provide new analytical and screening technologies, such as nucleic acid arrays
   and robotic identification of peptides in DNA.
4) Tools lead to entirely new ways of delivering drugs, such as encapsulation systems.

[42]By cataloguing the entire protein content of a cell, proteomics provides insights into the molecular basis of life and it also accelerates the identification of molecular targets for use in diagnostics and therapeutics. For example the antisense therapeutics are based on the concept of antisense molecules, which are stretches of single stranded nucleic acid that target and bind with a specific m RNA, interfering the expression of the disease protein. See Borman S., Chemical Engineering News, Vol.78, No.31, 2000, pp-31-37.

5) Tools that provide a generic approach to understand health intervention, such as multidrug resistance, tissue engineering and antisense therapeutics.
6) Tools that provide a novel approach to molecular characterization, such as biosensors.[43]

TNCs initially used these techniques as research tools and not as potential generators of products. In this context TNCs followed three strategies. First, they established their own linkages with university laboratories to utilize the developments in biotechnology research. Second, they established their own internal biotechnology research programmes and tried to internalize the biotechnology skills. Thirdly, they developed strategic partnerships with the small start-up biotechnology firms.

In the early 1980s, TNCs funded a number of research projects in universities with the aim of gaining access to intellectual property from academic laboratories. However, it was not easy for TNCs to internalize all the knowledge. Therefore, TNCs continued to collaborate with NBFs for novel products or processes. Hence the biotechnology industry remained separate from the pharmaceutical industry.[44]

Pisano (1991) compared the collaborative and vertical integration behavior of biotechnology firms and argued that collaboration preceded and is still important in comparison to vertical integration. He denies the dominance of integration behavior, because neither all the biotechnological R and D activities involve higher transaction costs nor it is easy to integrate all the activities related with manufacturing, legal approvals and marketing of the biotechnology drugs.

After discussing the nature of the components of the biotechnology industry in the US, it is apparent that although biotechnology has a well-established industrial structure in the country, it arose initially to fulfill the basic R and D requirements of the existing industry, especially the pharmaceutical industry. Some scholars see biotechnology as a complementary technology but it seems more of a supplementary nature. Complementary technologies are of complementing nature,

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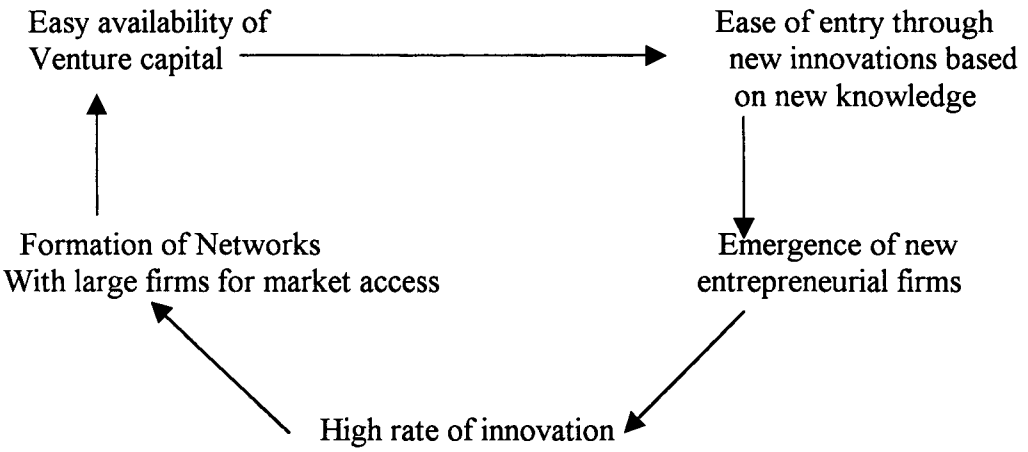
[43] Biosensors are self-contained integrated devices, using a biological recognition element (the biological receptors).

[44] Kenny and Davis 1997, Malerba et al. 1999.

each partner having an equally important role in completing a given task. Biotechnology is generally used as a production or process technique that is supplementary in nature. Possibly the present situation of the industry could be exemplified by the following diagram.

Fig.1 Convergence, Innovation and Industry Structure



The US biotechnology industry has more than tripled in size since 1992, with revenues increasing from $ 8 billion in 1992 to $ 27.6 billion in 2001.[45] Currently there are 1,457 biotechnology companies in the United States, out of which only 342 are publicly held. The regulatory system in the US seems to be in accordance with the needs of industry as the major portion of investment for the US biotechnology industry comes from the private industrial sector.[46] The Food and Drug Administration (FDA), the Environmental Protection Agency (EPA) and the US Department of Agriculture (USDA) regulate the biotechnology industry in the US with the help of a number of legislation and regulations[47] and public also seems to

[45] "Biotechnology Industry Statistics" http://www.bio.org/news/stats/asp

[46] The US biotechnology industry spent $ 15.6 billion on research and development in 2001. For further information, visit http://www.bio.org/news/stats/asp.

[47] Some of the important web sites for these regulations are: http://www.aphis.usda.gov/biotech/OECD/usregs.htm; http://www.aphis.usda.gov/ppq/biotech, http://www.epa.gov/opptintr/biotech/pdf/fs-002.pdf; http://www.epa.gov/opptintr/biotech/presstxt.htm, http://vm.cfsan.fda.gov/~lrd/biotechm.html; http://www.bio.org/foodag/wto.asp, http://www.usda.gov/agencies/biotech.

have faith in the system.[48] This might be an important reason for the development of biotechnology industry in the US.

3.7. Patents in Biotechnology

Patenting is seen as a tool appropriating returns from innovative activities. Patent represents first an invention that has business impact and second identifies the focus of research area. Patent mapping of a firm illuminates its area of technology thrust. But it is difficult to map the technology trajectory of a firm through patents. Firms have a different propensity to patent in different national markets for exploiting their inventions commercially. Process developments and scale-up processes in biotechnology require intensive information exchange between product developers and process engineers. Much of the information is highly proprietary but cannot be effectively protected by patents. Some of the recent patents in biotechnology are listed in table 3.

[48] Pisano, 1991,op.cit. Ref. no. 21.*Source*: Ernst & Young LLP, *Annual Biotechnology Industry Reports*, 1993-2002

Table 3: Patents in Biotechnology

Firm	1996	1997	1998	1999	2000
Incyte	7	18	102	245	122
Isis	37	41	38	78	76
Chiron	48	113	137	101	66
Genetech	75	83	129	54	59
HGS	4	11	27	60	36
Amgen	31	28	42	45	33
Dekalb Gentcis	18	1	8	43	31
Alza	66	41	33	57	29
Millenium	0	3	14	30	29
Immunex	30	13	22	18	21
Genzyme	17	18	31	32	20
Affymetrix	2	3	10	17	20
Elan	7	8	9	18	13
Nexstar	10	27	49	22	13
Vertex	3	8	9	23	12
COR therapeutics	4	15	26	13	11
Life Technologies	21	11	11	19	10
ICOS	7	13	22	22	10

Source: Bowonder, B., P.S. Yadav, and S. Krishnan, 'The Emerging Technology Trajectory', *Chemical Innovation*, 2001, vol. 31, no. 3, pp. 35.

So it is obvious that the US biotechnology industry developed through the interaction among academic institutions, established pharmaceutical companies, new biotechnology firms, venture capital and patents. The presence of active networks facilitates commercialization of biotechnology products. Patents in biotechnology give insights into the areas of focus in the present context but neither all the inventions in biotechnology got patented, nor all patentable are necessarily inventions. However, patents are driven by commercial aspects of technology and not always give true idea about the ongoing developments in the field of biotechnology research.

MAJOR EVENTS IN COMMECIALISATION OF BIOTECHNOLOGY

1973 - First gene cloned
1974 - First expression of a gene cloned from a different species in bacteria
- Recombinant DNA (rDNA) experiments first discussed in a public forum (**Gordon Conference**)
1975 - U.S. Guidelines for rDNA research outlined (**Asilomar Conference**)
- First Hybridoma created
1976 - First firm to exploit rDNA technology founded in U.S. (Genentech)
Genetic Manipulation Advisory Group (U.K.) started in U.K.
1980 - **Diamond vs. Chakrabarty** (U.S. Supreme Court rules that micro-organisms can be patented under existing law)
- Cohen- Boyer patent issued on the technique for the construction of rDNA
- United Kingdom targets biotechnology (**Spink's Report**)
- Federal Republic of Germany targets biotechnology (**Leistung's Plan)**
- Initial public offering by Genentech sets Wall Street record for fastest price per share increase ($35 to $89 in 20 minutes)
1981 - First monoclonal antibody diagnostic kits approved for use in the U.S.
- First automated gene synthesizer marketed
- Japan targets biotechnology (Ministry of International Trade & Technology declares 1981 "The Year of Biotechnology")
France targets biotechnology (**Pelissolo Report**)
Hoechst- Massachusetts General Hospital Agreement
Initial public offering by Cetus sets Walls Street record for the largest amount of money raised in an initial public offering ($115 million)
- Industrial Biotechnology Association (IBA) founded
- Du-Pont commits $120 million for life science R&D
- Over 80 NBFs had been formed by the end of the year
1982 - First rDNA animal vaccine (for *colibacillus*) approved for use in Europe
- First rDNA pharmaceutical product (human insulin) approved for use in U.S. & U. K.
- First R&D limited partnership formed for the funding of clinical trials
1983 - First plant gene expressed in a plant of different species
- $ 500 million raised in U.S. public market by NBFs

(Source: Commercial Biotechnology: An International Analysis",1984, Science and Technology Division, Molenwerf 1, 1014AG. Amsterdam, The Netherlands, Elsevier Science Publishers B.V.)

CHAPTER 4

BIOTECHNOLOGY INDUSTRY IN INDIA

Introduction

To recapitulate, biotechnology encompasses techniques applied to living organisms or parts thereof to identify, design or produce substances or to modify organisms for specific applications. Cell fusion techniques, recombinant DNA technology protein engineering and structure-based molecular design are considered modern biotechnology.[1]

There is a basic difference between the biotechnology industry in the US and the one in India. In the US, largely industry promotes and supports the R and D in biotechnology whereas in India biotechnology research is mainly funded and promoted by the state. So, here in India the state is responsible for the creation of promotional, legal and social structures for the growth of the biotechnology industry. The Department of Biotechnology (DBT) is the nodal agency in India to promote and develop the biotechnology industry in the country. A number of research institutes get support from the Government of India to develop and promote biotechnology R and D.

The Indian biotechnology industry is nascent at the present time and accounts only for 2% of the global biotechnology market. However, the Indian biotechnology industry is ranked third in the world in terms of stem cell research. The US Institute of Health Research has identified the National Center for Biological Science (NCBS) in Banglore and Reliance Life Sciences as premier embryonic stem cell research institutes.[2] The Indian medical biotechnology industry offers various products and services. In the products segment, vaccines and diagnostics are the major constituents while services are provided largely in the field of clinical trials and contract research.

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[1]P.K., Ghosh, "Biotechnology in India: Current Status and Future Challenges", *Invention Intelligence* July-Aug 1999, pp. 149-160

[2]Kiran Mazumdar Shaw, "India's Emerging Biotechnology Industry", paper presented at BIOTECH India 2003, 5-8 February, New Delhi. Available at http://www.biotech-india.com/exhibition_cov.htm.

4.1. Department of Biotechnology

The Government of India acknowledged and accepted biotechnology as a crucial factor for national development in the 1980s. The National Biotechnology Board (NBTB) with six members was set up in 1982. The main objective of NBTB was to coordinate the biotechnology research efforts in various ministries and research establishments.[3] The Technology Policy statement of 1983 of the Government of India stated that:

> "Special attention will be given to promotion and strengthening of technology base in newly emerging and frontier areas such as information, material science, electronics and biotechnology."

The Government of India, vide its notification dated 27th February 1986, announced the formation of a separate Department of Biotechnology (DBT) in the Ministry of Science and Technology. The main objective of DBT is to identify, initiate and promote activities that are conducive for further development in biotechnology priority areas.[4] A vision document giving a ten-year perspective for research, demonstration, commercialization and application of biotechnology in India was released in the year 2001. According to the strategy presented in the document, the current emphasis should be on consolidation and utilizing the existing infrastructure for promoting all aspects of the biotechnology research and application. It also acknowledges the development of human resources in the fields of genomics, molecular biology, computational and structural biology, immunology and genetics, as important areas.

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[3] Ministry of Science and Technology, Ministry of Health, Ministry of Agriculture, Ministry of Human Resource Development, Council of Scientific and Industrial Research and Department of Scientific and Industrial Research are funding R and D in biotechnology. In 1983 NBTB created a programme covering investment in the field of agriculture, healthcare, human resource development, biosafety regulations and patent strategies.

[4] The Department of Biotechnology (DBT) is the nodal agency for policy, promotion of R and D, international cooperation and manufacturing activities in the field of biotechnology in India. See Appendix 1.

In India there are six major agencies for promoting and funding biotechnology, viz. Department of Science and Technology (DST), Department of Biotechnology (DBT), Department of Scientific and Industrial Research (DSIR), Indian Council for Medical Research (ICMR), Indian Council for Agriculture Research (ICAR), Council for Scientific and Industrial Research (CSIR), and University Grants Commission (UGC). Among all these agencies, DBT is the only agency dedicated to R and D in biotechnology. The budgetary allocations given to these agencies during the last twenty years are pointed out in the following table.[5]

Table 1: Budgetary allocations of Major Funding Agencies in India

Rs. In Million

Agency	1990-91	2000-01
DSIR	131.3	583.8
DST	2588.9	7798
DBT	655	1361
ICAR	3236	13990
ICMR	396	1470
CSIR	2351	9120
UGC	3495	14070

Source: RIS, based on the Ministry of Finance, GOI, http://www.ris.org.in.

In India the developmental allocations are generally made for five years under the National Five Year Plans. The Tenth Five Year Plan (2002-07) has proposed an outlay of Rs. 20,750 million for DBT, which marks a sharp increase of 234% from the budgetary provisions made for the Ninth Five Year Plan (1997-2002) which totaled at Rs. 6,215.42 million. The budget allocations in current prices for the biotechnology sector by the Government of India have grown up more than ten times since the establishment of DBT. The following table gives an account of DBT budget allocations in the biotechnology sector over the years.

[5] *Research and Development Statistics,* 2001-02, published by the Government of India, Ministry of Science and Technology, Department of Science and Technology. Also see Appendix 7.

Table 2: DBT Budget (1986-87 to 2002-03)

Year	Rs. In Crores
1986-87 (Revised Estimates)	17.94
1987-88 (Budget Estimates)	40.99
1988-89	NA
1989-90 (Actual Expenditure)	53.82
1990-91 (Actual Expenditure)	59.35
1991-92 (Actual Expenditure)	64.03
1992-93 (Actual Expenditure)	76.13
1993-94 (Actual Expenditure)	81.04
1994-95 (Actual Expenditure)	84.01
1995-96 (Revised Estimates)	88.14
1996-97 (Actual Expenditure)	91.38
1997-98 (Actual Expenditure)	95.44
1998-99 (Actual Expenditure)	114.25
1999-2000 (Actual Expenditure)	127.77
2000-01 (Revised Estimate)	150.89
2001-02 (Budget Estimates)	186.34
2002-03 (Budget Estimates)	235.58

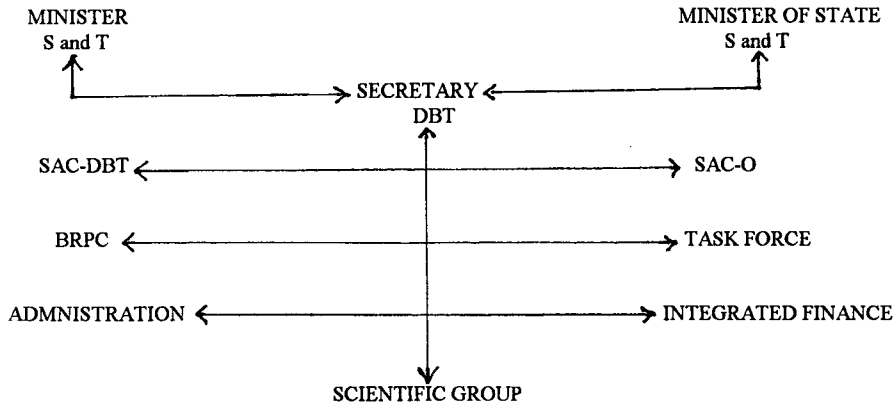
Source: DBT Annual Reports (1986-87, 1993-94, 1996-97 to 2001-02) and *Performance Budgets* (1991-92 to 1996- 97), Department of Science and Technology, Ministry of Science and Technology, New Delhi.

4.1.a Organizational Structure of DBT

Under the Ministry of Science and Technology (MST), the Government of India, DBT functions with the advice of Scientific Advisory Committee (SAC-DBT) and Standing Advisory Committee Overseas (SAC-O). These committees review the ongoing research programmes, identify new research areas and monitor the development of inter-institutional and interdisciplinary projects. A Biotechnology Research Promotion Committee (BRPC) and 16 Task Forces are also established to recommend and provide networking for new research proposals.[6] These committees meet twice or thrice a year. A National Bioethics Committee, consisting of scientists and representatives of various governmental organizations, is also constituted to overview the ongoing activities on human genome, genetic research and services, including programmes on gene therapy.

[6] See Appendix 2.

Fig. 1: The Structure of DBT



4.1.b Major Functions of DBT

DBT supports a variety of activities related to biotechnology, for example, research and development, biotechnology process and product development, human resource development, setting up biotechnology repositories and facilities, supporting various programmes. DBT also facilitates the commercialization of indigenously-developed biotechnology and products through institutions like the National Research and Development Corporation and the Biotechnology Consortium of India Limited. Some of the major activities of DBT are highlighted here.

1. Development of Infrastructure

Since biotechnology research in India is mainly a state-promoted activity, DBT took initiatives to develop the required infrastructure and human resources. Infrastructural facilities include setting up of biotechnology repositories, research centers, providing equipment and facilities and support to various biotechnology programmes. In total, 37 national repositories, two technology parks and six units in various labs or universities have been established or supported by the DBT. DBT has been spending a substantial amount of its budget on developing infrastructural facilities. During the early years, the proportion of expenditure on infrastructure was

sufficiently high to enable the development of a strong base for the biotechnology sector.

Table 3: DBT spending on building Infrastructural Facilities

Year	Rs. In Crores	% of the Total Budget (App.)
1986-87 (Revised Estimates)*	7.95	44.3
1987-88 (Budget Estimates)*	22.5	54.9
1989-90 (Actual Expenditure)	11.33	21.1
1990-91 (Actual Expenditure)	8.48	14.3
1991-92 (Actual expenditure)	9.61	15
1992-93 (Actual Expenditure)	10.19	13.4
1993-94 (Actual Expenditure)	8.15	10.1
1994-95 (Actual Expenditure)	9.1	10.8
1995-96 (Revised Estimates)	7.5	8.5
1996-97 (Actual Expenditure)	7.94	8.7
1997-98 (Actual Expenditure)	12.3	12.9
1998-99 (Actual Expenditure)	10.23	8.9
1999-2000 (Actual Expenditure)	8.27	6.5
2000-01 (Revised Estimates)	25.95	17.2
2001-02 (Budget Estimates)	11	5.9

Source: DBT Annual Reports (1986-87, 1993-94, 1996-97 to 2001-02) and *Performance Budgets* (1991-92 to 1996- 97), Department of Science and Technology, Ministry of Science and Technology, New Delhi.

* Includes infrastructural facilities and establishment of R and D units for new products generation.

During the Ninth Five Year plan (1997-2002) a total of Rs. 680.46 million (10.95% of the budget) was allocated for the development of infrastrucutral facilities, which increased to Rs. 900.00 million (4.34 % of the budget) during the Tenth Five Year Plan (2002-07). However, the percentage share of the budget allocation has gone down.[7]

2. Research and Development

DBT has recognized certain priority areas to develop indigenous capabilities, to generate new knowledge and to provide a base required for understanding of the basic and applied research in the field of biotechnology. A number of projects in various disciplines have been supported by the DBT. According to the Annual Report

[7] See Appendix 7.

of DBT (2001-02), 150 projects out of total 600 received, have been approved by the DBT. Currently there are 16 areas of focus in the field of biotechnology where R and D activities are carried out.[8] DBT is spending a substantial part of its budget on R and D activities.

Table 4: DBT Spending on Research and Development

Year	Rs. In Crores	% of the Total Budget (App.)
1986-87 (Revised Estimates)*	1.28	7.1
1987-88 (Budget Estimates)	3.1	7.6
1989-90 (Actual Expenditure)	12.88	23.9
1990-91 (Actual Expenditure)	18.07	30.4
1991-92 (Actual Expenditure)	22.71	35.5
1992-93 (Actual Expenditure)*	28.63	37.6
1993-94 (Actual Expenditure)	34.02	42
1994-95 (Actual Expenditure)	36.77	43.8
1995-96 (Revised Estimates)	39.49	44.8
1996-97 (Actual Expenditure)	37.9	41.5
1997-98 (Actual Expenditure)	34.97	36.7
1998-99 (Actual Expenditure)	43.22	37.8
1999-2000 (Actual Expenditure)	51.56	40.4
2000-01 (Revised Estimates)	43.35	28.7
2001-02 (Budget Estimates)	77.25	41.5

*= Research Schemes funded from NBTB core fund and New projects and Research Proposals.

Source: DBT Annual Reports (1986-87,1993-94, 1996-97 to 2001-02) and *Performance Budgets* (1991-92 to 1996- 97), Department of Science and Technology, Ministry of Science and Technology, New Delhi.

The DBT budget for basic and product based R and D projects reflects the level of importance given to various areas (Table 5).

[8] These areas are described in Appendix 2 under the head 'Task Forces'.

Table 5: DBT Budget for Basic and Product based Research and Development Projects (Rs. In lakhs)

Branch	89-90	90-91	91-92	92-93	93-94	94-95	95-96	96-97
Veterinary Biotechnology	11.8	39.1	99	237	126	238	150	250
Aquaculture & Marine Biotechnology	2.3	77.6	91.6	53.5	102	121	100	100
Medical	129	298	527	487	524	538	600	500
Fuel, Biomass Green cover Biotechnology	80.5	72.8	140	157	238	291	284	250
Microbial and Industrial	18.9	47.3	364	259	325	470	400	400
Biochemical Engg. & Bioconservation	0.87	28.9	244	114	58.2	79	100	4
Biological control of pests, weeds via BT	39.6	89.7	96.2	33.7	404	283	250	330
Immmunological Approaches to fertility control	190	177	105	66.7	125	119	130	130
Other Research and Development	244	449		658	684	6	0	0
Basic research & Emerging areas	572	527	138	236	373	515	450	350
Environmental Biotechnology						103	150	130
Medical and aromatic plants								100

*Source: DBT Annual Reports (*1986-87, 1993-94, 1996-97 to 2001-02) and *Performance Budgets* (1991-92 to 1996-97), Department of Science and Technology, Ministry of Science and Technology, New Delhi.

It becomes clear from the above table that the medical biotechnology area has got priority over other branches. The R and D spending in terms of current prices in the medical biotechnology area has increased substantially (from Rs. 128.53 lakhs in 1989-90 to Rs. 600 lakhs in 1996). Focus on medical biotechnology R and D possibly explains the need for various diagnostic kits and therapeutics for a number of emerging and reemerging infections in the country.

The Ninth Five Year Plan allocation for medical biotechnology R and D was Rs. 808.9 million (13.6% of the total budget allocation), which has increased up to Rs. 4130 million (31.46% of the total budget allocation) during the Tenth Five Year Plan. The main areas of focus in medical biotechnology R and D are genomics, stem cell biology, cancer research, and vaccine and diagnostics production. Some of the diseases having the main focus of vaccine R and D activities are tuberculosis, HIV, malaria, cholera, Japanese encephalitis, hepatitis, leprosy, rabies, amoebiasis and leishmaniasis.[9]

[9] Vaccines for Rabies, Leprosy and Japanese encephalitis have been successfully developed. See *DBT Annual Report*, 2001-02, Ministry of Science and Technology, GOI, p.74

3. Human Resource Development

Training and teaching has been an integral part of biotechnology activities. Recognizing the requirements of the human resource development in biotechnology, DBT has initiated an integrated human resource development programme. The main objective of the programme is to generate adequate and appropriately trained personnel in the field of biotechnology through several schemes and courses, and popularizing the public understanding of biotechnology. DBT is currently supporting as many as 51 programmes through 39 academic institutes.[10]

University Grants Commission (UGC) under the Ministry of Human Resource Development (HRD) also takes care of human resource development in the field of biotechnology. The budget allocation for UGC was Rs. 3495 million during 1990-91, which rose to Rs. 14070 million in 2000-01. Besides certain awards, scholarships and placement for jobs are also provided to the students. However, the total budget allocation for HRD in the Tenth Five-Year Plan has come down from Rs.1000 million (16.09% of the budget) in the Ninth Five-Year Plan, to only Rs.160 million (0.77% of the budget). The DBT expenditure on HRD over the years is as follows:

[10] *DBT Annual Report*, 2001-02, Ministry of Science and Technology, GOI, Appendix 7, pp. 168-69. Presently, there are 20 M.Sc. Programmes in general biotechnology, 4 in agriculture biotechnology, one each in medical and marine biotechnology and others are diploma courses in molecular and biochemical technology.

Table 6: DBT Budget for Human Resource Development

Year	Rs. in Crores	% of the Total Budget (App.)
1986-87 (Revised Estimates)	3.65	20.3
1987-88 (Budget Estimates)	6.5	15.9
1989-90 (Actual Expenditure)	6.74	12.5
1990-91 (Actual Expenditure)	7.46	12.6
1991-92 (Actual Expenditure)	5.54	8.7
1992-93 (Actual Expenditure)	4.22	5.5
1993-94 (Actual Expenditure)	5.81	7.2
1994-95 (Actual Expenditure)	7.8	9.3
1995-96 (Revised Estimates)	6.5	7.4
1996-97 (Actual Expenditure)	6.43	7
1997-98 (Actual Expenditure)	7.05	7.4
1998-99 (Actual Expenditure)	9.46	8.3
1999-2000 (Actual Expenditure)	9.82	7.7
2000-01 (Revised Estimates)	10	6.6
2001-02 (Budget Estimates)	10	5.4

Source: DBT Annual Reports (1986-87, 1993-94, 1996-97 to 2001-02) and *Performance Budgets* (1991-92 to 1996-97), Department of Science and Technology, Ministry of Science and Technology, New Delhi.

According to Visalakshi and Sharma (1993) the requirement of specially qualified personnel in biotechnology is increasing. This could be explained by the shift of emphasis towards specialized functions associated with biotechnology. Though R and D remains a major function requiring human resources in biotechnology which had increased 3-4 times from 1992 to 2000, the requirement of human resources for production (16-20 times approximately), marketing (4 times) and other (4-7 times) jobs is also increasing.

Table 7: Maximum and Minimum Manpower Estimates In the field of Biotechnology in India in 2000

Functions	Specialization				Total
	Genetic Eng.	Hybridoma	Plant Tissue Culture	Enzyme	
Research					
Max.	4,000	1,000	2,000	800	7,800
Min.	1,500	700	700	700	4,600
Production					
Max.	2,000	500	8,000	600	11,200
Min.	1,000	500	6,000	500	8,000
Marketing					
Max.	500	500	500	200	1,700
Min.	500	200	300	200	1,200
Training					
Max.	800	700	500	200	2,200
Min.	400	400	500	200	1,500
Extension					
Max.	NA	4,000	300	NA	4,300
Min.	NA	2,500	200	NA	2,700
Total					
Max.	7,300	6,800	11,300	1,800	27,200
Min.	3,400	4,300	8,700	1,600	18,000

Source: Visalakshi, "Manpower requirements in biotechnology and Strategies to achieve them: International and Indian experience"; *International Journal of Biotechnology*, Vol.3, Nos. ½, *2001.*

4. Biotechnology Product and Process development and Technology transfer

The purpose of R and D projects is to develop a product, process or technology. To ensure the validity of products and processes, large-scale demonstrations and field trials are performed. Activities under this head focus on the validation, field trials, demonstration, technology transfers and biosafety issues related to biotechnology processes and products. DBT has taken into consideration many industry-oriented research projects related to: microbial and industrial biotechnology; food and nutrition; tissue culture; and also establishing micropropogation technology parks. Through the Biotechnology Patent Facilitating Cell (BPFC), the DBT is also creating awareness about patent-related issues among the scientists.[11] DBT also gives due care to put indigenously-developed technologies

[11] The total number of patents filed by the DBT is 99. See *DBT Annual Report*, 2001-02, p. 101.

into services and commercialize them.[12] The following table gives an idea about DBT spending on transfer of technologies and manufacturing activities.

Table 8: DBT Budget for Demonstration or Transfer of Technologies

Year	Rs. In Crores	% of the Total Budget
1986-87 (Revised Estimates)	N.A.	N.A.
1987-88 (Budget Estimates)	N.A.	N.A.
1989-90 (Actual Expenditure)	8.29	15.4
1990-91 (Actual Expenditure)	6.22	10.5
1991-92 (Actual Expenditure)	6.6	10.3
1992-93 (Actual Expenditure)	5.26	6.9
1993-94 (Actual Expenditure)	6.22	7.7
1994-95 (Actual Expenditure)	9.2	11
1995-96 (Revised Estimates)	9.3	10.6
1996-97 (Actual Expenditure)	7.06	7.7
1997-98 (Actual Expenditure)	10.29	10.8
1998-99 (Actual Expenditure)	9.19	8
1999-2000 (Actual Expenditure)	10.79	8.4
2000-01 (Revised Estimates)	11.18	7.4
2001-02 (Budget Estimates)	11	5.9

Source: *DBT Annual Reports* (1986-87, 1993-94, 1996-97 to 2001-02) and *Performance Budgets* (1991-92 to 1996- 97), Department of Science and Technology, Ministry of Science and Technology, New Delhi.

5. Bioinformatics

Information technology has been playing an important role in the development of the biotechnology industry. Access to comprehensive biological information is necessary in all the fields of biotechnology. India is one of the countries to establish a nationwide Biotechnology Information System Network (BTISnet) in 1986-87. BTISnet offers a single information resource in the country, covering various interdisciplinary areas of biotechnology and molecular biology. It covers almost the entire country through 57 centers. The BTIS network consists of 10 Distributed Information Centers (DICs) and 46 Sub-Distributed Information Centers (Sub-DICs). An apex Biotechnology Informatics Centre at DBT coordinates the activities of the entire network.

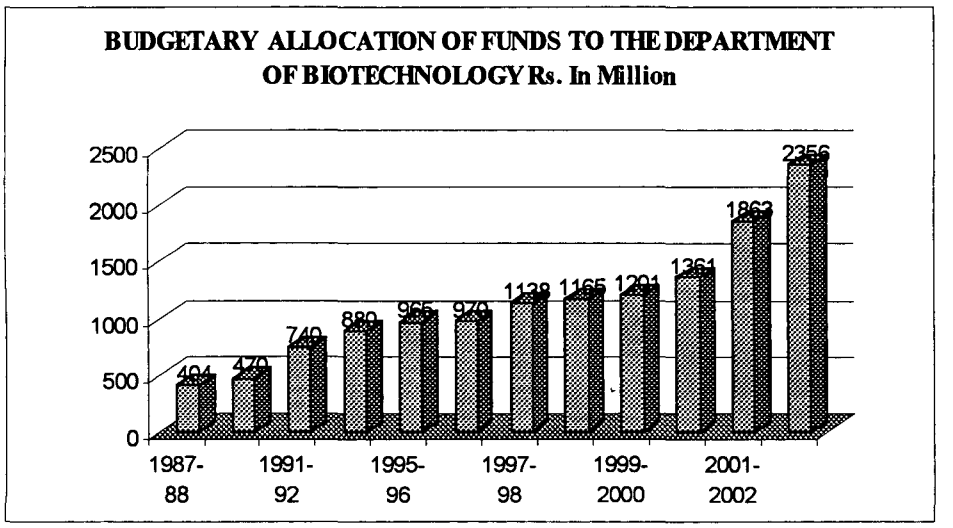
[12] See Appendix 3.

Human resource development has been recognized as an important area for sustenance of the bioinformatics programme. More than 20 short-term programmes run in various universities to train scholars in bioinformatics. Six National Facilities on Interactive Graphics are dedicated to the promotion of molecular modeling and related activities in bioinformatics. BTISnet has developed more than 100 databases on biotechnology. Several international databases required for application in genomics and proteomics have been developed in the form of Mirror sites as a part of the programme and are linked through high speed and large bandwidth network, to promote faster sharing of latest information in the field of biotechnology. DBT has also initiated various programmes to realize the exchange of scientists and technology through international cooperation, to absorb and adopt the recent developments in the field of biotechnology.[13]

Analysis

The budget allocations to the DBT over the years are shown in the following chart.

Fig.2



[13] e.g. SAARC Programme, G-15 Programme, Agriculture Resource Management and International Centre for Genetic Engineering and Biotechnology.

If we compare the DBT expenditure on major activities, i.e. human resource and development activities (HRD), technology demonstration, technology transfer and R and D, the following figures comes out.\

Fig.2.a

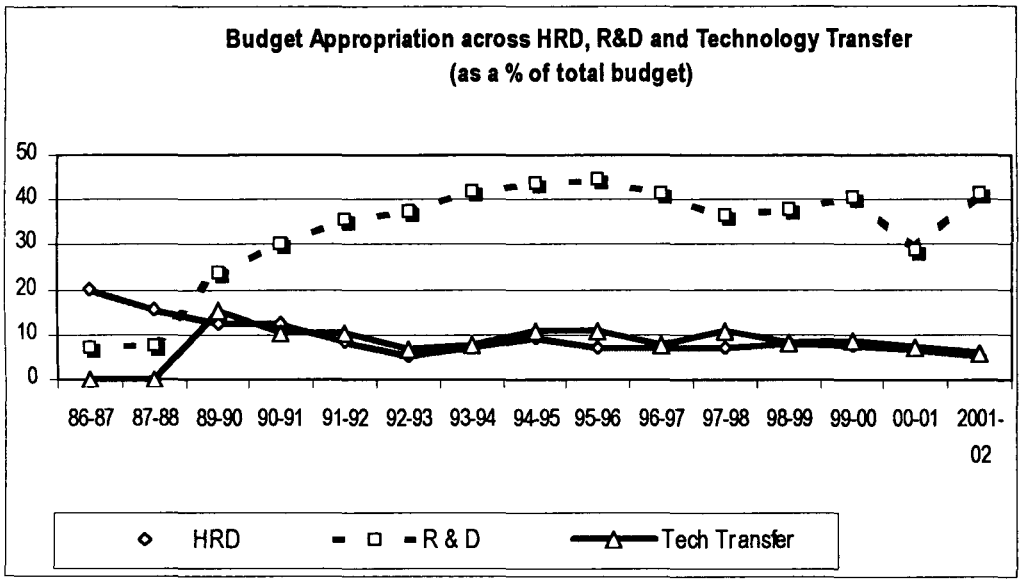
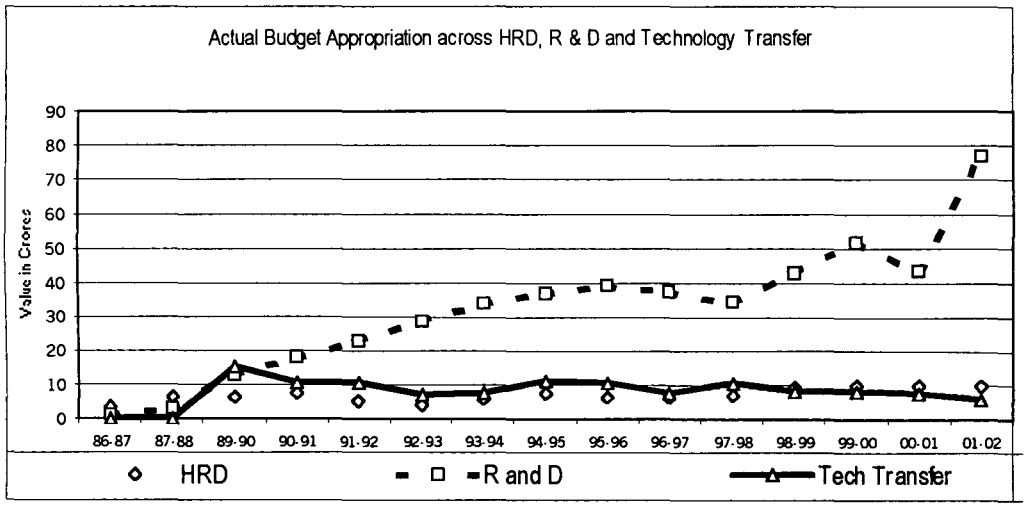


Fig.2.b :



The above charts show that the actual budget expenditure on the human resource development and technology transfer have gone down marginally from 1997-98 onwards, whereas the R and D expenditure has got a sharp increase in the year 2001-02. The percentage share of the expenditure on HRD and technology transfer activities is between Rs. 9 crores and Rs. 10 crores. The R and D expenditure

is increasing and currently accounts for 40% of the total budget. This explains the importance given to the R and D but it also infers that probably more expenditure on the other two activities might improve the quality and quantity of the human skills, and bring better commercialization prospects for the indigenously-developed technologies and products.

4.2. Overview of the Indian Biotechnology Industry

The Government of India supports and promotes a majority of R and D in biotechnology in India.[14] The private sector's contribution is meager as well as concentrated in selected research areas.[15] A number of government-funded research institutions in India have established a solid research base in the field of biotechnology. The government has invested more than $ 750 million in the field of biotechnology since 1985.[16]

The Indian biotechnology industry is focused and is developing through biotechnology clusters in various states. The main biotechnology clusters or bio-clusters are developed in the states of Andhra Pradesh, Himachal Pradesh, Karnataka, Kerala, Maharashtra, and Tamil Nadu. These states are developing, establishing and providing incentives to biotechnology companies as well as investing in construction of biotechnology research parks to promote the biotechnology industry. The bio-clusters developed by those states are expected to promote convergence and coordination among various academic and research institutions and different sectors of the industry that might eventually help growth of the biotechnology industry. For example, the Bangalore bio-cluster is focusing on coordination between its successful information technology industry and biotechnology industry, which is resulting into a growing bioinformatics industry.

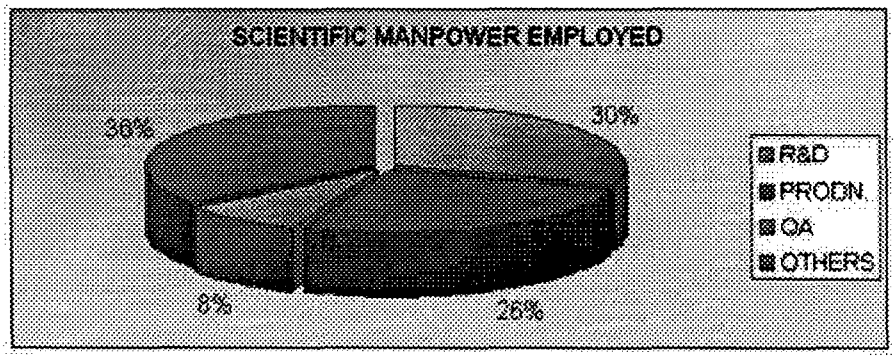
Biotechnology companies in India are active in the fields of agriculture, healthcare, and industrial, environmental or other biotechnology- related activities. There are discrepancies among the existing sources regarding the actual number of

[14] Ghosh 1999; Visalakshi 2001 (see table 7).
[15] Visalakshi 1995; Ramani et al. 1999, 2001.
[16] "Biotechnology Market in India", June 2002, at http://www.inforexport.ge.ca; and CII Report, "Biotech India 2003", at http://www.ciionline.org/busserv/biotechnology/index.html.

biotechnology companies in India. According to a survey conducted by the Confederation of Indian Industry (CII), there are 160 biotechnology companies in the country. Out of which, 60 are distinctly engaged in molecular biology and recombinant biotechnology.[17] More than 50 percent of these companies are located in two cities: Bangalore and Hyderabad.

The number of biotechnology companies in India is increasing, which consequently has resulted in increased demand for scientific manpower.[18] According to the CII survey the out of the total manpower consumed by biotechnology companies, 30% are involved in R and D activities, 26% in production activities, 8% in quality assurance services, and 36% in other activities.

Fig. 3:



Source: http://www.biotech-india.com/biotech_industry.htm.

4.2.a Consumption of Biotechnology products in India

According to the available estimates the size of India's market for consumption of biotechnology products varies between US $ 1.5 and $ 2.5 billion. Of this the value of agriculture biotechnology products market is estimated to vary between $ 400 and $ 500 million and the value of diagnostics or vaccines market

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[17] According to the Directory of Biotechnology Companies in India, 2000-01, published by BCIL, there are 176 biotechnology companies in India, of which 49% are in agriculture biotechnology, 38% in healthcare biotechnology, 2% in environmental biotechnology and remaining 24% in other instrumentation and consultancy services.

[18] Footnote no. 16. CII survey shows that more than 50% of the biotechnology companies in India have been set up after 1998. Visit http://www.biotech-india.com/biotech_industry.htm.

varies between $ 150 and $ 420 million.[19] In the year 1997, 72% of the total consumption of biotechnology products in India was produced locally and the rest was imported. During the same year, in human and animal healthcare segment, nearly 70% of the products consumed were produced locally. In the year 2000 the local production capacity of biotechnology products was estimated to be 74%. The production value of the Indian biotechnology industry in the year 2002 is estimated to be at $ 3.7 billion.[20] In 2002 the CII report shows that the medical biotechnology products constitutes approximately 37.5% share, followed by 30% agricultural and industrial products each, and the other biotechnology products segment occupies the rest of the total biotechnology products consumption market in India.[21]

[19] Sachin Chaturvedi, "Status and Development of Biotechnology in India: An Analytical Overview", at http://www.ris.org.in

Differing Perspective of Biotechnology Market in India'

	CII	DBT	The Economist
Biotechnology Market	$ 2.5 billion	$ 1,849 million	$ 1,475 million
Agriculture or Seed Market	$500 million		$450 million
Bioinformatics Market	$2.2 million		
Diagnostics Market	$420 million	$150 million	$375 million

Source: RIS based on: *Business Standard*, Dec.24, 2000; *Business Line*, July 9,2001; *Financial Express*, Oct. 10, 2001; *Economist*, Sep. 1, 2001.

[20] Ghosh 1999 and "The Biotechnology Market in India", June 2002. Visit http://www.infoexport.ge.ca)/.

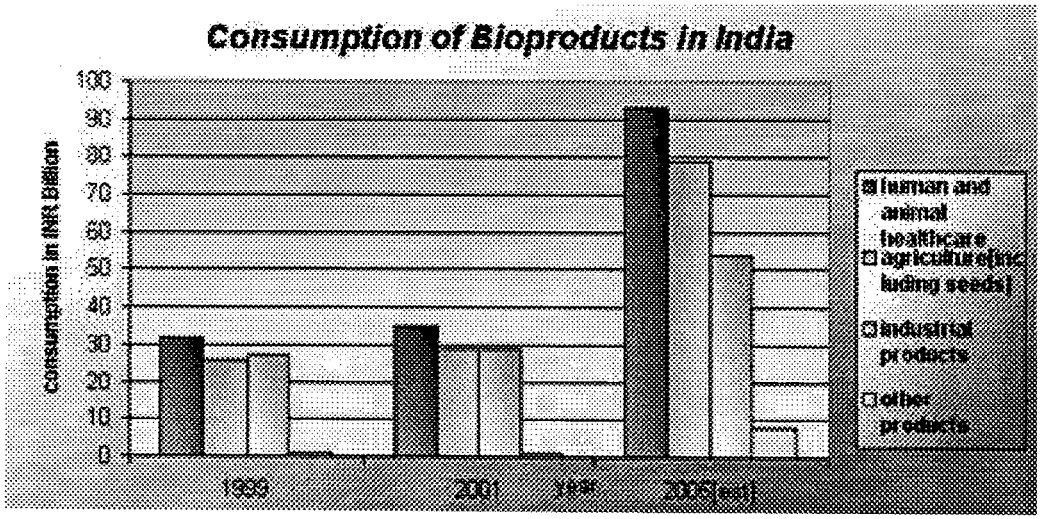
[21] Visit http://www.infoexport.ge.ca)/ and also see Som Dutt "Biotech Industry in India: Its Perspectives" at http://www.chempros.news.htm. The figure given here is a matter of debate. According to the above sites around 60% share of the total consumption of biotechnology products is devoted to human health applications, 10% to agricultural biotechnology and 30% to industrial applications, bioinformatics and genomics.

Table 9: Past Consumption and Future Consumption Estimates of Biotechnology Products in India (Rs. In Million)

Biotech Product	Actual	Future	Future
	1999	2005	2010
1. Human & Animal	32240	35320	93540
Healthcare Products	(37.5%)	(37.6%)	(40.0%)
2. Agriculture Products	25670	28880	78720
(Incl. Seeds)	(29.8%)	(30.7%)	(33.7%)
3. Industrial Biotech	27090	28500	53590
Products	(31.5%)	(30.3%)	(22.9%)
4. Other Biotech Products	1040	1300	7940
	(1.2%)	(1.4%)	(3.4%)
Total	86040	94000	233790
In Million US $	1789	2186	4270

Source: http://www.ciionline.org/busserv/biotechnology/index.html.

Fig.3:0



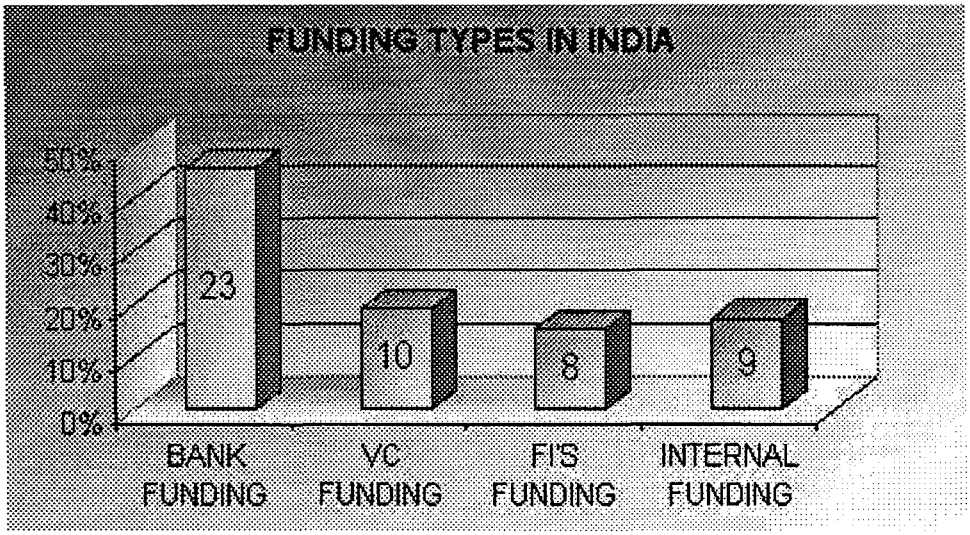
Source: http://www.biotech-india.com/biotech_industry.htm.

Table 9 indicates that healthcare products are likely to dominate the scene and may account for 40% of the market by 2010. The major share of the medical biotechnology R and D is used in vaccine research and genomics. The direction of growth and development of the biotechnology industry would become clearer by looking into funding patterns, regulatory system and incentives given to the industry.

4.2.b. Funding

The central and the state governments are encouraging jointly-funded private and public research initiatives on commercially viable projects.[22] Venture capital for biotechnology in India is limited.[23] DBT has initiated venture capital funding for small- and medium-sized biotechnology companies.[24] DBT is also looking for encouraged support from the State Governments in building biotechnology parks and research centers.[25]

Fig.4:



Source: http://www.biotech-india.com/biotech_industry.htm.

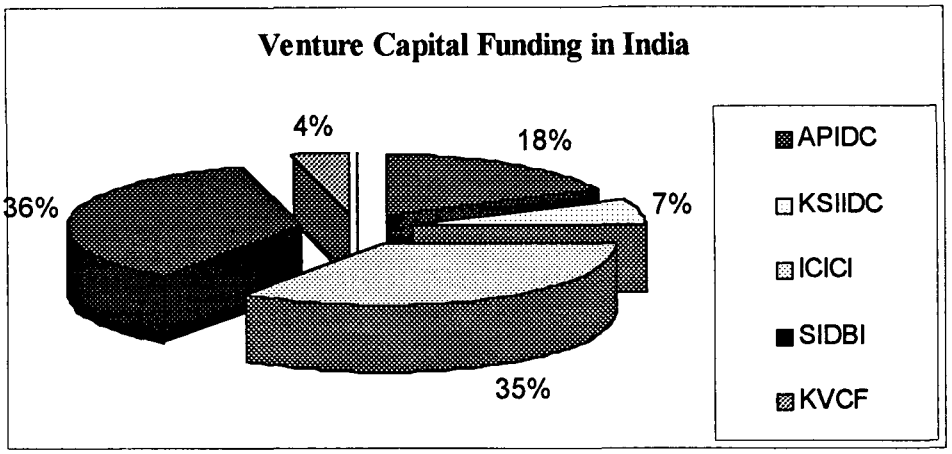
In contrast to the US, banks are still the major source of financing for the biotechnology industry in India. Here venture capital funding accounts for approximately 10% of the total funding to the biotechnology industry.

[22]Presentation made by the Indian Credit and Investment Corporation of India, "Funding Innovations in Biotechnology" at Biotech India 2003, Feb 5, 2003. Also visit http://www.biotech-india.com/exhibition_cov.htm .

[23]For details, visit http://www.biotech-dia.com/biotech_industry.htm&http://www.ris.org.in.

[24] Although the size of the fund has not yet been announced, it will be part of 'Technology Development Fund Programme'.

Fig. 5:



Source: Research Information System (RIS), **http://www.ris.org.in.**

The venture capital funding for the Indian biotechnology industry accounts for approximately Rs. 3000 million. Out of this, Indian Credit and Investment Corporation of India (ICICI) accounts for 35% (Rs.1000 million) and Small Industries Development Bank of India for 36% (Rs.1700 million).[26] Some states are also supporting biotechnology through venture capital funding, e.g. Kerala Venture Capital Fund has 4% share (Rs. 200 million), Andhra Pradesh Industrial Development Corporation (APIDC) share is 18% (Rs.500 million), and Karnataka State Industrial Infrastructure Development Corporation (KSIIDC) share is 7% (with Rs. 100 million) of the total venture capital in biotechnology in India.

4.2.c. Regulation

Two specific features of the Indian biotechnology industry are the stringent regulatory procedures and the long duration of time taken for testing and approving

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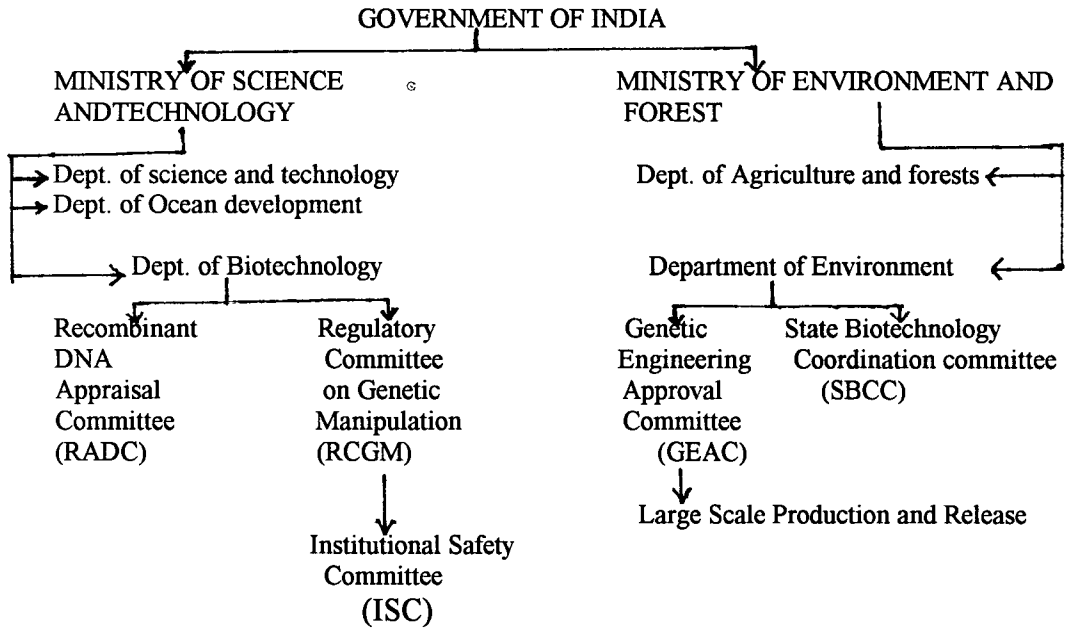
[25] *DBT Annual Report* 2001-2002, Ministry of Science and Technology, GOI, p. 156.

[26] ICICI Venture Funds Management Company Ltd., India's largest venture capital company, announced the creation of ICICI Biotechnology Incubator Fund in March 2002, with a target size of $ 32 million. The company has also invested in the local biotechnology companies including Biocon and Avesthagen. To stimulate technology development and commercialization, various programmes have been initiated to facilitate private investment in biotechnology R and D, such as: SPREAD (Sponsored Research & Development Programme), PACT (Programme for Advancement of Commercial Technology), and Technology Institution (TI) Programme.

the commercialization of biotechnology products.[27] The industry has to meet the obligations of five different departments under four different ministries to complete all formalities.[28] All kinds of approvals take up more than a year's time.

Fig 6: Regulatory Regime for Biotechnology Products in India



For this reason the biotechnology industry has been seeking a single independent regulatory authority that might set guidelines for all application of biotechnology-based molecules in all possible stages of development. Now DBT has taken up a proactive role in the promotion of domestic biotechnology industry. It has

[27] Since the field is new, experts are drawn from premier laboratories, research institutions and industry. They are involved in formulating appropriate regulatory guidelines for commercialization biotechnology products. There is still ambiguity over the rationalization of procedures and transparency in related matters. Besides that, a number of agencies are involved in regulation procedure, which takes time to finally approve a product for commercialization. This assessment is based on opinions from Subhash Chand, from the Department of Biochemical Engineering and Biotechnology, IIT, and Sanjay Sardana, "Adequate Policy Framework required to boost biotech industry", *Financial Express,* 11 August, 2001.

[28] These are Ministry of Environment and Forest, Ministry of Science and Technology, Ministry of Agriculture, Ministry of Health and Family Welfare and Ministry of Industrial Development. The different departments are Dept. of Biotechnology, Dept. of Ocean Development, Dept. of Science and Technology, Dept. of Environment, and Dept. of Agriculture and Forests. Indian Council of Agriculture Research, Indian Council of Medical Research, Council of Scientific and Industrial Research and Central Pollution Control Board are also involved in the implementation of the guidelines set for release of biotechnology products in India.

proposed a single window application-processing cell as a part of new regulatory system for the domestic biotechnology sector. The single window would receive the applications sent by the Review Committee on Genetic Manipulation (RCGM) and submit a scientific evaluation report within 60 days to the relevant approval committee.[29]

4.2.d. Export-Import Policy

All India Biotech Association (AIBA) was established in 1994 to represent the interests of the Indian biotechnology industry. Earlier there were up to 68% import duty on the imported reagents and equipments required in R and D and manufacturing of biotechnology products. In July 1998, the Minister of Commerce, Government of India, made some amendments to the Export and Import Policy, 1997–2002, in respect of the biotechnology products, for grant of concessions and incentives.[30]

4.3. Medical Biotechnology Industry in India

There are a variety of communicable diseases prevalent in India. The situation is worsened by a number of new emerging and re-emerging infective diseases, which require development of appropriate diagnostics and therapeutics. The number of technologies transferred to the industry from the DBT suggests that medical biotechnology is focusing on vaccines and diagnostics.[31] This also explains for the

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[29] For example, in case of agricultural products, it would go to the Genetic Engineering Approval Committee (GEAC), in case of pharmaceuticals products to the Drugs and Pharma Approval Committee (DPAC) and in case of food products to the Biotech Foods Approval Committee (BFAC). These committees in turn approve or reject the products within 90 days of receiving the evaluation report.

[30] AIBA, "Amendments in the Exim Policy 1997-2002 in Respect of Biotech Products", at http://www.aiba.online.com/development.htm. These amendments are being published in the gazette of India Extraordinary, Part II, Section 3, Sub-section (ii), vide the GOI, Ministry of Commerce, Notification No. 18 (RE.98) 1997-2002, dated 2nd September 1998. Pursuant to this Notification, Appendix I (Paragraph 9.5 of the EXIM Policy) has been amended and the minimum Net Foreign Exchange Earnings as Percentage of Exports (NEEP) requirements and the export performances under the EOU/EPZ/EHTP scheme have been revised. Under this amendment, the biotechnology sector would have just positive NEEP against 30% of profits gained and the minimum export performance for 5 years for this sector would be only US $ 0.50 million (against US $ 3.5 million for others).

[31] Appendix 8.

priority given to the medical biotechnology sector in the Tenth Five Year Plan over other sectors.[32]

The Indian medical biotechnology industry is strongly related to the pharmaceutical industry. The bulk of investment in biotechnology in India was in the pharmaceutical sector till 1997 and the situation continued to be the same in 1999.[33] The pharmaceutical market (both biotechnology-based pharmaceuticals and traditional pharmaceuticals) is estimated at $ 8 billion.[34] There are approximately 250 large research-based pharmaceutical companies and another 3000 companies active in manufacturing. The integration of biotechnology in pharmaceutical companies has resulted in the formation of biopharmaceutical companies. Currently 48 pharmaceutical firms have been listed in government directories as active entities in the field of biopharmaceuticals.[35] In the pharmaceutical field, generics manufacturers dominate the industry.[36]

Before sale, all pharmaceutical products including biopharmaceuticals must receive an approval from the Drug Controller General of India (DCGI). The New Drug Application (NDA) must be forwarded with all necessary information and, in general, phase III clinical trials must be conducted in India before the approval is given. If a product has not received marketing approval in other countries, some phase II trials may be required. But a drug is not likely to be approved for sale in India unless it is approved in the country of origin.

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[32] Appendix 7.

[33] *The Economist*, February 1997, Review of the Pharmaceutical Sector; Ramani and Venkataramnai, 1999

[34] *Indian Pharma Industry: Issues and Options*, published by Saket House, Ahmedabad, India; and, "The Biotechnology Market in India", at http://www.infoexport.gc.ca.

[35] Ramani Shyama V., "Who's interested in Biotech? R and D strategies, knowledge base and market sales of Indian biopharmaceutical firms", email.ramani@grenoble.infra.fr.
According to the BCIL 2001 Directory of Biotechnology Companies in India the current number of pharmaceutical companies diversified in the field of biotechnology is around 52.

[36] Ibid. Currently India follows the process patent system. It means that patents are given on the process but not on the product, and companies work backward from the finished product to develop new processes to manufacture a similar product. As a result most of these companies have good experience in process development or reverse engineering. These companies look forward to produce biotechnology based generic drugs, i.e. biogenerics.

4.4. Medical Biotechnology products in India

The current segmentation of the medical biotechnology industry in India is shared by medical biotechnology products, clinical trials and contract research services. Medical biotechnology products include human therapeutics (e.g. biogenerics, vaccines, recombinant therapeutic proteins), industrial products (industrial enzymes, diagnostics) and bioprocess equipment and instrumentation. Clinical trials and contract research services include rDNA technologies, genomics and bioinformatics. Clinical trials (also called medical research and research studies) are used to determine whether new drugs or treatment are both safe and effective. In other words, a clinical trial is a research study to answer specific questions about new drugs, new therapies, or new ways of using known treatments.[37]

A biotechnology-based therapeutic drug costs around $ 500 million and 10-15 years to reach the market.[38] In India, the development cost for a biotechnology drug is estimated to be $ 250 million, which places the country in a position to serve as a research centre for transnational pharmaceutical companies. Hence transnational pharmaceutical companies are interested to partner with local companies at the drug discovery stage of research, and also for contract research and manufacturing jobs.[39]

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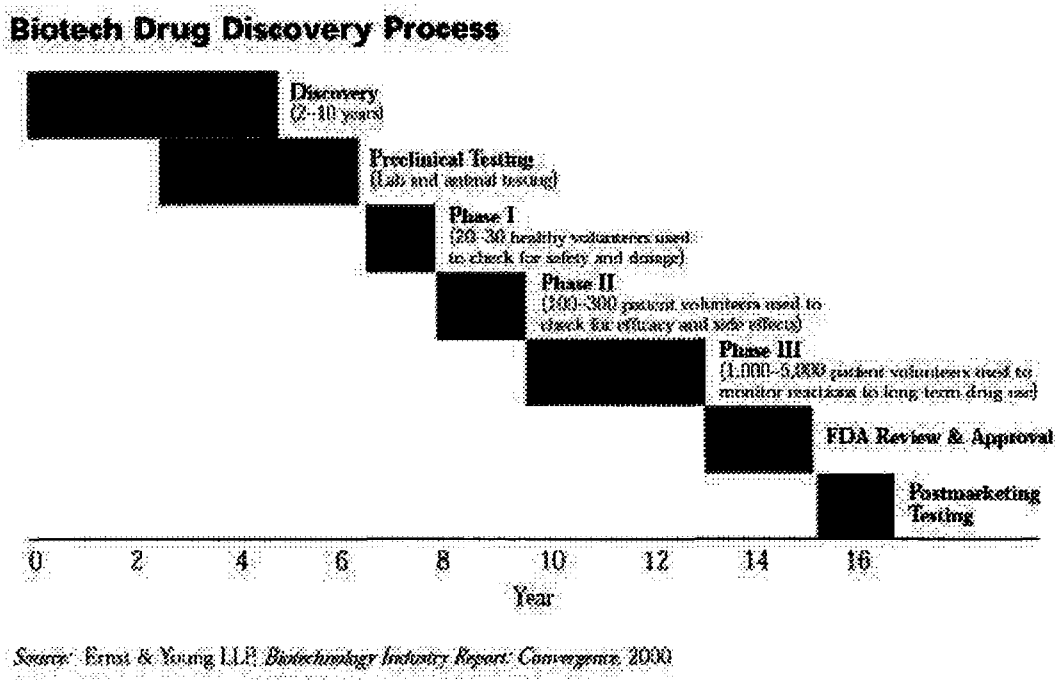
[37] A.S. Arvind, "Clinical research opportunities in India", paper presented at the Confederation of Indian Industries, Bangalore, 7 Feb 2003, available at http://www.biotech.india.com/highlights.htm.

[38] For details, visit http://www.bio.org.

[39] Goutam Das, "Scope and opportunities of contract Research services in India", at Biotech India 2003, 5-8 Feb 2003, New Delhi. for details, visit http://www.biotech.india.com/highlights.htm. Also visit http://www.biotech-india.com/exhibition_cov.htm and http://www.biotech-india.com/highlights.htm.

Fig. 7:



Source: Ernst & Young LLP, *Biotechnology Industry Report: Convergence 2000*

In human healthcare products there are three subcategories: vaccines; diagnostics; and therapeutic recombinant proteins. These are discussed in detail here.

4.4.a.i. Vaccines

The Indian Expanded Programme of Immunization (EPI) was initiated to control and prevent major infectious diseases prevalent in India in 1978. It was expanded as the Universal Immunization Programme (UIP) in 1985. UIP was adopted as a Technology Mission by the Government of India and was designed to set up, undertake, promote and monitor R and D activities in vaccinology and achieve self-sufficiency in vaccine production. Currently, eight national health programmes are running for the eradication of malaria, tuberculosis, filaria, HIV, leprosy, iodine deficiency, blindness, and mental health. In addition, health schemes for the prevention of kala-azar, Japanese encephalitis and dengue are also implemented.[40] Thus, vaccines constitute a key product of the medical biotechnology industry and

DBT is undertaking research for the development of various biotechnology vaccines.[41] DBT has been producing several vaccines in collaboration with many developed and developing countries. The main objective is to share knowledge with other countries on recent developments in vaccines, training and exchange of information and scientists.[42] Consumption of some of the major vaccines in India is summarized in Table 10.

Table 10: Current and Estimated Future Consumption of Vaccines

Vaccine	Consumption (Ml. Doses)		Estimated Consumption (Ml. Doses)
	1997	2001	2005
DPT	110	114	124
DT	54	57	65
Tetanus Toxoid	192	200	222
BCG	41	43	47
Oral Polio	110	160	225
Measles	25	32	45
MMR	7	8	10
Hepatitis B	7	18	45
Rabies	5	7	12
Typhoid (Injectable)	0.4	0.8	2.5

Source: P.K. Ghosh, "Market size and Future demand for Biotech products", available at http://www.ciionline.org/busserv/biotechnology_market.html.

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[40]According to the *Annual Report of the Ministry of Health and Welfare, 2001-02, GOI*, total budget allocation for Health Schemes is Rs.1450 crores and 54% of the allocated money is spent on T.B., malaria, leprosy, HIV etc.

[41] *DBT Annual Report*, GOI, 2001-02, p. 61. DBT has developed biotechnology vaccines for Rabies, Leprosy and Japanese encephalitis. Biotechnology vaccine for leprosy has been made indigenously but it has not come to the market for commercial use due to biosafety concerns. Also see *Times of India*, "Leprosy Vaccine not cleared for general use", 7th May, 2001.

DBT asserts that indigenous leprosy vaccine (leprovac) has been proved effective in treating the disease. But the Ministry of Health maintains that the drug controller has cleared the marketing of the vaccine for the trial studies. The Ministry also maintains that the reported use of 24 lakh doses of the vaccine by voluntary agencies is not true.

[42] Earlier in 1987, the DBT initiated the Indo-US Vaccine Action Programme (VAP), a joint bilateral programme on applied research and development of vaccines and immunodiagnostics. The Joint Working Group (JWG), which was constituted by the two governments, identified viral hepatitis, rotavirus, cholera, E. coli, typhoid, pertussis, Pneumococcus, Haemophillus influenza, canine rabies, respiratory syncytial virus, and polio as priorities for collaborative research under the Indo-US VAP. The JWG also reviews the progress of implementation of VAP in both countries. In addition, two projects on typhoid vaccine evaluation were authorized at AIIMS, New Delhi, and at the Tuberculosis Research Center (TRC), Chennai.

Comparatively analyzing the requirement, consumption, production and import rates over the years, it becomes clear that India depends on domestic production in the case of DPT (diphtheria, pertussis, tetanus booster) and DT (diphtheria, tetanus booster). The estimated demand of oral polio vaccines is mainly satisfied by imports. For some of the other major diseases, such as typhoid and Hepatitis B, domestic production is not enough, while imports meet only a portion of the demand.[43] Human diploid cell culture based vaccines against measles, mumps and rubella (MMR) are being locally produced as well as imported. Vaccines against influenza and vericella are imported and consumed. The current imports of these vaccines individually vary between one and three million doses per annum, which are considered low, primarily due to their high unit costs.

The total turnover of sera and vaccines produced locally for human ailments in India are worth more than Rs. 1600 million, and Rs. 2700 million worth of vaccines are imported and utilized.[44] The Indian vaccine market is growing at the rate of 8-10% per annum but a major portion of the requirement is met through imports. Hence, research in human vaccine development against several viral bacterial and parasitic diseases is required.

The Government of India has taken some more market-oriented initiatives to promote domestic production of vaccines. The New Drug Policy of 1994 states that the genetically-engineered drugs produced by recombinant DNA technology and specific cell or tissue culture targeted drug formulations will not be under price control for five years from the date of manufacturing in India. Private companies have largely focused on high-priced vaccines, and this is reflected in their research priorities, e.g. Hepatitis B, MMR and oral typhoid vaccines.[45]

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[43] See Appendix 11. The whole cell cholera and typhoid vaccines, which were produced and used in India, performed so poorly that mass immunization with these vaccines was discontinued. DBT has also identified the pertussis component of the DPT vaccine as of low efficacy and highly reactogenic. An improved pertussis component, an acellular (sub-unit) vaccine, is in advanced stage of clinical trials. The BCG vaccine for TB that is currently used worldwide is also of doubtful efficacy.

[44]Ghosh, "Biotechnology in India Current Status and Future Challenges", *Invention Intelligence,* July-Aug 1999, pp. 149-160.

[45] For example, Hoechst India and Cadila have focused on development and import of oral and injectable vaccine against typhoid. Hoechst (India) is also producing a rabies vaccine. Cadila has a genetically engineered vaccine against hepatitis B. Another division of the Cadila group, Alidac, is importing and marketing an anti-rabies vaccine. Glaxo, Biological Evans Ltd., and Serum Institute of

4.4.a.ii. Diagnostics

The present turnover of the diagnostics industry in India is estimated to vary between $ 150 million and $ 420 million. Although most of the immuno-diagnostic kits are imported, a number of diagnostic kits have been developed and transferred to the industry through the DBT's R and D initiatives. There are more than 11,500 hospitals and also more than 14,000 pathological laboratories in the country which are indicators of large infrastructure already available to support the local consumption of large volumes of diagnostics. A sizable portion of Indian population, estimated to be about 180 million, utilizes 50% of the locally produced diagnostic products through various national health programmes.[46] Some of the major diagnostics consumed in India are mentioned in Table 11.

Table 11: Consumption of Major Diagnostics in India

Diagnostic Test	Estimated Consumption (Ml. Tests)		
	1997	2000	2005
Early Pregnancy	12	23	37
Quilation	2	4	8
T3, T4, TSH	5	14	42
HIV Infection	9	17	27
HBY Infection	20	33	53
HCV Infection	3	8	12
Rheumatoid disorder	0.4	0.5	1
Cancer	0.5	1	2
Kidney function tests	34	52	104
Liver Function tests	35	58	116

Source: Ghosh, "Market Size and Future Demand for Biotech products", available at http://www.ciionline.org/busserv/biotechnology_market.html.

The consumption of diagnostic products in private hospitals is also substantial. DBT is promoting local development of technologies with extensive R and D support and facilitating transfer of technologies to the industry. DBT has

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India account for a large share of Indian DTP production. Firms such as Panacea Biotech and Shantha Biotech have taken up R and D work on Hepatitis B and oral polio vaccine. Also see Appendix 3.

[46] *Annual Report 2001-02, Ministry of Health and Family Welfare, GOI*, New Delhi, at http://www.MOHFW.NIC.in. Also see Appendix 4 for major companies active in the field.

developed diagnostic kits for Hepatitis A and C, cortisol, progesterone, dengue, leishmaniasis and filariasis.

4.4.a.iii. Therapeutic Recombinant Proteins

Therapeutic proteins that are developed through recombinant DNA technology are called recombinant therapeutic proteins. Currently, about twenty-five recombinant therapeutic proteins have been marketed globally and ten are approved for marketing in India. These include insulin, alpha interferon, hepatitis B surface antigen based vaccine, GM-CSF, G-CSF, blood clotting factor VIII, erythropoietin, streptokinase, human growth hormone, tissue plasminogen activators and follicle stimulating factor.[47] Only Hepatitis B surface antigen based vaccine is produced in the country and all others are imported.

Efforts to develop expertise and R and D base in the area of therapeutic proteins are ongoing and certain institutes have developed expression hosts and modified cell lines that could express biologically active therapeutic proteins (e.g. insulin, gonadotropin, interferon, interleukins). However, the expression levels are found to be low.[48] The market size for consumption of some of these recombinant proteins in India is as follows:

Table 12: Consumption of Therapeutic Recombinant Proteins

Name	Consumption		
	1997	**2000**	**2005**
Human Insulin (Kgs.)	95	110	270
Erythropoietin (gms.)	1500	2000	4000
Interferon (million doses)	0.2	0.5	2
Streptokinase (million doses)	0.5	1.5	3

Source: Ghosh, "|Market Size and Future Demand for Biotech products", at http://www.ciionline.org/busserv/biotechnology_market.html.

[47] Ghosh, 1999. The world growth rate of recombinant proteins is estimated at more than 25% per year.

[48] See n. 43 above.

Problems for Biogenerics

Food and Drug Association (FDA) of the US classifies most of the proteins-based biogenerics as biologicals and requires clinical trials in order to approve them for commercial use. This has resulted in higher pricing of the product.[49] There are some inherited scientific differences between chemical generics and biogenerics. That is why many regulatory authorities all over the world are taking initiatives for streamlining separate legal processes for biogenerics. Another problem is that the raw material for manufacturing biogenerics is not easily available. The shelf life and storage conditions are comparatively distinct and perhaps costly for biogenerics. For example, if a generic antibody differs slightly from its innovator counterpart, it could behave differently in patients. So, acceptance of biogenerics might be risky from the patients' point of view.[50]

Table 13: Description of some Biogenerics patents' expiry in near Future

Brand	Description	Marketer	Patent expiry
Humulin	Insulin	Eli- Lilly	2001
Inton	Interferon A	Schering Plough	2002
Avonex	Interferon 1a	Biogen	2003
Humatrope	Human Growth Factor	Eli- Lilly	2003
Epogen	Epoetin- a	Amgen	2004
Recormon	Epoetin- B	Roche	2005
Activase	Alteplase	Genentech	2005
Neupogen	Filgrastim	Amgen	2007

Source: A.N. Nagappa, P. A. Thakurdesai and P. L. Kole, "Biogenerics: Novel opportunities", at http://www.pharmaexpress.com

[49] Biologicals are products that are derived from any living cell to be used for therapeutic, diagnostic or some other purpose of human welfare. To produce the protein identical to a branded drug and to comply with current regulatory requirements, the manufacturer must conform to the same protein expression and purification protocols as an innovator. The biogeneric drugs are generic versions of already tested biologicals. The manufacturers insist that this procedure of assigning biogenerics the status of biologicals bring more cost to the final product. However it is important to note that only slightest difference the branded biological and its biogeneric version may bring altogether different results in patients.

[50] A.N. Nagappa, P. A. Thakurdesai and P. L. Kole, "Biogenerics: Novel Opportunities", at http://www.pharmaexpress.com.

4.4.b. Clinical Trials

The number of biotechnology drugs approved by the FDA till date is only 95. However, a recent Mckinsey report suggests that there are 371 biotechnology medicines in development by 144 companies for nearly 200 diseases. It shows the importance of clinical trials. Clinical trials are conducted in four phases. Each phase has a different purpose and helps scientists answer different questions.

Phase I trials: test a new drug or treatment in a small group of healthy people (20-80) for the first time to evaluate its safety, dosage range and possible side effects

Phase II trials: study the drug or treatment given to a selected group of patients (100-300) to confirm effectiveness and evaluate safety.

Phase III trials: study the drug or treatment given to a large group of patients (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to conventional treatment and collect information.

Phase IV trials: post-marketing studies done to get additional information including drug's risks, benefits and optimal use.

Globally, every year over 80,000 clinical trials are conducted and $ 9 billion are spent on clinical research studies. Currently, India is having 0.7% share of global clinical research market.[51]

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[51] V. Srinivasan, "Clinical Research–Path and Pitfalls" and Rajiv Gulati "Clinical Research in India: from Intent to Consent", Biotech India 2003, 5-8 Feb 2000, New Delhi, at http://www.biotech-india.com/exhibition_cov.htm.
Also visit http://www.expresspharmapulse.com and Business World Oct. 2002.

Table14: Disease States under study The pipeline of human therapeutic products under development					
Category	Phase I	Phase II	Phase III	NDA	Total
AIDS/ HIV	10	15	4	1	30
Autoimmune Disorder	9	8	2	0	19
Blood Disorder	3	3	3	0	9
Cancer	97	39	20	7	163
Diabetes	3	5	4	1	13
Digestive Disorders	1	6	1	1	9
Eye Condition	1	0	2	0	3
Genetic Disorder	8	1	1	0	10
Growth Disorder	1	1	2	0	4
Heart Diseases	13	11	4	3	31
Infectious Diseases	11	15	10	5	41
Infertility	1	1	2	0	4
Neurological Disorder	12	9	4	2	21
Respiratory Disease	6	9	4	2	21
Skin Disorder	5	7	2	9	14
Transplantation	9	6	0	1	16
Other	5	14	5	0	24
Total	195	150	70	23	438

Source: PhRMA (Pharmaceutical Research and Manufacturer of America) Report 2001.

Clinical trials provide access to the latest data and advances in medicine and could be a mechanism for knowledge transfer. India has positive as well as negative aspects related to conducting clinical research services.[52]

4.4.c. Contract Research

Research done by an external source, other than the company, for a company or institution is defined as contract research. The need for contract research in medical biotechnology arises primarily in the case of transnational (bio)pharmaceutical companies, where the cost of R and D affects future production of products. R and D costs are higher overseas. Also, a number of approvals given by the FDA suggest that the rules for drug approval are stringent in the United

[52] See Appendix12.

States, and approximately 30% of patented drugs cannot even recover their R and D cost during their patent lifetime. All these contribute to higher cost of discovering new drug molecules.[53] In India the R and D cost is lower (i.e. $ 250 million as compared to $ 500 million in the Western countries) and world-class scientific skills are available at lower wages. Hence India is seen as a good alternative for TNCs for contract research and manufacturing services.[54] India has several advantages for contract research services.

In India the number of companies pursuing contract research is increasing. According to a CII survey, most of the biotechnology companies in the private sector are established after 1998 and out of 52 companies surveyed, 32 were in contract research services.[55]

To summarize, the biotechnology industry in India is mainly a State-supported industry. DBT is the main institution in India for supporting the biotechnology sector. The main thrust of DBT is on R and D as compared to human resource development and transfer of technologies to the industry. The contribution of the private sector is meager. Further, this contribution is in selected product segments. In the medical biotechnology sector, vaccines and diagnostics kits are the main products in India. Many biotechnology companies are pursuing the biotechnology services sector. The services sector includes clinical trials and contract research services. Most of the new biotechnology companies are active in this field. An analysis of the Indian medical biotechnology companies might provide insights into the nature and focus of these companies.

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[53] Goutam Das, "Scope and Opportunities of Contract Research Services in India", at Biotech India, 2003, 5-8 Feb., New Delhi. Visit http://www.biotech-india.com/exhibition_cov.htm.

[54] See Appendix 6.

[55] Visit http://www.ciionline.org/busserv/biotechnology_market.html.

CHAPTER 5

EMPIRICAL STUDY

5.1. Methodology and Selection of Data

The present empirical study focuses on the contribution of the private sector companies active in the field of medical biotechnology in India. The public research institutions active in the same field had been studied in detail earlier and are excluded from the present study.[1] The study is based on primary as well as secondary sources. It includes a description of the major biotechnology companies existing, especially in the Hyderabad bio-cluster. Description and assessment of the basic features of these private companies is based on the secondary survey. A set of biotechnology companies in Delhi is also taken for a case study.

There are two main primary sources from which it is possible to choose a set of medical biotechnology companies in Delhi. The first one is the list of companies in India, complied by the Department of Scientific and Industrial Research (DSIR). The second is the Directory of Biotechnology Companies in India (2000-01), published by the Biotechnology Consortium India Ltd. (BCIL). The first list includes companies from various sectors, including biotechnology, whereas the second enlists only the biotechnology companies in India. The BCIL Directory has been chosen as a source to select a set of the medical biotechnology companies situated in Delhi.[2]

The survey of these selected biotechnology companies is based on company-to-company personal visits and contacts with their biotechnology experts and officials. Although the actual number of medical biotechnology companies in the BCIL Directory was found to be 14, only 8 companies (57% of the sample) could be located by their official addresses. The problem arose during the study was that all the official addresses and contact numbers of these biotechnology companies given in the directory were not updated. An enquiry about the companies, which are not found by

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[1] M Phil. Dissertation by Deepak Sardana (2002), from the Centre for Studies in Science Policies, School of Social Sciences, under the title "Triple-Helix: University, Industry and Government Partnerships: A Case Study of Biotechnology Sector in Delhi Region".

[2] In fact a senior official from the DSIR suggested taking the BCIL Directory as a source for listing biotechnology companies in Delhi.

their official addresses, was done through personal contact with the locals and whenever possible from the local security system. Besides, help was also taken from the telephone exchange, for the updated addresses and contact numbers of these companies. The companies, which were accessible, showed a positive response and information about 43% of the survey sample was obtained with their cooperation. The survey is based on informal interaction with the biotechnology experts and officials of these companies.

There was difficulty in having access to the true nature of the biotechnology companies active in Delhi. Many of the companies, which had been visited, tell that they are planning to enter into the field of medical biotechnology, but not actually active currently. This was mainly due to poor quality of the data available and discrepancies prevalent among the existing data from various sources.[3] It was also not possible to assess the qualification standards set for the recruitment of technical personnel in these companies. Most of the companies in the sample hire doctoral and post-doctoral students from universities on a project basis, but none of the companies in the survey sample has agreed to have any permanent contract with universities or academic institutions for the placement of students. In turn, it was not possible to assess whether the skills required in the industry are met through the current courses provided by the academic institutes and human skills developed thereby.[4]

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[3] According to the Biotechnology Industry Guide released by the DBT speaks (without giving the details) of 459 units active in biotechnology. According to CII there are 160 biotechnology companies, whereas BCIL Directory enlists 176 biotechnology companies active in India. These discrepancies in the information are indicative of a lack of coordination among the high level agencies. However, Ramani and Visalakshi, 2001 acknowledge this phenomenon quite similar among European countries. Two companies namely, Kee Pharma Ltd. (a biopharmaceutical company) and ACE Diagnostics (a diagnostics company) were found to be operational in Delhi, at a later stage of the study, from other sources. But these were not included in the BCIL Directory. So it was not possible to access these companies before the completion of the study and could not be included in the survey.

[4] Samir Brahamchari , Director of the Centre for Biochemical Technology (CBT), points out that the education curriculum for biotechnology in the country does not reflect the requirements of the industry. *Front line*,Vol.17,Issue 18, Sep.2-15, 2000. However the Research Pofile of Biotechnology Activities, published by DBT, about 60% of the human resources developed in India are consumed in research activities and 14% goes to the industry whereas the remaining go abroad. Personal interaction with Dr. Visalakshi confirmed this view. She based on her recent unpublished study told that the industry do not find enough appropriate human resources and skills in the country.

5.2. Development of Bio-Clusters in India

Networking among various actors of the biotechnology sector is said to be conducive for the growth of the biotechnology industry (Ramani 1998, 1999, 2001; Ramani and Venkataramani 1999). The development of the biotechnology industry in India is seen as a result of the developing biotechnology clusters (Bowonder 2001). In order to harness biotechnology to the maximum possible extent and develop an environment for the growth of the biotechnology industry, various states in India have taken initiatives to develop bio-clusters. These states are trying to develop and promote capabilities in the biotechnology manufacturing and services sector through various programmes, policy initiatives and tax incentives.

These bio-clusters are based on intrinsic academic and entrepreneurial relationships. Key features of these bio-clusters are the availability of biotechnology parks, centers of biotechnology research, fiscal incentives and policy initiatives. The Department of Biotechnology under the Government of India has proposed a programme for setting up biotechnology parks in various states, for which grants would be given according to the nature of the business plan. Presently there are five bio-clusters in India: Banglore Bio-Cluster; Tamil Nadu Bio-Cluster; Pune Bio-Cluster; Himachal Pradesh Bio-Cluster; and Hyderabad Bio-Cluster. These are discussed here.

5.2.i. The Banglore Bio-Cluster

Banglore is the country's largest bio-cluster, where the government of Karnataka has set up a vision group on biotechnology as a public-private partnership, to evolve a pragmatic biotechnology policy for the state.[5] The vision group has set up the Institute for Bioinformatics and Applied Biotechnology (IBAB) to develop trained bioinformatics personnel for the industry. In addition, a biotechnology park has been planned to house start-ups, an incubator facility (a common facility for shared instrumentation), and a patent cell. The state government has already invested $ 2

[5] Kiran Mazumdar Shaw, Biotech India 2003, 5-8 Feb., New Delhi. Available at http://www.biotech-india.com/exhibition_cov.htm

million in various biotechnology programmes. The Karnataka State Industrial Investment and Development Corporation (KSIIDC) is a state-sponsored biotechnology venture capital fund. Another initiative is 'Banglore-Bio', an annual event to show case the state's biotechnology initiatives and progress.

The Banglore bio-cluster owes its success to the presence of a large number of research institutions there, viz. Indian Institute of Science (IISc), National Centre for Biological Sciences, Jawaharlal Nehru Centre in Advanced Scientific Research and University of Agriculture Sciences (UAS); and an array of biotechnology entrepreneurial companies.[6] The bio-cluster activity in Bangalore spans enzymes (Biocon), biotherapeutics (Biocon, Gangaen), bioinformatics (Strand Genomics, Keshma, Bigtec, CDC Linux, Molecular Connections), plant genetics and genomics (Avesthagen, Monsanto, Metahelix, Advanta), contract R and D (Syngene, Aurigene, Genotypic Technology, Avesthagene, Banglore Genei) and bioprocess and bioinstrumentation (Sartorious, WIPRO-GE, Photonics and Biomolecules, Banglore Genei, Millipore).

5.2.ii. The Tamil Nadu Bio-Cluster

The government of Tamil Nadu has announced a plan to develop 'Biotechnology Enterprise Zones' or 'Bio-Valleys' to exploit the state's biological resources. Four biotechnology parks and a bioinformatics and genome centre will be established under this plan. The present bio-cluster encompasses two premier biotechnology research centers at Anna University and Madurai Kamraj University in Tamil Nadu. The Southern Petrochemicals Industries Corporation (SPIC) Biotech is the largest corporate entity in the state.

The Tamil Nadu Industrial Development Corporation (TIDCO) has entered into a technical service agreement with Cornell University, USA, for setting up a biotechnology park in Chennai, christened Tidco Centre for Life Sciences (TICEL). The park proposes to attract fresh investment from new companies to be set up in the park and encourage bio-entrepreneurship. Tamil Nadu is the only state with such kind

[6] Ibid, Presently 70 companies, which account for 40% of the national total.

of collaboration. This initiative might bring global network of Cornell to Chennai, which has technical collaboration in 36 countries.[7]

5.2.iii. The Pune Bio-Cluster

The government of Maharashtra has announced the establishment of a biotechnology park in Pune, to house a pilot plant facility for start-up companies, on lease. The state government has also announced seed capital for biotechnology companies.

The presence of the National Chemical Laboratory (NCL) and the University of Poona, having one of the best bioinformatics programmes in the country, gives Pune a natural advantage in establishing a bio-cluster.[8] Besides that a number of companies are active there in the biotechnology field. Prominent among them are Alfa Laval, Praj Industries (bioprocess), Serum Institute (vaccines), Mahyco, Syngenta (genetically modified crops), Wockhardt (biotherapeutics) and Advanced Biochemicals (enzymes). The presence of a large pharmaceutical sector in the state of Maharashtra is expected to generate interest in biotherapeutics, diagnostics and vetinary products.

5.2.iv. The Himachal Pradesh Bio-Cluster

Himachal Pradesh is the only northern Indian state that has prepared a blueprint for promotion of biotechnology industries in the state. This includes setting up a biotechnology park at Solan, conservation and exploitation of its bioresources, intensification of R and D, and promoting biotechnology entrepreneurship through tax concessions and other incentives in the state.[9] It is also proposed to provide research- based support to private companies in the form of access to database of bio-resources, along with endangered medicinal plants. Apart from this a germ plasm

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[7] *Pharmabiz.com*, 28th August, 2001

[8] Sachin Chaturvedi, "Status and Development of Biotechnology In India: An Analytical Overview"; at http://www.ris.org.in

[9] *The Economic Times*, April 6, 2001.
State's rare herbal medicines, are supposed to enhance country's share in the global market

collection, culture facilities and bioinformatics networking are also being established in Himachal Pradesh.

5.2.v. The Hyderabad Bio-Cluster

The state of Andhra Pradesh had launched a Biotechnology Policy of its own in the year 2001. The aim of the policy is to leverage the existing strengths of the state in pharmaceuticals, agriculture and information technology for rapid commercialization of biotechnology. The policy speaks of funding the biotechnology start-up companies in the state through the Andhra Pradesh Industrial Development Corporation (APIDC). APIDC has allocated Rs. 500 million exclusively for the biotechnology sector.[10]

As a part of its biotechnology policy, the government of Andhra Pradesh has taken certain steps to encourage bio-entrepreneurship in the state. For example, biotechnology companies would enjoy a sales tax of just one percent on sales of all biotechnology products produced within the state, whereas the sales tax on biotechnology products produced outside the state is 8-16%. The government had also announced the establishment of 'Genome Valley', which will focus on genomics-based R and D. Private biotechnology companies with manufacturing plants in the state would be able to book space at the Genome Valley at concessional rates. The state government is also trying to use the strengths of the information and software technology industry for the growth of bioinformatics. Satyam Infosys (a private company) has announced collaboration with the Centre for Cellular and Molecular Biology (CCMB) in bioinformatics.

The government of Andhra Pradesh, in collaboration with the Industrial Credit and Investment Corporation of India (ICICI), has also set up a knowledge park at Turkapally near Hyderabad.[11] The park has been licensed under Section 25 of the

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[10] *The Economic Times*, 9th May 2001.
It is 18% share of the total amount available at the national level, while Karnataka State Industrial Infrastructure Development Corporation's (KSIIDC) share is 7%.

[11] Rs. 310 million have been invested in the knowledge park, developed on a 200-acre site. It is a joint initiative of the ICICI and Andhra Pradesh Government. ICICI has signed a memorandum of understanding (MoU) with the Indian Institute of Chemical Technology (IICT), Centre for Cellular and Molecular biology (CCMB) and the University of Hyderabad for new 'knowledge network initiative'.

Companies Act, 1956, and is approved by the Department of Scientific and Industrial Research, Government of India, for the benefit of customs duty exemption and excise duty waiver. Under the initiative, partners in the knowledge park will get on-line access to library-based information, expertise from the national labs and university system. This would also encourage undertaking collaborative research between corporate and research companies based in the park. The park has identified 20 premier research organizations and universities during the first phase of the programme. During the first phase the park will focus on therapeutics, diagnostics and industrial biotechnology.

Hyderabad has emerged as an important bio-cluster with the Centre for Cellular and Molecular Biology (CCMB), International Crop Research Institutes for Semi-Arid Tropics (ICRISAT) and Osmania University forming the academic backbone. Companies such as Shantha Biotechnics, Bharat Biotech, Biological Evans and Dr. Reddy's Labs form the industrial cluster. For the rapid growth of this sector, the government of Andhra Pradesh has identified diagnostics, therapeutics, pharmacogenomics, bioinformatics, marine and industrial biotechnology and contract research as some of the thrust areas.[12]

The focus of this bio-cluster is largely on vaccines and bio-therapeutics, which might be attributed to the presence of a large pharmaceutical industry in Hyderabad.

5.3. Medical Biotechnology Companies

The medical biotechnology companies in India can be divided into three broad categories:

1) The large pharmaceutical companies or diversified biopharmaceutical companies that have incorporated biotechnology in their work plan (e.g. Dr. Reddy's Laboratory, Ranbaxy Laboratories, Wockhardt Limited).

The Department of Scientific and Industrial Research (DSIR) have assisted this project to set up a virtual information network.

[12] Contract research is generally a piece of research performed by an external source or agency, not related to the parent company; for the parent company. In order to minimize the cost and time spent in research work large transnational companies generally give contracts to high quality specialized firms in other developing countries to perform a piece or full research for them.

2) The small start-up companies or dedicated research companies that have indigenously developed biotechnology products (e.g. Shantha Biotech, Bharat Biotech).
3) The group of start-up companies that are emerging as either contract research organizations (CROs) or agencies for transnational companies (e.g. Aurigene, Banglore Genei, Syngene)

The present study focuses on some of the leading examples of the above categories from the Hyderabad bio-cluster.

Dr. Reddy's Laboratory (DRL)

DRL is from the first category of companies. DRL is a big pharmaceutical company, established in 1984. DRL started as a formulations manufacturing unit in 1985 and received FDA approval in 1987. In the late 1980s, DRL took up production of quinolone antibiotics, launched Norfloxacin (its first quinolone drug) in 1988, Ciprofloxacin in 1989 and Pefloxacin in 1991. DRL is also trying to strengthen its position in the domestic formulations market, including the over the counter products (OTC) segment. The company has identified biogenerics as a significant market area in 1997. Now DRL is setting up biotechnology production facilities as per the US Food and Drug Association (FDA) specifications. The company took over the American Remedies, a manufacturing company in 2000. In 2001 DRL launched generic fluoxetine in the US. DRL has also formulated new chemical entities (NCEs) with two licensed to Novo Nordisk and one to Novartis. After the merger with its sister company Cheminor Drugs, DRL also gained entry into the US generics market. In August 2001 it was the first company to launch generic version of Fluoxetine 40 mg dosage form and enjoyed six-month exclusivity to market the same. The biotechnology facilities planned by DRL include setting up three bulk recombinant protein production suites and new formulations facility.

Thus the biotechnology activities of the company include therapeutics, vaccines and diagnostics. DRL has a research alliance with the Center for Cellular and Molecular Biology (CCMB), Hyderabad. DRL has also established a research

subsidiary in Atlanta called 'Reddy US Therapeutics Inc.', as well as a contract research subsidiary that will focus on genomics.

Shantha Biotechnics Private Limited

This Hyderabad-based company is one of the leading examples of the second category of companies, i.e. small start-ups with their own biotechnology products. Shantha Biotechnics Pvt. Ltd. was established in 1993 as a dedicated biotechnology company and the current R and D expenditure of the company is Rs. 770 lakhs.[13] The company has an active biotechnology programme since 1994. Shantha Biotechnics Pvt. Ltd. has the credit of developing India's first world-class Hepatitis-B vaccine and making it available at one-third of the prevailing market price of the imported vaccine. Now Pfizer Ltd., a TNC, has obtained the rights from Shantha Biotechnics for exclusively marketing the products to be developed by the latter in future. Earlier, Pfizer entered into a co-marketing with Shantha Biotech for marketing the latter's recombinant DNA vaccine for Hepatitis–B. Shantha Biotech has pioneered another recombinant product, interferon alpha 2b, launched under the brand name Shanferon and is also developing several therapeutic human monoclonal antibodies along with its US subsidiary, Shantha West Inc. in San Diego, USA. Shantha Biotech is currently in discussion for collaboration with one European and three US-based pharmaceutical companies for its research projects.[14]

The company plans to research on protein purification, molecular cloning and expression of native and synthetic genes. Shantha Biotech is working on polyclonal and monoclonal antibody development and formulation for certain types of vaccines. It has developed in-house expertise in recombinant DNA technology and has also developed cell lines for development of recombinant products. The company sources said to have invested Rs. 100 million in biotechnology facility with external funding from the Bank of Oman.[15]

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[13] http://dsir.nic.in/a_report/english/2002-03E/annexure.pdf
[14] Bowonder, 2001

[15] Sachin Chaturvedi, "Status and Development of Biotechnology In India: An Analytical Overview"; http://www.ris.org.in

Bharat Biotech International Limited

Bharat Biotech International Pvt. Ltd. is a venture capital company established in 1996 in Hyderabad, which has developed Hepatitis B vaccine through R and D alliance with the Indian Institute of Science. According to the available sources, the total investment of the Bharat Biotech in 1998-99 was Rs.1500 lakhs and the turn over for the same year was Rs. 2300 lakhs. However the present (2002-03) expenditure of the company on R and D is Rs. 515 lakhs.[16] The company has developed streptokinase, for which a US patent has been granted. Bharat Biotech has developed the technology by high expression of the streptokinase gene in E. *coli* is made possible, using its in-house R and D facility.

The company's research model involves joint research with other R and D organizations in the drug discovery phase. Currently it has collaborations with Centre for Biochemical Technology, Council of Scientific and Industrial Research, Department of Science and Technology, and Technology Development Board. The Gates Foundation has sponsored a research project to develop a vaccine for malaria.

The major products of the company are Hepatitis B Vaccine, streptokinase and human insulin.

Biological Evans Limited

Biological Evans Limited is one of the pioneering companies to introduce anti TB drugs in India. The company was established in1953 as a healthcare company and currently active in the field of vaccines, anticoagulants, anti-TB drugs and formulations. This company is working in the field of vaccines, genomics anticoagulants, bulk drugs and formulations. Total investment of the company in 1989-99 was Rs. 4323.30 lakhs and turnover for the same year was Rs. 12885.29 lakhs. The company's current (2002-03) expenditure on R and D is Rs.140 lakhs. Biological Evans' R and D centre has been approved by the Department of Science and Technology. The research activities of the company include organic synthesis, micro array techniques, formulation research and Ayurvedic research. Its partner

[16]http://dsir.nic.in/a_report/english/2002-03E/annexure.pdf

research organizations are the CCMB and the M. S. University of Baroda. Besides, Bharat Biotech, Haber (Aventis), Paterur Merieux Connaught (France) and Biotech (Cuba) are also having collaborations with the company.

GVK Biosciences Private Limited

GVK Biosciences Pvt. Ltd. is a Contract Research Organization (CRO), which offers services in the areas of informatics, medicinal chemistry, process R and D, preclinical and clinical trials. GVK Biosciences is a part of the GVK, a $ 500 million Hyderabad-based enterprise with business interests in power, hospitality, finance, petrochemicals, infrastructure and construction. GVK Biosciences has entered into a three-year partnership with the US-based, $ 50-million drug discovery company Ricerca, a belonging to the SG (Societe Generale) bank. GVK Biosciences would undertake medicinal chemistry and discovery services for Ricerca's clients and also take up jointly owned proprietary discovery programmes. For its drug discovery and development activities, GVK Bio is planning to focus mainly on two segments: anti infectives and oncology.

GVK Biosciences, with manpower of 60, is setting up a new facility at the ICICI Knowledge Park with 30 scientists and an initial investment of Rs. 5 crores to work in the field of medicinal chemistry and drug discovery. The company's activity also includes biotechnology process development and bioinformatics, for which it has come in collaboration with the Molecular Simulations Incorporation and Silicon Graphics.

5.4. Evolution of Bio-Clusters

The developments associated with the biotechnology industry are many and varied, and clustering is one of them.[17] Development of Hyderabad into a bio-cluster represents a microcosm of developments associated with cluster formation. The presence of developing pharmaceutical, information and engineering industries, along with a strong network of local academic institutions, facilitates interaction and

[17] B. Bowonder, 'Globalization of R and D: The Indian Experience and Implications for Developing Countries', *Interdisciplinary Science Reviews*, Vol. 26, No. 3, 2001.

convergence of skills. The networking of biotechnology firms with local research institutes like the CCMB helped Hyderabad to become a biotechnology centre through knowledge creating and augmenting activities. The availability of skilled manpower and research facilities within the state have attracted transnational companies to Hyderabad both as producers and consumers. These foreign companies bring financial aid and utilize local human resources and infrastructure. The subsidiaries of these foreign companies through their manufacturing plants help in developing engineering and managerial skills. It is a combination of low wages by international standards and the professional skills of local Indians which has attracted the foreign firms. Besides that, the incentives and initiatives given by the government of Andhra Pradesh encourage investment in the biotechnology industry. The technology parks set up facilitate intra-firm and firm-research institution interaction, which in turn leads to division of labour (or specialization of human skills) in the biotechnology industry. In sum, the evolution of Hyderabad as a bio-cluster has shown following characteristics responsible for its growth:

1) Presence of excellent academic institutions
2) State support
3) Availability of capital
4) Generation of forward and backward linkages.

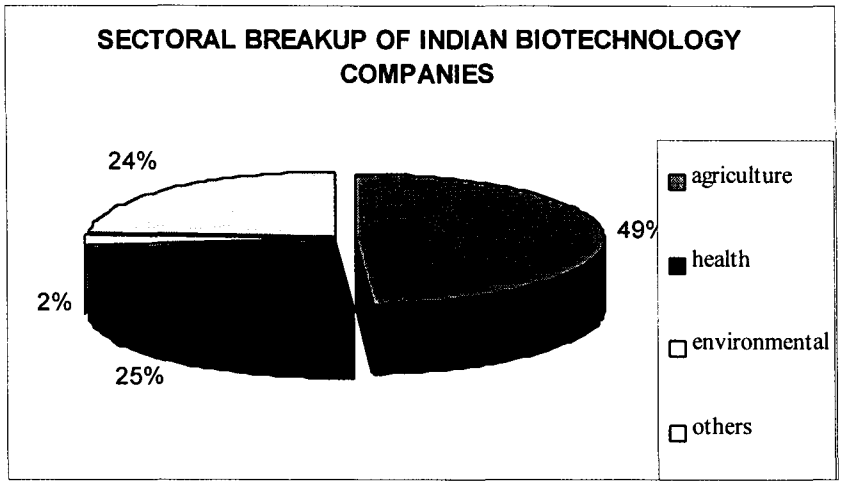
The bio-clusters in India are still in the developing phase and are providing support to the local biotechnology industry through various incentives. However, one thing in common with all those bio-clusters is that they are providing incentives to encourage private sector participation in the field of biotechnology and promoting collaboration between R and D institutes and industry through technology parks. The state governments are trying to provide a base for the development and rapid commercialization of indigenous products and processes.

5.5. CASE STUDY OF DELHI

According to the Directory for Biotechnology Companies in India (2000-01), there are 176 biotechnology companies in India. Out of which 85 (i.e. 49% of the

total) are agriculture-based companies. Around 44 companies (i.e. 25% of the total) are active in health-related medical biotechnology activities, only 4 (i.e. 2% of the total) of the companies are involved in the environmental biotechnology and the rest of the 24% of companies have varied interests, including instrumentation and consultancy services.

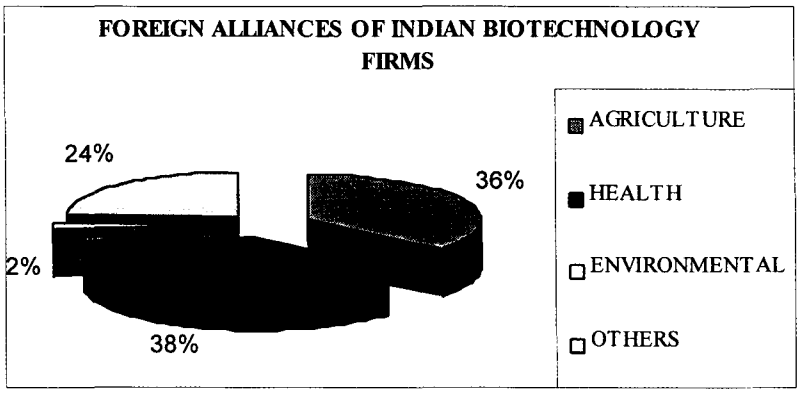
Fig.1.



Source: RIS, based on BCIL Directory, 2000-01, http://www.ris.org.in

The number of medical biotechnology companies is lesser than those active in the agriculture sector but they account for a much higher proportion of foreign alliances.

Fig.2.



Source: RIS, based on BCIL Directory, 2000-01, http://www.ris.org.in

The growing external orientation of the Indian medical biotechnology companies suggests a change in the business profiles of these companies. Actually a large number of generic pharmaceutical companies are diversifying into molecular research and stem cell research.[18] According to the information available in the BCIL Directory, from a total of 44 medical biotechnology companies in India, 38 are involved in manufacturing; two are dedicated to research and development only (Dr. Reddy's Laboratories and Zandu Foundation for Healthcare): and the remaining do only marketing of biotechnology products.

According to the Directory of Biotechnology Companies in India (2000-01), Delhi has a set of 25 biotechnology companies in total. Out of which, 14 companies are active in the field of medical biotechnology.[19] Out of these 14, only eight (approximately 57 %) are found to be actually existing; others (approximately 43%) are either dead or do not exist any more in Delhi.[20] The survey is based on informal interaction with the officials of these companies.[21] From the eight existing companies, six were interviewed (approximately 43%) and the other two could not be interviewed (approximately 14%) due to unavailability of the officials.[22]

The result of the survey shows that in Delhi, only three companies are active in the field of medical biotechnology R and D, and those are: Ranbaxy Laboratories Limited, Panacea Biotech Limited. and J. Mitra and Company Limited. The remaining Delhi-based biotechnology companies are basically involved in marketing of the biotechnology products.

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[18] Sachin Chaturvedi, http://www.ris.org.

[19] The profile of these companies as given in the directory, relates them with the medical biotechnology field.

[20] This information is based on the survey conducted in the month of March 2003.

[21] Majority of officials were company's biotechnology experts but in a couple of cases the human resource development executive were consulted due to unavailability of the biotechnology expert.

[22] These were Ranbaxy laboratories and Kothari Fermentation and Biochem Ltd. Ranbaxy has its R and D branch in Gurgaon near Delhi, but the public relations officer there told that all the required information about the company's biotechnology activities and products is available on the net, hence denied meeting with any of their official. Description of this company is based on secondary sources. Whereas, Kothari Fermentation and Biochem Ltd. could not be contacted due to inaccessible telephone contact and unavailability of any personnel from the company. However, the description of the company's activities available on the net suggests that the company is dealing in the field of yeast culture, but no information was available about the strength of the R and D personnel of the company.

Ranbaxy Laboratories

This is one of the oldest post-independence pharmaceutical firms which was founded in 1968. Today Ranbaxy is the largest pharmaceutical company in India and the 11th largest Generic Company Worldwide.[23] The company is creating new formulations of existing drugs, and half a dozen molecules are under development. To develop new formulations and technologies, Ranbaxy has collaborated with several European and US companies. For example, Ranbaxy and Vectura Ltd. (Bath, UK) announced in 2001 that the Indian company's subsidiary (The Netherlands, Antilles) will develop oral formulations using Vectura's controlled release drug delivery technology, with Ranbaxy providing clinical development, scale up, manufacturing and marketing expertise.

Ranbaxy has set a model in India in terms of drug development. The model suggests that a domestic company can afford development of a molecule up to the first phase of the clinical trial and then outsource it to a leading transnational company for further development and later on explore the possibilities for marketing tie-ups.[24] For example, Ranbaxy has made co-marketing arrangements with Glaxo-Wellcome for marketing Ceiphalexin in India. Ranbaxy has its manufacturing plants in six countries and is marketing its products in 22 countries. The core strength of the company is in the field of therapeutics and anti-infectives.

Table 1. New Molecules developed by Ranbaxy

New entity	Application
RBX 2258 (1999)	Benign prostitis
RBX 4638(2000)	Respiratory disorders
RBX 6198	Urology
RBX 7635	Antifungal agents
RBX 7644(2002)	Antibacterial agents

Source: Various News Clippings, Bowonder, 2001 and http://www.ranbaxy.com

[23] Visit http://www.ranbaxy.com/profile.htm. With sales of more than $500 million in the year 2000.
[24] *The Economic Times*, September 3, 2001.

Panacea Biotech Limited

This is also a pharmaceutical company engaged in the biotechnology research. Panacea was established in 1927 as a marketing agency for drugs and pharmaceuticals. Earlier it was known as Panacea Drugs Private Limited. Presently Panacea is ranked 43rd among the Indian pharmaceutical companies. The Ministry of Science and Technology, Government of India, has recognized the company for the quality of its manufacturing practices. The company is active in the field of development of new drug molecules, biologicals, drug delivery systems and conventional and novel formulations. From 1993 onwards, the company had started focusing on biotechnology-based products. Panacea has been awarded the GMP (Good Manufacturing Practices) certificate by WHO. The total investment of the company during 1998-99 was Rs. 14067 lakhs. The current (2002-03) expenditure of the company on R and D activities is Rs. 1259 lakhs.

The company deals mainly in pain management, diabetes and therapeutic vaccines category. It is having a WHO certified oral polio vaccine plant in New Delhi, which supplies to UNICEF. The company has a joint venture with Heber Biotech S. A. and Centre for Genetic Engineering and Biotechnology, Cuba, for development of recombinant Hepatitis B vaccine; and with Chivon of Italy for development of oral polio vaccine. The company has patents for 10 molecules in India and abroad.

J. Mitra and Company

J. Mitra was established in the year 1969, as a marketing agency for drugs and pharmaceuticals. This is basically a diagnostics company involved in the production and marketing of medical diagnostic kits in India for diseases such as AIDS, Hepatitis B, C and blood sera. It is the first company in India to get Drug Manufacturing License for Hepatitis C Rapid and Elisa Tests. It is also the first company in India for introducing HIV TRI-DOT that has separate dots for HIV-1 and HIV-2 and has been recognized by the Department of Biotechnology, Government of India, for this (i.e. western

blot for HIV-1 and 2). J. Mitra is also collaborating with the Programme for Appropriate Technology in Health (PATH), USA for diagnostic test for detection of Hepatitis B. The company has been awarded a certificate for good manufacturing practices (GMP) by WHO.

The total investment of J. Mitra during 1998-99 was Rs. 235 lakhs and the turnover for the same period was Rs. 3,444 lakhs. The current (2002-03) R and D expenditure of the company is Rs. 122 lakhs.

5.6 Summation

The analysis of these companies confirms the previous assumption of the study that medical biotechnology in India is related with the pharmaceutical industry. Most of the companies in the study are pharmaceutical companies which were earlier related to only drugs and pharmaceuticals. Later these companies diversified into the field of biotechnology products and processes. After analyzing the profiles of these companies, it becomes clear that these companies had started integrating biotechnology within their business, only in the 1990s. The R and D expenditures of these companies have increased as they tried to integrate biotechnology in their existing business activity (Visalakshi 1995; Ramani et al. 1999). However the R and D expenditure of the India companies is very small as compared to what transnational companies spend on research and development.

Besides, most of the companies are active in the field of independent development of already existing biotechnology products, rather in creation of new products. Marketing of foreign biotechnology products, providing services in the clinical trials and contract research services are also prevalent among the Indian biotechnology companies. This in turn infers that lack of financial resources, required skills and raw materials induce companies to acquire agency behaviour (i.e. marketing of foreign products) in order to gain financial and managerial profits. This fact is also supported by most of the officials of the companies, who were interviewed during the course of the present study. So, it is likely that these companies follow a strategy to become financially sound and look forward to take R and D later.

CHAPTER 6

CONCLUSION

Man invents tools and the tools change man, so goes the adage. But the changes are not instantaneous; their inventors see three phases in the process. First, the people use a new technology to accomplish something they have been doing all along, to do it better. Second, they move on to put the discovery to new uses to accomplish new goals. Finally, a stage arrives when a new technology is put to altogether new applications, different from those initially conceived. So, it is hard to assess the exact and full impact of these new applications and of their perception in society.

New technologies may change the way people and firms conduct business. But the future is difficult to predict due to the inherent uncertainty of a new technology's impact. New technologies take time to develop and might develop in a way and have uses that were not anticipated earlier.[1]

From a technological perspective, biotechnology is not yet a mature science. The nature of discoveries across various scientific fields is changing due to emergence and convergence of various technologies. Thus the technological innovations in the field of biotechnology are a result of the convergence of many interdisciplinary activities.[2]

The development of biotechnology techniques requires extensive research, which costs money. Product and process development costs even more. Commercialization of innovations in a new science-based sector is a collective process that depends on the existence and functioning of networks between a variety of institutions and agents.

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[1] Katherine Campbell, Duane Helleloid, "Perspective: An Exercise to Explore the Future Impact of New Technologies", *Journal of Product Innovation Management*, Vol 19, No. 1, Jan 2002, pp. 69-80.

[2] Parthasarthy A., "Acquisition and Development of Technology: The Indian Experience", *Economic and Political Weekly,* Vol.XXII, No.48, 1987.

Technological innovation may be described as the process by which the knowledge to produce a product, improve the performance of an existing product or reduce its cost or market the product more efficiently is made possible, which otherwise not possibly available in the market. Technological innovation can be visualized as a process that has a number of linked processes.

In developed countries the private sector share in biotechnology R and D is large as compared to developing countries where the main source of the share in biotechnology R and D comes from the State. For example, contribution of the private sector in the US biotechnology industry is more than 80 % of the total R and D expenditure in biotechnology, as compared to 62% in France and 15% in India (Ramani et al. 2001). In the US, public research is funded and promoted by the State and the market is expected to generate new firms and products through innovation. It becomes possible in the US to convert knowledge into technology due to the presence of active networks, which facilitate the commercialization of biotechnology products and processes. The US has a complex web of large firms, new biotechnology firms (NBFs) and public laboratories for the creation of innovations; and the industry seems to support the result of R and D in the research institutions. But there is a substantial gap between the industrial competence of biotechnology in the USA and latecomer countries in Europe. Furthermore, there are differences between the latter and a developing country like India.

In the US most of the companies, including both large and small, are interested in pursuing the creation of radical innovations (i.e. new products). On the other hand in most of the European countries only the large firms are investing in the creation of radical innovations. Compared to this, in India even most of the large firms are pursuing independent development of existing biotechnology products. Besides the availability of financial, human and technological resources is also different among developing countries. This is to say that biotechnology industry in developing countries must be of fundamentally different type from that of developed countries.

Obviously, a developing country like India certainly could not imitate the US model of development of the medical biotechnology industry. Probably there could be three explanations for that. First, the advanced technologies utilized in the medical biotechnology research and developments are interrelated and complex and cannot be developed from scratch. The foreign companies, possessing the matured, straight away workable technologies, are unlikely to transfer those technologies. Besides that, it is not always possible to integrate and adopt a foreign technology completely.

Second, the financial constraints of a developing economy like India are formidable, where the State exists with small funds which are thinly spread among a number of companies and sectors (*The Economist* Dec. 2002, Chaturvedi 2002). Thirdly, there is virtual absence of networking among the various actors in the biotechnology sector.

Economic liberalization and globalization of the industry has led many transnational companies to expand their biotechnology business activities in India either through establishment of wholly owned new subsidiaries (e.g. Monsanto, Pfizer, Unilever, Du-Pont, Bayer) or share holding-based majority or minority ownership (e.g. Glaxo Smithkline, Novratis, Aventis) or joint venture companies (e.g. Eli-Lilly and Ranbaxy, Monsanto and Mahyco, Piramal and Boehringer). But the foreign companies are reluctant to transfer the mature technologies. In fact in an endeavor to search for newer markets these foreign companies offer their product marketing rights to the local entrepreneurs (Parthasarthy 1987, Ghosh 1999). These factors result in the development of consumption markets for biotechnology products in a developing country like India.

The Government of India and several well established pharmaceutical companies in the country are investing in medical biotechnology R and D, but this is very small in comparison to the research expenditure of transnational companies in developed countries. Even a developing country like China has invested more money in biotechnology research than India. One thing which should be noticed here is that the major share of money in the Chinese biotechnology R and D comes from the State. In China the production units are set up as fully integrated units with the research and development programmes and distribution of the fund is concentrated on a lesser number of biotechnology companies.[3] On the other hand, the public R and D units in India are independent bodies and have poor linkages and knowledge of the industry and its requirements. This in turn led to disinterestedness of the industry in buying indigenous technologies and products.

Many Indian scholars have assessed the quality of Indian biotechnology R and D and found that it is not the quality of indigenous research, but the weak commercialization process which is responsible for the slow development of

[3] *The Economist*, Dec. 2002, pp. 75-77.

indigenous biotechnology industry (Visalakshi 1992, 1995, Kumar 1992, Ramani et al. 1999, 2001) The reasons for poor commercialization in turn ranges from poor quality of public R and D products (Redwood 1994, Chandrashekhar 1995), availability of cheaper foreign substitutes (Parthasarthy 1987, Sasson 1993,Avramovic 1996) and problems in the upscaling process (Parthasarthy 1987, Ramani and Venkataramni 1999).[4]

At the present time many biotechnology startup companies are pursuing revenue earning business strategies (Visalakshi 1995) which has negatively affected the R and D activity of such companies (Basant 2000).

In sum, the biotechnology industry is a knowledge-oriented or human capital-intensive industry and globalization has tended to increase the commercialization of R and D.[5] In order to develop and promote biotechnology industry there is a need for cooperation in research and technology development.[6] There is also a need to assess the local capabilities in order to rationalize unnecessary flow of foreign investment in stronger areas. In other words, it is necessary for India to carefully frame its policies to promote indigenous R and D in a few areas in which human and financial resources could be concentrated and ensure a link between the R and D institutes and Industry.

The Indian biotechnology industry is going through the initial phases of development that are not much different from is witnessed in many of the European countries. Thus, proper policies, allocation of funds and development of human resource positively result in developing Indian biotechnology industry suitable for Indian conditions.

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[4] Parthasarthy, above n. 2; and S.Ramani and S. Visalakshi, "The Chicken or the Egg Problem Revisited: The Role of Resources and Incentives in the Integration of biotechnology Techniques", *International Journal of Technology Management*, 2001.

[5] Ashok V. Desai 1980, Rakesh Basant 2000, Visalakshi, 2001.

[6] Ramani et al. 1999, 2001.

List of Medical Biotechnology Companies in Delhi

Company	Status	Collaboration	Sector	Investment	Turnover	Employees		Website
						Total	Technical	
J.Mitra & Company Ltd.	Pvt.Ltd.	DBT, PATH	Mfg.,Mktg., R&D	235	3444	250	80	www.jmltd.com and jmitra4u.com
Panacea Biotech Ltd.	Pub. Ltd.	Italy, CGEB (Cuba)	R&D (Recognised byMST), Mfg., Mktg	14067	11354	1047	87	www.Panacea-Biotech.com
Ranbaxy Laboratories Ltd.	Pvt. Ltd.	CSIR, Univ. of Bath (UK), Bayer AG, Glaxo-Wellcome (Co- Marketing arrangements for ceiphalexin in India), Eli- Lilly	Mfg, Mktg, R&D	11589	15598300	5347	NA	www.ranbaxy.com
Supriya Pharmaceuticals Ltd.	Pub. Ltd.	Nil	Mfg.	492	NA	628		
Carewell Biotech Pvt. Ltd.	Pvt. Ltd.	Cy- Bio- AG (Germany)	Mfg.,R&D, Consultancy	3	50	52		www.mediein.li/_mt_index/_ca/ca
Genetix	Properitor	Foreign	Mktg.	200	500	52	10	www.genetix.co.uk
Hysel India Pvt. Ltd.	Pvt. Ltd.	NA	Mktg.	NA	NA	18	8	www.hum-molgen.de/companies/profile.php 3/1826
Indtech India Pvt. Ltd.	Pvt. Ltd.	NA	Mktg., Consultancy	25	NA	6	2	www.indtechinfo.com
Bio Business Development Agency	Private	Switerzland, USA, Germany	Mktg.	NA	NA	12	1	www.rapidmicrobiology.com/companies/1115php

Wipro Biomed	Pvt.	Japan, Swiss, Germany, Singapore	Mktg.	NA	NA	25	NA
ACE Diagnostics	Pvt.	NA	Mfg.	NA	NA	15	5
`Towa Optics (India) Pvt. Ltd.	Pvt. Ltd.	Nil	Mktg.	200	NA	38	19 www.business.vsnl.com/towa_optics
Kothari Fermentation & Biochem Ltd.	Pub. Ltd.	Nil	Mfg.	1200	NA	100	20 www.bakeryindia.com/khotari/-
Pasteur Merieux India Ltd.	Pub. Ltd.	France	Mktg.	NA	140	8	NA www.biopharmalink.com

Appendix 1

The DBT had been formed with the following vision:

> "Attaining new height in biotechnology research and shaping biotechnology into a premier precision tool of the future, for creation of wealth and ensuring social justice- specially for the welfare of the poor."

The Department of Biotechnology was formed in 1986 with the following mandate:

- Support R and D and manufacturing in biological techniques
- Identify and set up centers of excellence for R and D
- Promote large scale use of biotechnology
- Integrated program for human resource development
- Establishment of infrastructure
- Facilities to support R and D and production
- Serve as nodal point for the collection and dissemination of information relating to biotechnology
- Promote university and industry interaction
- Evolve biosafety guidelines
- To serve as nodal point for the specific international collaborations
- Manufacture and application of cell based vaccines
- Responsibility for autonomous institutions

Appendix 2

Scientific Advisory Committee of DBT (SAC- DBT)

Scientific Advisory Committee for DBT was constituted on 4th July 1986 with Secretary DBT as its chairman and other members, representing the heads of various scientific agencies, research institutions, national institutions, national institutions and manufacturing concerns.

SAC- DBT mainly advice DBT on the following matters:

- Short and long term programmes in different areas of biotechnology, for financial support by the government
- Recommend, developing linkages between academic institutions and R and D system on one hand and the industry on the other
- Advise on scientific, technical and industrial activities on biotechnology based industries
- Assess the technological status of Indian biotechnology industry with a view to update Indian technology and strengthen or start R and D programmes for meeting the future technological requirements of the industry
- Put forward views on the IPR and technology transfer related to biotechnology
- To advice on other matters as may be referred to it by the DBT

Standing Advisory Committee- Overseas (SAC- O)

The SAC- O was initially set up in 1988 for four years. The SAC- O consists of recognized scientists from abroad, who provide valuable inputs to the DBT for advancements in the biotechnology field. Wide range of issues related to biotechnology, discussed in SAC- O meetings are:

- Programmes related to biotechnology in the areas of agriculture, medicine etc.
- Assessment of programmes and ways of improving them
- Assessment of infrastructural facilities and ways to improve them
- Patenting related issues
- Initiation of biotechnology related programmes for the socio-economic upliftment of the rural masses
- To hold joint scientific collaboration programmes with foreign research institutions with the help of some of the SAC- O members
- Certain policy related issues which can give impetus to the biotechnology sector
- Discussions on the biological standards and facilities for the biotechnology sector
- Setting up science parks
- Help identify certain appropriate specific technologies for transfer to India both at pilot and commercial scale
- Interaction with scientific counselors of Indian missions abroad to help non resident Indian scientists to find suitable placements in India or to

assist in the placement of biotechnology trainees from India in various laboratories and specialized fields, abroad

Biotechnology Research and Promotion Committees (BRPC)

BRPC was constituted in April 1997, can consider and recommend all projects costing above Rs.1 crore. Following are the aims of BRPC:

- Only proposals recommended by task forces would be considered by BRPC
- Proposals of programme support, mission projects, integrated multi institutional projects and projects above Rs. 1 crore would be placed directly before BRPC for consideration, after obtaining the comments of the respective expert committees

BRPC had also constituted Monitoring Committees for the recommended projects costing above Rs.1 Crore. Each committee comprises of 3-4 experts in the related subject area, monitors the projects and report to BRPC.

Task Forces:

Under the auspices of SAC, DBT has constituted various task forces in the areas of: agriculture and marine biotechnology; animal biotechnology and veterinary sciences; animal husbandry and leather biotechnology; basic research; new emerging areas and R and D facilities; biochemical engineering; downstream processing and instrumentation; bioinformatics; biological pest control; environmental biotechnology; fuel, fodder, biomass, horticulture and plantation crops; sericulture; industrial biotechnology; integrated manpower development; medical biotechnology; integrated manpower development; medical biotechnology, microbial biotechnology; plant molecular biology and agricultural biology.

The main job of these task forces is to generate time bound programmes with clear objectives in the field of biotechnology and then to monitor it till its completion. The GOI had issued Rules and Procedures for handling genetically modified organisms (GMOs) and hazardous organisms through a gazette notification No. GSR 1037 (E) dated 5th Dec.1989 from the Union Ministry of Environment and Forests. It details about following things:

- Nature of the containments (Biological, Physical and Chemical)
- Biosafety levels
- Guidelines for DNA research activities
- Impact of release into the environment
- Import and shipment
- Quality control of biologicals, produced by rDNA technology
- Containment facilities and Biosafety Practices

Recombinant DNA Safety considerations (w.r.t. microorganisms, large scale operations, plants and agriculture and environment)

Appendix 3

Major Companies In Vaccine production in India:

Private
- Shantha Biotechnics (Joint Venture with Biocon and Oman)
- Bharat Biotech
- Indian Immunological Ltd.
- Serum Institute of India
- Bharat Serums

Public
- Central Research Institute (Kasauli)
- BCG Laboratory (Chennai)
- Haffkine (Mumbai)
- Bharat Immunological and Biological Corporation Ltd. (U.P.)

Source: EU- India Joint Initiative for Enhancing Trade and Investment, Biotechnology Sector Report, p. 37 See:
http://europa.eu.int/comm/europeaid/projects/asia-invest/download2002/eu-iji_biotechnology.pdf

Appendix 4

Major Diagnostic Companies in India:

- Accurex
- Aimil Ltd.
- Aksigen Hospital Care
- Amar Immunodiagnostics
- Bhat Biotech India
- Biomed Importers
- Bharat Serums and Vaccines
- Dr. Reddy's Laboratory
- EI Instruments India
- Hi Media Laboratories
- J. Mitra and Company Ltd.
- Kopran Laboratories
- Lilac Medicare
- Medispan
- Monozyme India
- New India Chemical Enterprises
- OSB Agencies Pvt. Ltd.
- Pasteur Biologicals
- Ranbaxy Diagnostics
- Reckon Diagnostics
- Remi Sales And Engineering
- Span Diagnostics
- Spectrum Medical Industries
- Stimulus Speciality Diagnostics
- Suyog Diagnostics Pvt. Ltd.
- Transasia Biomedical Ltd.
- Transgene Biotek Ltd.
- Tulip Diagnostics ltd.
- Zydus Pathline (Cadila)
- Jubilant Organosys

Source: EU- India Joint Initiative for Enhancing Trade and Investment, Biotechnology Sector Report, p.37- 38
http://europa.eu.int/comm/europeaid/projects/asia-invest/download2002/eu-iji_biotechnology.pdf

Appendix 5

Major companies in clinical trials in India

1. Quintiles India (subsidiary of quintiles trans-national)
2. Clinigene (from Biocon)
3. Siro Clinpharm Pvt. Ltd.
4. Wellquest (clinical research division of Nicholas Piramal)

Source: EU – India Joint Initiative for enhancing trade and investment, Biotechnology sector report, p.39

Appendix 6

India's major Contract research companies (in drug discovery)

- Aurigene (from Dr. Reddy's Laboratories)
- Avesthagene
- Banglore Genei
- Chembiotech International Limited (The Chatterjee group)
- Gangagen (fully owned by Gangagen San Francisco)
- Genequest (genomics division of Nicholas Piramal)
- GVK bio (from GVK group)
- Reliance
- Syngene (from Biocon)

Contract Research Companies (in Bioinformatics):

- Astrazeneca
- CDC Linux (tie –up with CSIR)
- Dr. Reddy's (in house unit)
- DSQ biotech
- GVK Bio (from GVK group)
- Ingenovis (division of I labs)
- Jubilant Biosys (subsidiary from Jubilant Organosys)
- Landsky solutions
- Molecular connections
- Ocimum Biosolutions
- PrayogNET computing
- Questar Bioinformatics
- Satyam (partnership with CCMB)
- Strand Genomic
- Spectramind Services
- TCS (tie up with Center for DNA Fingerprinting and Diagnostics)

Source: EU – India Joint Initiative for enhancing trade and investment, Biotechnology sector report, p. 38
http://europa.eu.int/comm/europeaid/projects/asia-invest/download2002/eu-iji_biotechnology.pdf

Appendix 7

Allocations for Biotechnology under Five-Year Plan (Rs. In million)

Name of the scheme	9th plan	10th plan
Biotech Facilities, Centres of excellence and Programme Support	680.46 (**10.95%**)	900 (**4.34%**)
Reseach and development		
Agriculture BT	1651.26 (**26.5%**)	550 (**2.65%**)
Medical BT	808.9 (**13.01%**)	4130 (**31.46%**)
Environmental BT	128.72 (**41.65%**)	7280 (**35.08%**)
Human resource development	1000(**16.09%**)	160(**0.77%**)
Bioinformatics	700(**11.2%**)	120(**0.58%**)
IPR & Biosafety	7.5 (**0.12%**)	100(**0.48%**)
Bio Process & Product Development	513.05(**8.25%**)	500(**2.4%**)
Total*	6215.42	20750

*Rest of the amount of the total budget expenditure goes to the various autonomous institutes supported by DBT.

Source: RIS, based on *DBT Annual Reports*, http://www.ris.org.in

Appendix 8

Technologies transferred and Launched in the Market

Technology	Developed by	Launched by
Leprosy Immunomodulator	NII, New Delhi	M/s Cadila Pharmaceuticals Ahmedabad
Leshmaniasis detection kit	CDRI, Lucknow	Span Diagnostics Ltd.
Western Blot for HIV-I and II	CRI, Mumbai	M/s J. Mitra and Co., New Delhi
Naked Eye agglutination system for HIV-I and II	Univ. of Delhi, South Campus	Cadila Pharmaceuticals, Ahemadabad
Hepatitis C Diagnostics ELISA Based	ICGEB, New Delhi	Xcytron, Banglore

Technologies under Negotiation

Technology	Developed by
LDH based ELISA for Malaria	CDRI, Luchnow
DAT for Toxoplasmosis	AIIMS, New Delhi
Reagents for thyroid and steroid hormones	AIIMS, New Delhi; IICB Kolkata
Peptide based ELISA system for protection of HIVI and II	NII,New Delhi
Skin Culture Technology for use in burn Cases	NCCS, Pune
Medium for preservation of Cornea	NCCS, Pune
Haemagglutination Assay for Kala -azar	CDRI, Luchnow
IFA for Rabies	AIIMS, New Delhi
Systems for Steroid	IICB, Kolkata
Tests for Species Specific Snake Bite	VM Scienific Research Foundation ,Banglore
PCR based diagnostic tests for tuberculosis	AIIMS, New Delhi; CDRI, Lucknow

Source: DBT Annual Report, 2001-02, GOI, p.67

Appendix 9

The Chronology of Key Events in the Indian Biotechnology Industry

1978 Banglore: Country's first Biotech company Biocon was established for industrial enzymes and later (biotechnology) therapeutics.

1981 Hyderabad: Center for cellular & Molecular Biology (CCMB) established (for DNA & DNA based research).

1984 Chandigarh: Institute for Microbial technology (IMTECH) (for R & D in microbial bioprocessing).

1986 New Delhi: Department of Biotechnology (DBT), set up by Govt. of India for promoting modern biology and biotechnology at academic and industry levels.

1987 New Delhi: National Institute of Immunology (NII) set up by DBT for immunology research.

1989 Bangalore: Bangalore Genei starts operations to produce restriction enzymes and other tools for DNA based R and D.

1991 Banglore: National Center for Biological Sciences (NCBS) to pursue R and D in molecular biology.

1994 Banglore: Syngene International country's first CRC (promoted by Biocon) to offer R and D services in drug discovery based modern biology.

1997 New Delhi: Center for Biochemical Technology (CBRT) to focus on Bioinformatics and genomics.

1997 Hyderabad: Shantha Biotech launches India's first recombinant product i.e. Hepatitis B vaccine.

1998 Bangalore: Monsanto research establishes an R and D center at Indian Institute of Science for plant genomics.

1998 New Delhi: DBT approves 'Mahyco-Monsanto' to conduct Bt cotton trials.

1999 Banglore: NCBS scientists set up Avesthagene a plant genomic company.

2000 Four states Andhra Pradesh, Karnataka, Maharashtra and Tamil Nadu announce different programmes at the state level related with biotechnology activities promotion.

2000 Banglore: Country's first Bioinformatics company Strand Genomics formed by four IISC professors.

2000 New Delhi: Country's first joint venture Genome established between CBT (Institute) and Nicholas Piramal (Industry) to pursue pharmaco- genomics.

2001 Reliance sets up Reliance Life sciences to pursue stem cell based research and product development.

2001 Mumbai: GEAL approved Wockhardt's erythropoietin (EPO).

2001 National Institute of Health (NIH) approves NCBS and Reliance Life Sciences as 2 out of 10 labs worldwide for stem cell lines.

2001 Drug Authority implements General Clinical Practices (GCP) guidelines for clinical trials.

2001 Millennium Biotech Policy, the first state level Biotechnology Policy, announced by Govt. of Karnataka.

2002 Banglore: Institute of Bioinformatics and Applied Biotechnology, (IBAB) a jointly funded initiative between Govt. of Karnataka and ICICI commences academic programme.

2002 GEAL approves Bt cotton for commercial planting.

2002 Hyderabad: GEAC approves Shantha Biotech's Interferon Alpha 2b.

Source: Kiran Mazumdar Shaw, http://biotech-india.com

Appendix 10

SWOT Analysis of Indian Biotechnology Industry:

Strengths:

1) Trained manpower and knowledge base
2) Good network of research laboratories
3) Rich Biodiversity
4) Well developed base industries (e.g. pharmaceuticals, seeds)
5) Access to intellectual resources of NRIs in this area
6) Extensive clinical trials and research (access to vast and diverse disease populations)

Biodiversity ~ India's diverse human gene pool is an opportunity for genome study.

Weaknesses:

1) Weak link between research and commercialization
2) Lack of venture capital
3) Relatively low R and D expenditure by industry compared to developed countries

Indian industry doubts about ability of Indian products to meet international standards of quality

Opportunities:

1) Large market for consumption of effective biotechnology products
2) Lower cost of R and D and contract research services
3) Availability of large number of patients covering wide range of diseases

Threats:

1) Anti- biotechnology campaigns
2) IPR policies have to understood well before application

Source: Kiran Mazumdar Shaw, http://biotech-india.com

Appendix 11

Table: Growth Rate Comparison in Requirement, Production and Import of Important Vaccines in India (in million doses)

	Requirement			Consumption			Production			Import		
Vaccines	1994-95	1999-00	Gr/Yr	1997	2005(E)	Gr/Yr	1985-86	1994-95	Gr/Yr	1985-86	1994-95	Gr/Yr
DTP	105	114	1.7	110	124	1.6	71	97	4.1			
DT	50	57	2.8	54	65	2.5	28.3	45	6.6			
Tetanus	75	200	33.3	192	222	2.0	54.9	75	4.1			
BCG	41	24.3	-8.1	41	47	1.8	17.8	10	-4.9			
Oral Polio	105	134	5.5	110	225	13.1				17.8	90	45.1
Measles	42	46	1.9	25	45	10.0	3.8	23	56.1		0.1	
MMR	5	7.5	10.0	7	10	5.4		4.5				
Rabies	4	6.5	12.5	5	12	17.5		5.5			1	
Hepatitis B	1.1	45.2	801.8	7	45	67.9					0.37	
Typhoid	10	50	80.0	0.4	2.5	65.6					1	
Influenza	1	5	80.0									
Meningitis	0.5	2	60.0									

Source: Sachin Chaturvedi and Beena Pandey "Vaccine Policy in India" in *Biotechnology and Development Monitor*, No.25, Dec. 1995 and
P.K. Ghosh, "Market size and Future demand for Biotech products" http://www.ciionline.org/busserv/biotechnology_market.html

Appendix 12

Advantages and Limitations of performing Clinical Research and Contract Research Services in India

Advantages:

- Patient diversity
- Patient heterogeneity
- World class medical infrastructure
- Cost competency (patient recruitment, shorter timelines, manpower)
- General Clinical Practices (GCP) implementation
- Project management competencies
- Network of academic and medical centers or hospitals
- Regulatory guidelines and government policies – helping clinical research in India (Ministry of Health, Indian Council for Medical Research, Department of Biotechnology, Drug Controller General of India)

Limitations:

- High customs duty (30-68%) on equipment, consumables and clinical trial samples
- Lesser number of hospitals or clinic infrastructure to meet GCP standards
- No established GCP standards ethics committees
- Lesser number of central labs with General Lab Practices (GLP) standards
- Lesser number of clinical researchers equipped with sound understanding of GCP in clinical trials
- No well defined and transparent regulatory guidelines
- Poor record maintenance of the studies done[1]

[1] See Appendix 5

Appendix 13

Major Indian Bio- Pharmaceutical Companies

Company	Areas of Product Development
Biocon	Fermentation methods for industrial enzymes, rDNA Contract research (Syngene)
Shantha Biotech	Hepatitis B,C,E; Alpha Interferon, Streptokinase, Betacarotene, Mab for lung cancer
Bharat Biotech	Hepatitis B, Insulin,Epidermal growth factor, Streptokinase, Urokinase, other vaccines
Banglore Genei	Tools for rDNA research
Wockhardt	Hepatitis B, Recombinant Erythropoeitin,Insulin, Anti cancer drugs, Chirals
DSQ Biotech	Agri Biotech, Genomics (Bioinformatics)
Nagarjuna Biotech	Genomics
Biological E	Vaccines, Genomics
Serum Institute	Vaccines
Span Biotech	Hepatitis B, Leishmaniasis diagnosis
Cadila Pharma	Leprosy
Lupin Labs	HIV I and II immunodiagnostics
Piramal	Recombinant gamma interferon
Ranbaxy	Drug discovery, Rational Drug Design, Bio- Drug, Pregnancy detection
Dr. Reddy's Lab	Diabetics therapeutics
Panacea Biotech	HepatitisB, Erythropositin

Source: EU- India Joint Initiative for Enhancing Trade and Investment, Biotechnology Sector Report p.40

Major Indian Companies in the Biotechnology Industry

Avesthagen Technologies	Plant Genomics, GM Rice, Contract research
Banglore Genei	Restriction enzymes, Plasmids,bacterial host strains, gel documentation systems
Bharat biotech	Hepatitis B vaccine, GCSF, Interferon, Streptokinasse
Biocon India	Enzymes, Gamma Interferon,GCSF, Streptokinase, Human Insulin, Monoclonal antibodies
Clingene International	Human genomics, bioinformatics, contract clinical research
Dr. Reddy's Labs	GCSF, Interferon
Genotypic technologies	Array based HTS Contract Research
Panacea Biotech	Hep. B vaccine, GCSF,Interferon
Reliance Industries	Stem cell research
Wockhardt	Hep. B vaccine, EPO, GCSF, Human Insulin

Shantha Biotech Pvt. Ltd.	The first company to indigenously produce the first genetically engineered Hepatitis B vaccine
Bharat Serum	
Biological E	
Advanced Biochemical Limited (ABL)	Thane based company has tied up with Pacific Corporation of South Korea to manufacture genetically engineered industrial enzymes
East India Pharmaceuticals	Tied up with US based Cleveland Clinical Foundation for research in biotechnology and molecular biology
Chembiotech International Ltd.	One of India's first contract research organization based in Calcutta has tied up with two major European companies- Bayer and P and G pharmaceuticals

Joint Ventures in Biotechnology in India

Wockhardt with Rhein Biotech (Germany) for tecomb HBSAg vaccine terminated and Rhein Biotech sold out its share to Wockhardt
Nicholas Piramal and Cytran (USA) joint venture in immunology, clinical trials, marketing
Torrent with Sanofi (France) for research and development in healthcare products
UB Group and Roussel Sante (France) for recombinant insulin

Eupropean Subsidaries in India

Astra Zeneca, Sweden
Novo Nordisk, Denmark
Bio Merieux, France
Bayer, Germany
Nunhems ProAgro, Netherlands
Aventis, Germany
Glaxo Smithkline, UK
Sartorius AG, Germany

Source: EU- India Joint Initiative for Enhancing Trade and Investment, Biotechnology Sector Report, p.35
http://europa.eu.int/comm/europeaid/projects/asia-invest/download2002/eu-iji_biotechnology.pdf

Appendix 14

The History of Biotechnology

Description	Year
Austrian botanist and monk Gregor Mendel proposes basics laws of heredity based upon his cross-breeding experiments with the pea plant. Although a local journal published his theories, they are ignored for over thirty years.	1866
German embroyolgist Walther Fleming was examining salamander larve under a microscope when he noticed tiny threads within the cell's nucleus that appeared to be dividing. These tiny treads are later identified as chromosomes.	1882
The term eugenics is coined by Francis Galton, a cousin of Charles Darwin. Galton is an early advocate of improving the human condition via selective breeding.	1883
Twenty-eight years after Fleming obsevred chromosome within a cell's nucleus, biologist Thomas Hunt Mrogan's experiments with fruit flies reveal that some genetically determined traits are sex linked. In addition his work verifies that the genes reside on chromosomes.	1910
U.S.biologist Hermann Muller discovers that x-rays can cause genetic mutations in fruit flies.	1926
Oswald Avery, Colin Macleod and Maclyn McCarty demonstrate that DNA, not protein, is the hereditary material in most living organisms. This was accomplished based upon their work with the pneumococcus.	1944
UK physcian Douglas Bevis demonstrates how amniocentesis can be used to test fetuses for the their RH factor compatability. The prenatal test will later be used extensively to screen for a number of genetic disorders.	1950
James D. Watson and Francis Crick publish their paper on the very nature and structure of DNA. They concluded the paper with the medical understatement of the century, "this structure (DNA) has novel features, which are of considerable biological interest."	1953
UC-Berkeley biochemist Heinz Fraenkel-Conrat takes apart and then reassembles the tobacco virus, demonstrating *"Self Assembly."*	10/1956
Using one strand of natural viral DNA to assemble 5,300 nucleotide building blocks, Nobel Laureate Arthur Kornberg's Stanford group synthesizes infectious viral DNA.	12/67
Science reports that Stanford Geneticist Leonard Herzenberg develops the flourescence-activated	11/69

cell sorter, which can identify up to 5,000 closely related animal cells.	
UC-Berkeley virologists Peter Duesberg and Peter Vogt discover the first oncogene in a virus. Dubbed *SRC, t*he gene has been implicated in many human cancers.	12/70
Stanford immunologist Hugh McDevitt reports in *Science* genes which control immune responses to foreign substances, suggesting predictable susceptibility to some diseases.	1/72
UC-Berkeley biochemist Bruce Ames develops a test to identify chemicals that damage DNA, The Ames Test becomes a widely used method to identify carcinogenic substances.	3/73
The *Proceedings of the National Academy of Sciences USA (PNAS)* publishes a paper by Stanford Geneticists Stanley Cohen and Annie Chang, and UCSF Biochemists Herbert Boyer and Robert Helling describing the first construction of a recombinant DNAmolecule containing the genetic material from two different species.	11/73
PNAS publishes a paper by Stanley Cohen and Herbert Boyer in which they demonstrate the expression of a foreign gene implanted in bacteria by recombinant DNA methods. Cohen and Boyer show that DNA can be cut with a restriction enzyme, joined together with other enzymes, and reproduced by inserting the DNA into *Escherichia coli*	5/74
Science publishes a letter by Stanford Biochemist Paul Berg and others calling for National Institute of Health Guidelines for DNA Splicing. The letter requests that scientists desist from certain types of recombinant DNA experiments until questions of safety can be addressed	7/74
Researchers and academicians convene a three-day meeting at Asilomar to debate scientific concerns about gene splicing. A year later the NIH issues guidelines.	2/75
UCSF virologists J. Michael Bishop and Harold Varmus show that oncogenes appear on animal chromosomes and alternatives in their structure or expression result in cancer.	3/76
UCSF biochemists Bill Rutter and Howard Goodman report in *Science*the isolation of the gene for rat insulin.	6/77
Genentech Inc. reports expression of the first human protein produced in a microorganism, somatostatin, a human growth hormone-releasing inhibitory factor.	12/77
After two years of discussion between Stanford and the NIH, the federal government affirms that universities can hold patents and license recombinant DNA inventions.	3/78
Genentech Inc. and The City of Hope National Medical Center announce the successful laboratory production of human insulin using recombinantDNA technology.	9/78
At the American Federation for Clinical Research, UCSF endocrinologist	5/79

John Baxter and his colleagues report the cloning of the gene for human growth hormone.	
The U.S. Supreme Court holds that life forms can be patented when it allows General Electric's Ananda Chakrabarty a patent covering genetic manipulation techniques.	6/80
Genentech Inc. conducts the first biotech initial public offering. The stock price climbs from $35 to $89, settling at $71.25 at the end of the first day.	10/80
Stanford receives a process patent to make mirror-image molecules known as chimeras, an important step in developing new pharmaceuticals.	12/80
Cetus completes what was at the time the largest IPO (Initial Public Offering) in U.S. History. Net proceeds top $107 million.	3/81
Chiron Corp. Chairman Bill Rutter and Research Director Pablo Valenzuela report in *Nature* a yeast expression system to produce the hepatitis B surface antigen.	6/81
Alza Corp. receives FDA approval to market the first product (for motion sickness) based on a transdermal or skin patch, delivery system.	8/81
Applied Biosystems Inc. introduces the first commercial gas phase protein sequencer, reducing the amount of protein sample needed to sequence a protein.	3/82
UCSF neurologist Stanley Prusiner describes a new pathogen, dubbed "prion," which contains little or no genetic material and contributes to degenerative brain diseases.	4/82
UC-Berkeley Plant pathologist Steve Lindow requests government permission to test genetically engineered bacteria to control frost damage to potatoes or strawberries.	9/82
Eli Lilly & Company receives FDA approval to sell Genentech Inc.'s human insulin, the first product of recombinant DNA technology to reach the market.	10/82
UCSF pediatric immunologist Arthur Ammann warns the Centers for Disease Control that tainted blood can transmit AIDS. Nine months later, the blood bank at Stanford School of Medicine becomes the first to screen blood to prevent AIDS transmission.	12/82
Syntex Corp.'s diagnostics and drug monitoring subsidiary, Syva Co., receives FDA approval for a monoclonal antibody based diagnostic test for *Chlamydia Trachomatis*.	1/83
Applied Biosystems Inc. begins supplying DNA synthesis instruments using phosphoramadite chemistry, to manufacture synthetic DNA used in probes, primers and gene constructs.	3/83
SRI International files for a patent for an *E. coli* expression vector.	8/83

Three months later SRI unveils a five year biotechnology business plan.	
Jay Levy's UCSF lab isolates the AIDS virus at almost the same time it is isolated at the Pasteur Institute in Paris and at the NIH.	11/83
Cal Bio scientists describe in *Nature* the isolation of a gene for anaritide acetate, which helps regulate blood pressure and control salt and water excretion.	6/84
Stanford receives a patent for prokaryote DNA	8/84
Chiron Corp. announces the first cloning and sequencing of the entire human immunodeficiency virus (HIV) genome.	9/84
Genentech's Axel Ullrich reports the sequencing of the human insulin receptor in *Nature* . Bill Rutter's UCSF team describes the sequencing in *Cell* two months later.	2/85
Cal Bio clones the gene that encodes human lung surfactant protein, a major step toward reducing a premature birth complication.	2/85
Genentech Inc. receives FDA approval to market human growth hormone. The first recombinant pharmaceutical product to be sold by a biotechnology company.	10/85
Science reports Cetus Corp.'s GeneAmp™ polymerase chain reaction (PCR) technology, which allows the generation of billions of targeted gene sequence copies in only hours.	12/85
Disclosure of Advanced Genetic Sciences Inc. "Roof-Top" experiments with ice-minus bacteria leads to heightened EPA regulation of open-air trials of engineered organisms.	2/86
Molecular Devices receives a patent covering a method employing light-generated electrical signals for detecting chemical reactions on the surface of semiconductor chips.	5/86
The FDA grants Chiron Corp. a license for the first recombinant vaccine, to battle the hepatitis B virus.	7/86
Chiron Corp. and Ortho Diagnostics Systems Inc. reach agreement to supply AIDS and hepatitis screening and diagnostic tests to blood banks worldwide.	11/86
Science publishes a paper by UC-Berkeley chemist Peter Schultz describing how to combine antibodies and enzymes creating "abzymes" to create pharmaceuticals.	12/86
Calgene Inc. receives a patent for the tomato polygalacturonase DNA sequence and its use to produce an antisense RNA sequence, to produce extended shelf life fruit.	1/87
Advanced Genetic Sciences Inc. conducts the first field test of a recombinant organism, *Pseudomonas Syringae,* a frost inhibitor, on a Contra Costa County strawberry patch.	4/87
The NIH (National Institute of Health) awards IntelliGenetics Inc. a	10/87

$17.2 million over five years to administer GenBank(R), the national computerized data bank of nucleic acid sequences.	
Genentech Inc. receives FDA approval to market Activase(R) (genetically engineered tissue plasminogen activator) to treat heart attacks.	11/87
The "Harvard Mouse," created by molecular geneticists Philip Leder and Timothy Stewart, now at Genentech Inc., becomes the first mammal patented in the U.S.	4/88
SyStemix Inc. receives a license on a patent application for the SCID -hu mouse, an immune deficient mouse with a reconstituted human immune system.	6/88
Genencor International receives a patent for a process to make bleach-resistant protease enzymes to use in detergents.	7/88
The first International Biotechnology Expo & Scientific Conference opens in Oakland, CA. IBEX is now the largest conference to focus on the biotech industry.	10/88
Hoffman-La Roche Inc. and Cetus Corp. reach a licensing agreement for two anti-cancer drugs, interleukin-2 and Polyethylene Glycol modified IL-2. The move leads the way for further cross-licensing between companies with parallel patents.	12/88
XOMA Corp. files for FDA approval to market the first immunoconjugate, CD5 Plus, to treat acute graft-vs.host disease, a bone marrow transplant complication.	12/88
XOMA Corp. files for FDA approval to market E5, a monoclonal antibody-based therapeutic drug, to treat gram-negative sepsis.	3/89
Stanford University opens the $100 million Beckman Center to link fundamental molecular biology and clinical medicine. Nobel Laureate Paul Berg is named director.	5/89
Calgene Inc. conducts its first field tests of antisense tomatoes, to test reduced fruit rotting. This first antisense food product awaits FDAmarketing approval.	5/89
Syntex Laboratories introduces an anti-viral agent to slow the spread of life-or-sight-threatening cytomegalovirus infections in immuno-compromised patients.	7/89
Plant Gene Expression Center molecular biologist Athanasios Theologis reports in *PNAS (Proceedings of the National Academy of Sciences USA)* the cloning of a gene necessary to synthesize ethylene, the ripening hormone and gas.	9/89
Cutter Biological files for a new drug application for a recombinant Factor VIII biological, the blood-clotting protein missing in people with hemophilia.	9/89

The first daily, on-line biotechnology business newspaper, *BioWorld* begins publishing in San Mateo, California. The following April, a daily fax version is introduced.	10/89
Arris Pharmaceutical Corp.'s Monty Krieger describes in *Nature* the cloning of a gene that could lead to an atherosclerosis therapeutic for heart disease.	2/90
Science reports that scientists at Genlabs Technologies Inc. and the Centers for Disease Control cloned a portion of the hepatitis E virus.	3/90
Protein Design Labs Inc. reports in *Cancer Research* that its humanized, anti-IL-2 receptor antibody mediates antibody-dependent cellular toxicity against target T cells.	3/90
UCSF and Stanford issue their 100th recombinant DNA patent license. By the end of fiscal 1991, both campuses had earned $40 million from the patents.	3/90
Calgene Inc. announces the first successful field trial of genetically engineered cotton plants for use with the herbicide bromoxynil.	3/90
The FDA licenses Chiron's hepatitis C antibody test, removing a major threat to the nation's blood supply and the screening of donated whole blood.	5/90
An article in *Science* by researchers at Athena Neurosciences Inc. reports on events leading to the formation of the beta amyloid plaque found in the brains of Alzheimer's patients.	6/90
Two years after UC-Davis pomologists Gale McGranahan and Abhaya Dandekar report the transfer of a foreign gene into a walnut plant, the first woody crop field trial begins.	7/90
The California Supreme Court rules in the John Moore case that a patient does not have rights to profits from products derived from his own cell line.	7/90
The FDA approves for sale Burroughs Wellcome Co's synthetic lung surfactant, based on respiratory distress syndrome research conducted by UCSF physiologist John Clements.	8/90
The Bay Area Bioscience Center, a non-profit public service corporation founded by universities, companies and local government, open it's office.	9/90
UC-Berkeley epidemiologist Mary-Claire King reports in *Science*finding a gene linked to breast cancer in families with a high degree of incidence before age 45.	12/90
The first transgenic dairy cow, created by GenPharm International, Inc. is born. The cow will be used to produce milk proteins to make infant formula.	12/90
The Human Genome project begins: the goal is set of mapping the entire	6/90

human genome by 2005.	
Cancer patients are treated with a gene therapy that produces the tumor necrosis factor, a natural tumor fighting protein. Genes for deafness, colon cancer, inflammation, and sense of smell are discovered.	1991
Nature publishes the discovery by Plant Gene Expression Center research geneticist Sarah Hake that corn's developmental gene, *Kn1,* contains a homebox for regulating gene expression.	3/91
Genes are transferred to treat patients with hereditary high cholesterol, adult brain tumors and neuroblastoma (a nervous system cancer in infants and children. The genes for adult muscular dystrophy and childhood deafness are discovered.	1992
The first physical maps presented for chromosome 21 and chromosome Y.	6/92
Genes are transferred to treat patients with cystic fibrosis, malignant melanoma, small-cell lung cancer, and brain tumors. Researchers discover genes for hereditary colon cancer, Huntington disease, hyperactivity, Lou Gehrigs disease, the most common forms of alzheimer's disease, adrenoleukodystrophy, and adult-onset diabetes.	1993
USDA approves genetically engineered tomato and cow hormone that stimulates milk production.	6/93
The physical maps of the following chromsomes are published: 3,11,12,16,19 and 22.	6/95
"Dolly" becomes first the mammal cloned.	10/97
The Human Genome Project and Celara Genomics Inc. announce a major milestone in mapping the human genome.	6/2000

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