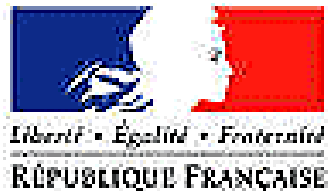


Biotechnology in India

Les biotechnologies en Inde

Report commissioned by the French Embassy in India

Directed by Drs Joël RUET & Marie-Hélène ZERAH
Main investigator and redactor: Augustin MARIA
With the scientific support of Pierre-Noël GIRAUD

Background

This report has been commissioned by the French Embassy in India, New Delhi. The has been realised by the CSH (Centre de Sciences Humaines, French Ministry of Foreign Affairs), based in New Delhi, and the CERNA, centre of Industrial Economics of the Ecole Nationale Supérieure Des Mines de Paris (ENSMP).

The Biotechnology research project has involved Augustin MARIA (3rd year student of the ENSMP with a major in Industrial Economics, Joël Ruet (Head of the economic department – CSH), Marie Hélène Zérah (Researcher from CERNA, based in Bombay), and Pierre-Noël Giraud (Head of CERNA).
This report is based on 60 interviews realised in India with leaders from firms and institutions identified as important players of the sector.

Executive Summary

What is happening with biotechnology in India? Here is the simple question we try to answer in this report. Biotechnology is surely a fashionable word in the Indian media. But what exactly does it refer to? Biotechnology considered with its widest meaning encompasses all practical applications of properties of living organisms to create value. Defined this way, biotechnology refers to the use of yeast to make beer as well as the use of a retrovirus[1] in order to modify the genetic patrimony of a complex living organism such as the human body. The common dynamic of economic development related to these different technologies is not obvious. Therefore, we tried to establish which techniques belonging to the range of biotechnology were involved in remarkable technico-economic dynamics in the specific area of India. Once these dynamics identified, we tried to identify the new models of organisation that are emerging from these evolutions both at the national and global levels, and the challenges the Indian companies have to face to take part in the reorganisation.

Worldwide, the most striking dynamics are related with modern techniques derived from the scientific advances in molecular biology and genetic engineering. The technique for the genetic modification of unicellular or vegetal organisms is now mature enough to find economic application such as the production of therapeutic proteins in hybrid yeast and bacteria, and the development of hybrid varieties of plants through genetic manipulation. More recently, the sequencing and mapping of the human genome has opened numerous new ways of enhancing the method of new drug development. This study mainly focused on the integration of these modern biotechnologies in the Indian economy.

The results of the interviews carried out with numerous Indian companies and Institutions show that there are now happening a lot of things with modern biotechnologies. Namely, several Indian companies are entering the market for biogenerics – generic therapeutic products produced through a process using modern biotechnologies – with a view of becoming competitive provider for the global market, an ambition comforted by the current commercial success of Indian chemical generic drugs. At the same time, a growing number of emerging companies are developing new business models based on the mastering of hedge technologies with the ambition of becoming privileged partners offering an attractive cost advantage at various stage of the complex chain of development of new drugs, and trying to emulate the development of the IT sector with a model of international outsourcing.

These evolutions have been initiated quite recently and the industry can still be considered in a phase of emergence of new models of organisation. These models of organisation do not only refer to the positioning of Indian companies on value chains destined to feed the domestic market. They also refer to the relations of the Indian companies with downstream and upstream foreign public or private partners, as well as the targeting by Indian companies of foreign markets. The main components of the Indian companies' strategies that are studied in the report are (i) the building of technical capabilities, (ii) the financial support, and (iii) the marketing strategy. We study how the existing background generated both by pubic action and the existence of related industrial activities allows entrepreneurs to build strategies in the new fields of biotechnology.

[1] A technical glossary is provided at the end of this report.

(i) Strategies for technology and competency development or acquisition are the central factor determining the success of these ventures. Indian policy of research support and human resource development through the funding of several public research and teaching institutions is of course a critical factor determining the technology availability. The interactions between those public institutions and the Indian companies were the object of a specific analysis. It appears that Institutions and Companies are learning to work together and the effects of this collaboration can help the companies at various stage of their development. It also appears that companies often adopt alternative solutions to collaboration with Indian institutes such as collaborations with foreign companies or institutions. The personal networks built by the managers of these Indian firms – many of them have had an international academic or corporate carrier – are the main determinant of those international connections.

(ii) Concerning the funding of biotech projects, it appears clearly that the most of the projects started so far were supported either by industrials or by individuals. The lack of venture funds with the money and competency necessary to support efficiently the development of an innovative Indian biotech industry has already been signalled by many analysts. Evolution are occurring from the public and private side towards an increasing of the availability of venture funding, and the next years should show if intermediated funding actually increase the rate of company creation.

(iii) Concerning the marketing strategies, the global character of the Indian firms' strategies is obvious. The companies entering the market for biogenerics are targeting foreign markets, and the most ambitious plan to enter the most regulated markets (US & Europe). As for the companies with business models based on research partnerships with other companies involved in drug development, their business is almost purely export oriented.

The question that remains concerns the vertical positioning of the Indian companies on the different value chains. Will the Indian integrated pharmaceutical companies focus on the generics or will they compete with the western research-based pharmaceutical companies in the race for new drugs development. As for the Indian companies looking for international partners for research partnerships, we can wonder if the partnership they will tie will be based on an asymmetric model of outsourcing or if their innovative capability will allow them accessing to intellectual property on the final product. The strategies observed in the industry shows that various opinions are still co-existing concerning this last question.

Résumé

Que se passe-t-il dans le domaine des biotechnologies en Inde ? Voici la question à laquelle cette étude s'attache à répondre. Les biotechnologies sont à l'évidence un sujet à la mode dans les médias indiens et on y trouve de nombreuses prophéties, prédisant aux biotechnologies indiennes un développement comparable à celui qu'ont connu les technologies de l'information dans le pays durant les quinze dernières années. Mais à quoi exactement se réfèrent ces affirmations? Les biotechnologies peuvent être définies de la manière la plus large comme 'toutes les applications de la connaissance du vivant utilisées pour créer de la valeur'. Prise dans ce sens, la définition englobe aussi bien l'usage de levures pour produire de la bière que l'utilisation d'un rétrovirus pour modifier le patrimoine génétique d'un organisme complexe comme celui de l'être humain. Les dynamiques économiques communes à ces deux technologies ne sont pas évidentes. C'est pourquoi nous nous sommes attachés à identifier quelles étaient, parmi les biotechnologies, celles qui pouvaient être reliées à des dynamiques technico-économiques remarquables sur le territoire de l'Inde. Une fois ces dynamiques identifiées, nous nous sommes attachés à identifier les nouveaux modes d'organisations émergeant à la suite de ces évolutions et les stratégies des firmes indiennes pour prendre part à cette réorganisation.

Au niveau international, les dynamiques de réorganisation technico-économiques les plus frappantes sont liées aux techniques modernes dérivées des progrès scientifique en biologie moléculaire et en génie génétique. Certaines techniques de modification génétique d'organismes unicellulaires ou végétaux sont maintenant suffisamment maîtrisées pour trouver des applications économiques telles que la production industrielle de protéines recombinantes par des cellules de levures ou de bactéries hybrides, ou le développement de variétés de plantes hybrides par manipulation génétique. Le sujet de cette étude a été restreint à l'étude de l'intégration de ces biotechnologies modernes dans l'économie indienne.

L'enquête menée auprès de nombreuses entreprises et institutions impliquée dans ce processus montre qu'il se passe en effet beaucoup de choses avec les biotechnologies modernes en Inde. Concrètement, plusieurs entreprises indiennes sont en train de rentrer sur le marchés des biogénériques – des médicaments génériques basés sur des produits obtenus par un procédé utilisant les biotechnologies modernes – avec pour objectif de devenir des acteurs compétitifs du marchés global pour ces médicaments génériques. Leur ambition est renforcée par le succès actuel que remporte l'industrie pharmaceutique indienne sur le marchés des autres médicaments génériques produits par synthèse chimique. Parallèlement, un nombre croissant d'entreprises développe des modèles d'affaire fondés sur la maîtrise de technologies de pointes, avec l'ambition de devenir des partenaires privilégiés offrant un avantage en terme de coût à différents niveaux de la chaîne de développement des nouveaux médicaments, en tentant de reproduire le schéma qui a fait le succès des industries de sous-traitance en Technologies de l'Information.

Ces évolutions ont démarré relativement récemment et l'industrie peut encore être considérée dans une phase d'émergence de nouveaux modèles d'organisation. Ces modèles ne se réfèrent pas seulement à l'organisation de filières technologiques destinées à alimenter le marché intérieur en produits de consommation finale, mais également aux relations qu'établissent les entreprises Indiennes avec des partenaires étrangers – public

ou privés – aussi bien en amont qu'en aval, et l'entrée de ces entreprises sur des marchés étrangers. Les principales composantes des stratégies des entreprises indiennes étudiées dans ce rapport sont (i) l'acquisition de compétences scientifiques et techniques, (ii) le financement, (iii) les stratégies de marketing et de croissance. Nous étudions la façon dont les conditions générées à la fois par l'action publique et l'exercice d'activité connexes permettent aux entrepreneurs indiens de construire des stratégies d'entrée dans les domaines des biotechnologies modernes sur la base de compétences scientifiques.

(i) Les stratégies de développement ou d'acquisition de technologie et de compétences constituent le facteur déterminant dans le succès des nouveaux projets. La politique Indienne de support de la recherche publique dans le domaine des biotechnologies est bien sur un élément déterminant pour la disponibilité de la technologie. Les interactions entre les entreprises et instituts indiens font l'objet d'une analyse spécifique. Il apparaît que la collaboration technologique fait encore l'objet d'un apprentissage de la part des deux parties. Il apparaît également que les entreprises indiennes ont des solutions alternatives à la collaboration avec des instituts de recherche indiens comme par exemple la collaboration avec des instituts ou entreprises basés à l'étranger. Les réseaux personnels construits autour des managers de ces entreprises indiennes – dont beaucoup ont eu une expérience académique ou privée à l'étranger – sont les principaux déterminants de ces connections internationales.

(ii) En ce qui concerne le financement des projets de biotechnologies en Inde, il apparaît que la plupart des projets en cours sont supportés par investissement direct, soit d'une entreprise, soit d'individus. Le manque de fonds de capital risque dotés des fonds et des compétences nécessaires pour supporter efficacement une industrie innovante des biotechnologies en Inde a été signalé par de nombreux analystes. La situation est en train d'évoluer grâce à des initiatives privés et publiques de développement de tels fonds et les prochaines années devraient montrer si le développement de ce type de financement augmente effectivement le rythme de création d'entreprise.

(iii) En ce qui concerne les stratégies marketing, le caractère global des stratégies des firmes indiennes est très clair. Les entreprises entrant sur le marchés des biogénériques ciblent d'emblée des marchés étrangers et les plus ambitieuses prévoient de se lancer sur les marchés les plus régulés (Etats-Unis et Europe). Quant aux entreprises avec des modèles d'affaires basés sur les contrats de partenariats de recherche avec d'autres entreprises impliquées dans la découverte de médicaments, leur stratégie est quasiment exclusivement tournée vers les pays étrangers les plus avancés dans les biotechnologies.

La question qui persiste concerne le positionnement des entreprises indiennes sur la chaîne de valeur. Est-ce que les entreprises indiennes de pharmacie vont concentrer leurs efforts sur les produits génériques, où vont-elles concurrencer les géants multinationaux dans la courses aux nouveaux médicaments brevetés ? Quand aux entreprises de haute technologie cherchant des partenaires internationaux, on peut se demander si les partenariats qu'elles noueront seront basés sur une relation asymétrique de sous-traitance, ou si la capacité innovatrice de ces entreprises leur permettra d'accéder à la propriété intellectuelle sur le produit final. Les stratégies observées montrent qu'il existe encore des avis divergents sur cette question.

Introduction

Definition: Conventional and modern biotechnology

Biotechnology's broadest definition can be given as "the application of all natural sciences and engineering in the direct or indirect use of living organisms or parts of organisms, in their natural or modified forms, in an innovative manner in the production of goods and services and/or to improve existing industrial process. The market application of outputs is typically in the general areas of human health, food production, industrial bio-processing and other public good and environmental settings."
Source Ernst & Young.

Nevertheless, the most frequent use of this term, or its abbreviation "biotech", refers to what can be called "modern biotechnology", that is technologies that involve understanding, mapping, manipulation or change of the genetic patrimony of a living organism. Following this definition leads us to exclude from the field of "modern biotechnology" the activities involving only the use of a living organism to produce a valuable good or service, as soon as this organism is considered as a "black box".

In this report we will now use the term biotech with the meaning of "modern biotechnology".

"Biotechnology sector" vs. "Technico-economic dynamics based on the development and diffusion of biotechnology"

The purpose of the study being an economic analysis of the **sector**[2] of biotechnology in India, a functional definition of this sector was needed.

Traditionally, a sector is defined by a certain kind of product. And the company with assets dedicated to the development production or marketing of this product are usually classified in this sector. Considering such a product, it is possible to list all the inputs that were used to produce the final good. This defines a **value chain** that can be represented as arborescence. In this arborescence, the nodes represent a certain operation with upward links representing each input of the operation, and the unique downward link representing the output of this operation that will be considered as input for another operation of the value chain or as the final product.

In traditional sectors, those sequences of operations are well settled, and some groups of operations are taken in charge together by the firms. This grouping of subsequent operations is called vertical integration. There are usually a few models of vertical integration in a traditional value chain, and the number of companies with the same model and at the same level on the value chain defines the intensity of the competition on this vertical segment of the sector.

In the case of biotechnology, we have to define the sector through inputs and not outputs. Indeed, the intuitive definition of a biotech company is the one of a company using biotechnology. In fact we will see that biotechnology can be an input in value chains with various kinds of final products. Therefore we think that rather than studying a hypothetical "biotech sector" in India, the purpose of our work should be to study the

[2] The words in bold characters have a specific role in the reasoning, and a specific attention to the meaning associated to them has to be given.

reorganisation and creation of value chains that are occurring in India thanks to the availability of new technologies belonging to what we coined “modern biotechnologies”.

Indeed, our starting assumption is that the amount of new technologies now available puts a certain kind of Indian companies in a process of industrial **reorganisation**. By this, we mean that a large number of brand-new business opportunities have appeared, and new **business models** emerging from this evolution are being experimented. This situation can be opposed to the situation where well settled firms are in an environment of price competition with a rather fixed vertical segmentation of the value chain. In this situation, the innovation occurring in the sector can be interpreted as the enhancement of its performance by one of the actors, this change having no direct consequence on the business of the other actors, except the change in the production function of the innovator. In the case of the biotechnology, we have observed that the spreading of biotechnology is linked with profound change in the organization of existing firms, or with the apparition of new firms with original business models. The business model of a certain firm is basically described by the value chain it gets involved in, the stage of this value chain the firm takes in charge, and the kind of contracts it signs, those contracts defining the tasks of the firms as well as its type of revenues. This term is mainly used in the description of the new companies created in order to exploit the opportunities offered by the development of Internet[3]. In the case of the biotechnology-enabled drug discovery as in the case of Internet we observe that new companies are being created with original combinations of assets and modes of revenues. One of the goals of the study will then be to establish general trends in these emerging business models and to analyse the articulation between the Indian business models and the one found on similar value chains in the western countries

Therefore, the term biotechnology used to define a certain set of companies composing the "biotechnology sector" is rather vague. In our study, we prefer to talk about a certain number of **Dynamics**. These dynamics have to be understood as the dynamics of reorganisation and creation of firms as an answer to certain business opportunities that have appeared thanks to technological advances in the field of biotechnology. That is what we chose to call “Technico-economic dynamics based on the development and the

[3] **Business Models: Example of the World Wide Web.**
The term of business model is mainly used in the sector of Information Technology, where the advances in the technical capabilities of treatment and transfer of information have produced tremendous opportunities in the management of these flows of information. The World Wide Web gives the clearest examples of new opportunities made available by a technical advance. By reducing dramatically the costs of communication, the Internet has brought dramatic changes in various value chains and new intermediaries have appeared in traditional value chains with business models based on the enhancement of the former value chain thanks to the tools provided by the Internet. The business models of on-line brokerage and on-line Business-to-Business marketplace belong to this group. But the changes brought by the Internet may affect all sort of processes, and the combination of processes enabled by the Internet in an original way have given birth to business models totally specific to what is called the net economy. One can mention business models such as the Internet Portals, also called Infomediary, but also Communities, or Subscription Models which are new combinations of assets and modes of revenues which have emerged thanks to the Internet.

diffusion of biotechnology". It has to be noticed that the dynamics we study are specific to the Indian market, since they are directly determined by local factors such as the domestic demand, the local technology availability, as well the ability of the domestic firms to integrate new technologies.

Restricting the scope: healthcare sector & agricultural sector

The new technologies involved in these Dynamics are too numerous and too complex to make an inventory and new combinations of existing techniques are being developed constantly and applied to new fields, therefore, it is hardly possible to imagine a process-based categorization of the biotech sector.
The only first step that one can do in order to reduce the range of his investigation into this field is to establish a end-use based categorization.

The following categorization is proposed by Ernst & Young and it is the one adopted for this research.

Table 1. End-use based categorisation of biotechnology.

Healthcare biotechnology	Medicines
	Vaccines
	Diagnostics
	Gene therapy
Agricultural biotechnology	Hybrid seeds
	Biopesticides
	Biofertilizers
	Plant extraction
Industrial biotechnology	Industrial Enzymes
	Polymers
	Biofuels
	Fermentation Products
Environmental biotechnology	Effluent & Waste Water Management
	Bioremediation
	Biosensors
	Creation of Germplasms

Source : Ernst & Young "Biotechnology a primer"

At this stage, we can first note the simple fact that from the four latter segments, the HealthCare and Agricultural ones are the most talked about in the Indian and the international media. The agricultural biotechnology, with the apparition of genetically modified crops has raised many questions more or less rational around the world. But if the healthcare sector is so present in the news, this is for a more complex reason, indeed, the segment is the one were the most technical advances of scientific knowledge about our organism are inserting themselves in a well settled process of chemical innovation: drug discovery. This meeting of two highly complex disciplines has produced a requirement in technical specialization that has led to the explosion of the number of biotech companies located in a very restricted part of the value chain of Drug Discovery.

Regarding our goal of analyzing how new business models were emerging thanks to new opportunities opened by technological advances, focusing on these two segments was made because of the general structure of the industry: the cross over between Health-Care Biotech, Agricultural Biotech, and the other domains are rather scarce. This can be understood when considering the complexity and the specificity of the technologies in actions.

Structure of the report

Interviews were then carried out with research institutions and companies susceptible of being involved in technico-economic evolutions within the Health-Care and Agricultural segment. The amount of information available about the Health-Care sector is much higher than the one about the Agricultural sector. Therefore, for our in depth analysis of the dynamics, we focused on the one occurring in the Health-Care segment. The interviews realised allowed us to identify two main Dynamics in the health-care sector. Those main Dynamics are:

- The manufacturing and marketing by Indian companies of biogenerics, i.e. therapeutic proteins already on the Indian market and abroad.
- The insertion of Indian companies at different stages of the development chain of new drugs or vaccines.

The difference between the dynamics of these sub-segments relies both on legal and technical factors.

- Legal factors such as the process of drug approval and the Intellectual property regime.
- Technical factors from the technical organisation of the drug discovery and development chain.

The first chapter of the report presents the public environment of biotechnology in India. We perform a transversal analysis of the different tools of public action available to build a favourable background for the development of domestic biotechnology activity, and use facts from interviews with the public and private sector in the health care as well as the agricultural sector to study the policy currently implemented by the different entities constituting the Indian public power.

The Second chapter focuses on the analysis of the two dynamics mentioned earlier. We analyse the biogenerics sector, defining and assessing the sector, analysing the strategies of Indian firms already interviewed, as well as the impact of the Indian public policy on these strategies. Then we present an analysis of the main business models that can be found in India in the sector of non-integrated participation in the new drug development chain.

A. Public environment of the biotechnology in India

In this section, we first give a general description of the way the public environment can influence the growth of the biotechnology sector in India. Then we attempt to understand the mechanisms of interaction between the public research institutions and the companies with biotech activities using the results of the 60 interviews carried out.

As a set of technologies with a broad range of application domain, biotechnology is under the influence of the action of numerous public bodies. These actions basically relate to three main groups which are
(i) public expenditure,
(ii) regulation,
(iii)and public initiative.
The fields where public expenditure has a critical role to play in the development of a sector such as the biotechnology one are basically human resource development, public research, and infrastructure development. The second group of public action is gathered under the name of regulation, that is, the definition of the legal environment, for example concerning the protection of the intellectual property, but also the appointment of public agency in charge of the different control procedures, as well as the definition of the different fiscal, trade, and investment norms. The third group of public actions gathers the actions that have principally a role of acceleration of emergence of a certain type of institutions. These actions are implemented in order to accelerate the development of a certain kind of activities and to direct this development in a certain ways (geographical location, technical choices, etc…).

Biotechnology has been a highly politicised term in India as soon as in the early 80's, that is, long before the dynamics we studied were initiated.
The formulation of a policy of capabilities development in the field of biotechnology was initiated in 1980 with the implementation of India's Sixth Five Year Plan (1980-85) which proposed an effort in fields such as immunology, genetics, and communicable diseases. The document recommended the Council for Scientific and Industrial Research (CSIR) to ensure coordination of the different initiatives.
The National Biotechnology Board (NBTB), an official apex agency dedicated to biotechnology development, was set up in 1982. This board was chaired by a Member of the Planning Commission and had representation from the Department of Science and Technology (DST), Council for Scientific and Industrial Research (CSIR), Indian Council for Agricultural Research (ICAR), Indian Council for Medical Research (ICMR), Department of Atomic Energy (DAE), and University Grant Commission (UGC). The NBTB issued the "Long term Plan in Biotechnology for India" in 1983. This document identified priority areas such as self sufficiency in food, clothing and housing, adequate health and hygiene, provision of adequate energy and transportation, protection of environment, gainful employment, industrial growth and balance in international trade. We can notice that these objectives cover a far larger range than the one identified as basic demand from the companies interviewed for this study. In 1986, the NBTB was

replaced by an actual government body called the Department of Biotechnology, under the Ministry of Science and Technology. The department of biotechnology has conducted many programs since its creation. Nevertheless, it is not sufficient to describe the effort of the public sector in the field of biotechnology only through the initiatives of the DBT. Instead, let us recapitulate the main tools of public action:

- Public expenditure.
  - Human resource development
  - Public research.
  - Infrastructure development
- Public initiative.
  - Creation of BT Parks
  - Industry development financing.
  - Networking.
  - Promotion.
- Regulation.
  - Legal environment.
    - Intellectual property protection.
  - Control procedures.
    - Research practices control.
    - Bio-safety.
    - Drug approval.
  - Fiscal regulation.
  - Trade regulation.
    - Price control
    - Export-Import control
  - Investment regulation
    - Licensing system.
    - Norms for foreign investment.

In the following section, we will detail the use of these different tools by the Indian central and state governments to promote the growth of the BT sector. We will restrict the analysis to policies specific to biotechnology and will not for instance deal with policies, such as telecommunication and electricity networks development, that can also have an impact on the sector. Regulations with specific considerations about biotechnology activities, that is the protection of intellectual property and the control systems, are also discussed.

A.1. Description of the public action in the field of biotechnology

1.1. Public expenditure

Human resource development

The University Grants Commission (UGC) is responsible for the coordination, determination and maintenance of standards and for the release of grants. The Central Government is responsible for major policy relating to higher education. It provides grants to the UGC and establishes central universities in the country. The Central Government is also responsible for declaration of Educational Institutions as 'Deemed to be University' on the recommendation of the UGC. Presently there are sixteen (16) Central Universities and another Central University in Mizoram is planned. There are 37 Institutions which have been declared as Deemed to be Universities by the Govt. of India as per Section of the UGC Act, 1956.The State Governments are responsible for the establishment of State Universities and colleges, and provide plan grants for their development and non-plan grants for their maintenance. The coordination and cooperation between the Union and the States is brought about in the field of education through the Central Advisory Board of Education (CABE).

The DBT is promoting the development of specialized degrees, such as MSc in Biotechnology or bio-informatics in several institutions.
There are now 24 university proposing MSc degrees in Biotechnology : 1) University of Allahabad, Allahabad; (2) Banaras Hindu University, Varanasi; (3) Calicut University, Kerala; (4) Devi Ahilya Vishwavidyalaya, Indore; (5) G.B. Pant University of Agriculture & Technology, Pant Nagar; (6) Goa University, Goa, (7) Gujarat University, Ahmedabad; (8) Gulbarga University, Gulbarga, (9) Guru Jambheshwar University, Hisar; (10) Guru Nanak Dev University, Amritsar; (11) Himachal Pradesh University, Shimla; (12) University of Hyderabad, Hyderabad; (13) University of Jammu, Jammu; (14) Jawaharlal Nehru University, New Delhi; (15) Kumaun University, Nainital; (16) M. S. University of Baroda, Baroda; (17) Madurai Kamaraj University, Madurai; (18) University of North Bengal, Siliguri; (19) Punjab University, Chandigarh; (20) Pondicherry University, Pondicherry; (21) University of Pune, Pune; ((22)Punjabi University, Patiala; (23) Tezpur University, Tezpur (Assam); & (24) Thapar Institute of Engineering & Technology, Patiala.
Other programs with the Biotechnology mention are proposed in several universities:

- MSc.Agri/Veterinary/Forestry Biotechnology Programme being offered at Birsa Agricultural University, Ranchi.
- M.Sc. Agri. and M.V.Sc. Biotechnology Programme at G. B. Pant University of Agri & Technology, Pant Nagar;
- M.Sc. Agri. Biotechnology Programme at 1) Ch. Sarwan Kumar HP Krishi Vishvavidyalaya, Palampur; 2) Indira Gandhi Agricultural University, Raipur; 3) Marathwada Agricultural University, Parbhani (Maharashtra); & 4) Tamil Nadu Agricultural University, Coimbatore.
- M.Tech (Biotechnology) Programme at Anna University, Chennai.

Public Research:
The table presented hereunder shows the allocation of the main agencies responsible for financing and supporting research in biotechnology. The share of each budget actually dedicated to biotechnology research funding is not available. Nevertheless, one can see that during the last decade, a pronounced effort has been done to develop an efficient

public research network in the country. The budget of major agencies such as the CSIR, the DST, the ICAR, and the UGC were multiplied by a factor of 3 to 4 between 1990 and 2000. One may notice that the budget of the DBT is rather low, and the increase of its budget was slower, the budget being roughly multiplied by 2 during the 90's. This does not mean that Biotechnology was not a priority in the general scientific policy, indeed, the institutes affiliated directly to the DBT represent a minority of the population of Indian Institutes working in this field. Nevertheless, it shows that the management of public research in biotechnology was not centralised at the DBT level, the role of this agency being regarded more as a role of coordination.

Table 2. Budgetary allocations of major funding agencies (Rs. Million)

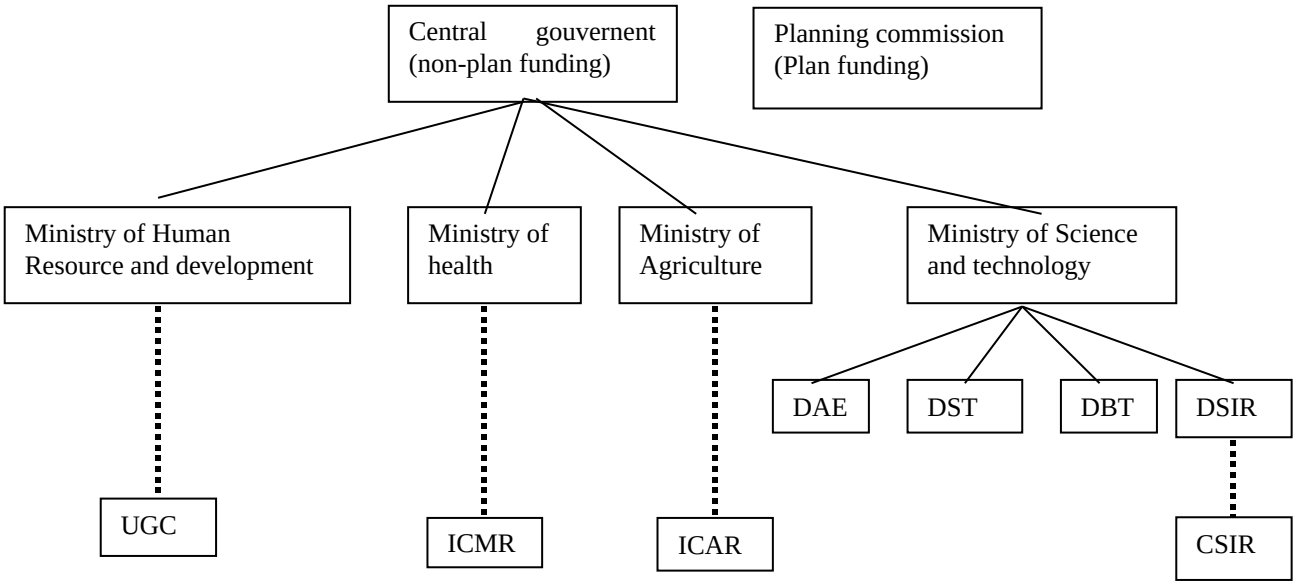
Agencies names	1990/91	2000/01	Growth (%)
Department of Scientific and Industrial Research (DSIR)	131	584	446
Council of Scientific and Industrial Research (CSIR)	2351	9120	388
Department of Science and Technology (DST)	2589	7798	301
Department of Biotechnology (DBT)	655	1391	212
Indian Council of Agricultural Research (ICAR)	3236	13990	432
Indian Council of Agricultural research (ICMR)	396	1470	371
University Grants Commission (UGC)	3495	14070	403

Source : RIS based on budgetary papers of relevant years, Ministry of Finance, Government of India.

The DBT is the only agency fully dedicated to biotechnology, and it is hard to assess the share of the presented allocations from the other institutions that have been dedicated to biotechnology.

Chart 1 attempts at giving an idea of the affiliation of these different entities.

Chart 1. Administrative organisation of the main public agencies involved in the funding of public research.



The funding of all these institutions is composed of plan funding, fixed in the main document of each five-year plan issued by the planning commission, and complementary non plan funding fixed by the government in its annual budget.

While the DAE, DST, DBT and DSIR are full fledged government bodies, the UGC, ICMR, ICAR and CSIR are independent bodies affiliated respectively to the ministry of human resource and development, ministry of health, ministry of agriculture, and department of scientific and industrial research - ministry of science and technology.
Those different entities have several programs and autonomous research centres under their supervision.
Under the supervision of the DBT are five research institutions: The National Institute of Immunology (NII), New Delhi, the National Centre for Cell Science (NCCS) Pune, the National Brain Research Centre (NBRC), the National Centre for Plant Genome Research (NCPGR) New Delhi, the Centre for DNA Fingerprinting and Diagnostics (CDFD) Hyderabad.
Although biotechnology can be part of the research of numerous labs, at least seven CSIR laboratories are involved in biotechnology related research: the Centre For Biochemical Technology (CBT) Delhi, the Centre for Cellular and Molecular Biology (CCMB) Hyderabad, the Indian Institute of Chemical Technology (IICT) Hyderabad, the Central Drug Research Institute (CDRI) Lucknow, the Institute of Microbial technology (IMT) Chandigarh, the Indian Institute of Chemical Biology (IICB) Calcutta and the Central Food Technological Research Institute (CFTRI) Mysore.

The Tata Institute of Fundamental Research (TFIR), which is funded by the department of Atomic Energy (DAE) has established the National Centre for Biological Science (NCBS) in Bangalore, which carries out basic research in biological sciences.
The Indian Council of Medical Research (ICMR) has established four centres for developing molecular medicine at Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS) New Delhi,, All India Institute of Medical Sciences (AIIMS), Lucknow, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh and Jawaharlal Nehru University (JNU), New Delhi.
The Indian Council of Agricultural Research (ICAR) has established a National Research Centre on Plant Biotechnology (NRCPB) at the Indian Agricultural Research Institute (IARI), Pusa.
Various other research programs are carried out in other institutions such as the IISc Bangalore or JNU in Delhi with funds from the public bodies mentioned earlier as well as grants from foreign foundations such as the Rockefeller foundation or the Bill and Melinda Gates foundation, and collaborative programs for research promotion between India and foreign countries such as France, Swiss, Netherlands, Germany, etc…
Some of the universities with the most active department in Biotechnology are : Jawaharlal Nehru University, New Delhi; Indian Institute of Science, Bangalore; Madurai Kamraj University, Madurai ; Bose Institute, Calcutta; University of Pune , Pune; M.S. University, Baroda; Osmania University, Hyderabad.
The dynamism of these different institutions is studied in section 2 through the results of interviews regarding the public-private partnerships the Indian companies interviewed were involved in.

1.2. Regulation

The research and development in biotechnology needs certain rules to be clearly fixed in order to reach its optimal level in a certain country. The first rule that needs to be fixed for the private as well as public research to have a reasonable incentive to invest in research leading to economic application is the rule of intellectual property protection. But, the application of biotechnology to such fields as alimentation and health raises important ethic questions and the politics are necessarily asked by the society to fix certain rules concerning the orientation and the methodology of the R&D in these fields. The controls imposed for these reasons have a critical importance on the business of the different companies and institutions involved in this type of research, since their standards and procedures will have a major influence on the costs of development. We will expose in this section the different aspects of the Indian regulation having an influence on the research activities in the field of biotechnology and their more recent evolutions.

Intellectual property

History of intellectual property protection

The problems arising from the lack of international regulation were acknowledged from the nineteenth century, a period of rapid technological progress. The problems the inventors had to face when applying for a patent in different countries led to the refusal of many of them to take part in the International Exhibition of Inventions in Vienna in 1873.

The subsequent Congress of Vienna for Patent Reforms, held the same year established the first principles of international patent protection. These principles were laid down in the first draft of such an agreement at the International Conference on Industrial Property in Paris in 1880, and the Treaty now called the Paris Convention for the Protection of Industrial Property (Paris Convention) was approved and signed in 1883. The Paris Convention was revised several times and lastly amended in 1979 is now the base on which the international agreements from the WTO are based.

Intellectual property regime in India

Indian intellectual property regime has witnessed its most important change in 1970[4]. The 1970 Act was designed to facilitate cheap technology acquisition and to enhance technological self reliance. It differed from the Paris Convention Standards in three main areas: patent protection, period of protection, and importation of patented products. In the case of food, chemicals, and pharmaceuticals, the 1970 Act restricted the range of patent protection concerning drug, food, and chemicals to only process patents. Namely, this excluded from protection the patents on products themselves. This legal background has been the starting point for the development of the Indian pharmaceutical industry that used reverse engineering competencies to develop generic drugs destined to the Indian market[5].

The length of patent protection provided under the 1970 Act was of 7 years for food, chemicals, and pharmaceuticals and of fourteen years for the other products, another difference from the Paris convention that granted a twenty year protection for all kind of products.

Concerning the statute of the importation of patented goods, the 1970 Act did not recognize the importation of patented goods as sufficient for the working of the patent[6] and permitted the revocation of the patent in such a case.

As a consequence of these provisions, India was not part of the Paris convention, for several years. However, as part of the founder countries of the WTO in 1995, India had to sign the Agreements regarding Trade Related Aspects of Intellectual Property Rights (TRIPs). [7]

These agreements negotiated as part of the Uruguay Round became effective with the creation of the WTO on the 1st January 1995. It requires all the members of the WTO to

[4] The first Indian legislation on intellectual property was enacted by the colonial government in 1856 with the ACT VI of 1856 amended with the act XV of 1859.
The period of protection was then of 14 years from the time of submission. Nevertheless, the office of the Controller of Patents was only created in 1911 under the Indian Patents and Designs Act, with the mission of examining and granting patents.
After independence, work to reform the 1911 Act began as early as 1948 with the appointment of a committee. A second committee was appointed in 1957, and its recommendations constituted the basis of the radical changes brought by the Indian Patent Act of 1970.

[5] Ref: for a history of the development of the Indian Pharmaceutical Industry: Ramani S.V., Venkataramani M.S., 2001. Rising to the technological challenge: possibilities for integration of biotechnology in the Indian pharmaceutical industry. *Int. Journal of Biotechnology, Vol 3., Nos. 1/2, 2001.*

[6] To be enforced, a property right granted by a patent has to be the object of an relevant attempt of exploitation. The commercial exploitation of a certain patent in a certain area is called the local working of the patent. The precise definition of the local working of a patent is subject to controversy.

[7] WTO, 1994. TRIPS: Agreement on trade-related aspects of intellectual property rights. *Annex 1C of the Marrakesh Agreement establishing the world Trade Organization, 15 April 1994.*

comply with the most recent version of the Paris Convention for the Protection of Industrial Property.
Developing nations were given a ten year period to harmonise their domestic laws and institutions with the WTO standards. India has now to comply with all the provisions of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) before the 1st of January 2005.
The main elements of these provisions are :

- Enforcement of product patent protection in all branches of technology, including drugs.
- 20 years of protection instead of 14 or 7 in the case of the Indian patent Act.
- No discrimination between imported and domestic products.
- Compulsory licensing[8].

The first amendment in this direction was adopted in March 1999, it establishes a "mailbox facility" for accepting product patent applications for pharmaceuticals during the pipeline protection period from 1.1.1995 to 31.12.2004. A new amendment has been recently adopted to confirm the evolution of Indian patenting environment toward the WTO standards.

The debate on generic drugs

Generics drugs - chemical as well as biological – are at the centre of one of the fiercest debate of the international scene. On one side, the pharmaceutical companies defend their right to be rewarded for their innovation and insist on the necessity of setting strong incentives for innovation through the settlement of a strict and global enforcement of the Intellectual Property Rights (IPR). The WTO has followed this logic while elaborating the TRIPS. On the other side, the poorest countries are denouncing a system which allows private firms to sell at a monopoly price a product that can save lives, such as tri-therapies for AIDS or antibiotics. Indeed, in the absence of any national health system in those countries, the monopoly prices adopted by the patent owning companies simply prevent most of the people to buy the medicines. By signing the TRIPs agreements without insuring the development of an efficient health system, the leaders of the poorest nations take a risky bet. Once the TRIPs agreements in action, either they will be able to exploit the flexibility of the international regulation to import or produce generic drugs, either they will have to face the discontent of the local populations deprived from life saving drugs. The most optimistic view is that the TRIPs will allow multinational pharmaceutical firms to invest in, or to collaborate with research and production unities based in developing countries, and doing so, reducing dramatically the cost of drugs.

[8] The Compulsory Licensing provision: it is stipulated in the TRIPs agreement that in certain situations of national emergency, certain patents can be subject to compulsory licensing. This means that the owner of the patent has the obligation to propose licensing for this patent at a reasonable cost. This provision is the cause of many uncertainties concerning the actual enforcement of intellectual property on certain drugs. Indeed, many people argue that AIDS epidemic in most developing countries should be considered as a situation of emergency. This would justify the enforcement of the Compulsory Licensing provision. More over, the judges of what is a “reasonable cost” should be the concerned states. Therefore, Compulsory Licensing could be a way for certain states to impose the selling of a license on recent AIDS therapies at a low cost to national pharmaceutical companies. More likely, the lack of agreement between the states and the companies would allow the state to neglect the protection on the patent and allow domestic company to produce a similar drug if they succeed in developing it.

In this debate, India occupies a very special position. Indeed, India is already both one of the largest market for generic drugs, and the Indian pharmaceutical Industry is the world largest exporter of generic drugs, the strategy of copying of existing companies adopted by Indian companies being considered by most of the Western Pharmaceutical companies as piracy. The potential strategies of the Indian Pharmaceutical Companies are presented in part B. in the analysis of the dynamics of integration by the Indian Industry of the new technology of production of recombinant proteins and genomics-based drug discovery.

Controls:

R&D activities control

The DBT as well as the state-level departments of biotechnology pursue an objective of "single window agency". Following recommendations from the Confederation of Indian Industries (CII), the DBT has established a simplified process for the treatment of new applications concerning new research projects by the different committees (Review committee on genetic Manipulation (RCGM), Genetic Engineering Approval Committee (GEAC), Drugs & Pharma Approval Committee (DPAC), and Biotech Foods Approval Committee (BFAC)). Similarly, the state governments are developing simplified procedures of examinations for new applications, such as applications for the settlement of a biotech manufacturing plant.

Drug approval:

In the case of biogenerics, not only the Indian approval process but the specific process of each country representing a potential market for the Indian companies has to be taken into account. Opening the world largest market, and being one of the most rigorous approval process, the United States Food and Drugs Administration (U.S.–FDA) system of drug approval is used as a reference for the Indian companies having a global strategy.
On the government side, the Union minister of health & family welfare has recently claimed its desire to see the central drug organisation evolving in the pattern of the US-FDA.

Chart 2. US-FDA System of drug approval

Clinical Trials

	Discovery/ Preclinical Testing		Phase I	Phase II	Phase III		FDA		Phase IV
Years	**6.5**		**1.5**	**2**	**3.5**		**1.5***	**15 Total**	
Test Population	Laboratory & animal studies	**File IND at FDA**	20 to 100 healthy volunteers	100 to 500 patient volunteers	1,000 to 5,000 patient volunteers	**File NDA at FDA**	Review process/ approval		Additional post-marketing Testing required By FDA
Purpose	Access safety, biological activity and formulations		Determine safety And dosage	Evaluate Effectiveness, Look for side effects	Confirm effectiveness, monitor adverse Reactions from Long-term use				
Success Rate	5,000 compounds evaluated		5 enter trials				1 approved		

A committee headed by director-general of the Indian Council for Medical Research (ICMR) was set up to evaluate new drug applications, while biotech-based drugs are to be under another expert panel. However, it remains a fact that there is a need for modernization of the central drug control organization. Whereas FDA approvals demand a important fee from the submitting companies and have clear defined time limits, the Drug Controller General of Indian only asks for a fee of Rs. 15 and the review can last for an indeterminate time, "Scanty staff and budget hamper the central drug organization" declared the minister of health.

The function to ensure safety, efficacy and quality of drugs supplied to the public is performed by the Central Drugs Standard Control Organisation (CDSCO), DGHS, Ministry of Health and Family Welfare with the Drug Controller General of India (DCGI) as the executive head.

Indian Prime Minister commissioned All India Biotech Association in June 2000 to analyse why Biotech industry growth had been poor in spite of a $500 million expenditure by the government in the last 15 years. The resulting report identified the drug approval system as the main constraint leading to a sluggish growth of the Biotech Industry. Compared to the US-FDA system, the Indian system is complex with various stages of control by various regional, sectoral and central committees. Moreover, whereas the US-FDA simply oversees the clinical trial process, its Indian counterpart, the Drug Controller General of India has to provide several clearances for allowing the clinical trial process to go on. These rigid procedures combined to a lack of manpower and infrastructure cause very long clearance processes.

At the same time a Pharmaceutical Research and Development Committee (PRDC) was set up under the chairmanship of Dr. R.A. Mashelkar, Director General, CSIR to study and identify the measures needed to strengthen R & D base of the Indian pharmaceutical industry. This committee recognised that the manpower and infrastructure facilities of

CDSCO did not allowed it to keep pace with the growing amount of clearance demand. Therefore it recommended increasing the means of this body, thanks to an increase of the fees at each stage of trial (these fees had remained at the same level since 1945). In return, the CDSCO should commit in respecting a strict program schedule.

Those different recommendations were taken into account by the minister of health and the DCGI (executive head of CDSCO). In 2001 the Union Minister for Health & Family Welfare disclosed a plan to bring the DGCI on par with the US-FDA in terms of efficiency. The plan included strengthening the regulatory body by training as well as additional manpower, augmenting testing facilities across the country, as well as modernisation and computerisation of the existing structures. The DCGI also issued guidelines for Good Clinical Practice (GCP) that insisted hospitals and investigators to meet certain criteria in order to qualify for clinical trials. These GCP guidelines, prepared by mostly in the lines of the USFDA norms, aim to enhance the quality and international acceptability of clinical trials conducted in the country.

Finally, the patterns towards the formation of an integrated national drug authority with extensive means of actions have been set by the *Pharmaceutical Policy 2002*, reviewing the *Drug Policy 1896*.

1.3. Public initiative

Public action is not restricted to the setting of rules and generation of public goods[9]. A political will to prioritize certain type of activities can emerge, and an "industrial policy" can be implemented. Within this gridline, the role of public action is to accelerate the building of a certain kind of institutions which are to evolve in independent institutions on a longer term. This kind of strategy is well known from the most industrialised countries which have started in the last decade to implement programs of public initiatives with a view of enhancing their respective "National Innovation Systems". These Systems are defined as "a set of institutions whose interactions determine the innovative performance of national firms" (Nelson, 1993[10]). In the section about public expenditure, we have presented the actions that the public powers have to take in charge because of problems of incentives. These problems of incentives refer to the representation of education and basic research as public goods, and the incentives lacking are the one for private investors to invest in the production of public goods. In this section, we present actions taken in charge to answer to problems of coordination. This lack of coordination is the one faced by an emerging industry, while trying to set up the autonomous institutions constituting the necessary nodes of the Regional Innovation Systems. Those institutions can be in charge of gathering the funds for new ventures,

[9] A public good is characterised both by its non-rivalry and its non-excludability. A good is non-rival when it can be used by several agents without the use of the good by any agent decreasing the utility the other agents can derive from the use of the same good. A good is considered as non-excludable when it is not possible or very costly to exclude anyone from the use of this good.

[10] Nelson, R. (ed.) (1993) National Innovation Systems, A Comparative Analysis, Oxford University Press, New York/Oxford.

developing the image of the national industry abroad, gathering information about the different companies, organizing events, etc…

Industry funding

As an innovative and emerging industry with high initial needs in investment, biotechnology's development is highly dependent from the availability of funds for projects at an early stage. Several schemes exist for private funding of such projects in the western countries. Funds are collected through mutual funds and venture funds, and there are now specialised funds investing in biotechnology at various stage of development, from the earliest days (seed capital) to the Initial Public Offer (IPO). Public schemes are also in place in certain countries such as USA, where Small Business Innovation Grants have attracted several entrepreneurs carrying biotech projects. In France, the National Association for Research Valorisation and Application (ANVAR) grants special tax holydays and loans to innovative projects.

In India, it was observed that venture capital has only played a marginal role so far in the funding of new projects. Indeed, most of the projects were promoted by existing industrial groups or by private investment from the promoter and some of their relatives or friends. Out of the 41 companies interviewed, four companies declared having received the support of a venture fund: Avesthagen and Bangalore Genei received a support from ICICI, Bharat was funded by IDBI, and XCyton by SIDBI. 7 Other projects initiated recently were funded by private investors: Bhat Biotech, Bigtec, Metahelix, Genotypics, Strand Genomics, CDC Linux, and Yashraj. The other projects were promoted by already settled companies.

This makes analysts think that the potential for Venture Capital in the Indian biotechnology industry is not realised.[11]

The venture capital investments for all sectors in India at Rs. 10 billions as on 1997 represented 0.1 percent of GDP, as compared to 5.5 percent in areas such as Hong Kong. The venture capital industry is dominated by public sector financial institutions such as Industrial Development Bank of India (IDBI), Small Industry Development Bank Development Bank of India (SIDBI), Industrial Credit and Investment Corporation of India (ICICI), Industrial Finance Corporation of India (IFCI)... A few private sector venture capital firms have been set up recently. At present there are about fifteen venture capital funds in India which have provided venture finance of over Rs. 4.6 billions to several ventures in various sectors.

Some actors such as ICICI and Unit Trust of India (UTI) have shown a strong interest for biotechnology project and are developing dedicated capabilities for the assessment of ventures of this kind. Nevertheless entrepreneurs see the Indian Venture Capital Funds as too much risk adverse, and lacking the technical knowledge that would enable them to propose good conditions of funding.

[11] References:

- Annual Report of Indian Venture Capital Association-2001.
- AIBA, 2000. Biotechnology Parks in the context of Indian Biotechnology Industry. An analysis of the sluggish Growth of Indian Biotechnology Industry. A plan for Remediation in the Context of Global Biotechnology. An Agenda For Action. *Report edited by AIBA in November 2000.*

From the public side, institutions such as the CSIR, the Technology development board (TDB)– under the department of science and technology -, and the Biotech Consortium of India Limited – an Independent institution promoted by the department of biotechnology – who have the mission to develop technology transfer from public research to the industry also provide some financial help to innovative private projects in the field of biotechnology. The lack of awareness of the companies about those sources of financing, as well as the fear of an administrative and rigid monitoring from the financing bodies can explain the scarcity of such public participation in private ventures.

Networking, promotion (IABA, DBT, BCIL, Karnataka vision group, CII)

Several entities are involved in the networking and the promotion of the India Biotech Community.

The department of biotechnology (DBT) organises conferences and meetings.

Biotech Consortium India Limited (BCIL) was set up in 1990 as a public limited company, with the objective of providing the linkages amongst research institutions, industry, government and funding institutions, to facilitate accelerated commercialisation of biotechnology. Promoted by the Department of Biotechnology (DBT), Government of India, its core capital of Rs. 5.37 Crores has been contributed mainly by the All India Financial Institutions, IDBI, ICICI, IFCI, UTI and IFCI Venture Capital Funds Limited and the corporate sector including Ranbaxy Laboratories, Cadila Laboratories, Glaxo India, SPIC etc. The BCIL issues regularly a Directory of Indian Biotech Industries and Institutions in India, as well as market studies in fields such as diagnostics and aquaculture.

All India Biotech Association (AIBA) was established in 1994 as a non-profit Society to provide common Apex forum at the national level to represent the interests of all those engaged in various aspects of Biotechnology. Since its creation, the association has organised a few seminars and the Prime Minister recently appointed the association to carry out a preliminary study for the funding by the World Bank of Biotech Park projects in India[12]. Nevertheless, this institution is not perceived by the industrial as an active networking element.

The state of Karnataka has established a Karnataka Biotech Vision group, in charge of carrying out studies and formulating policy recommendations. This group is composed of employees from the Karnataka ministry of IT and BT, as well as personalities from the academic and corporate world, the recommendations formulated by the Karnataka Vision Group constituted the core of the *Millennium Biotech Policy* issued by the government of Karnataka in 2001. An independent body, the Karnataka Biotechnology Development Council (KBDC) has then been appointed by the government to implement this policy.

In 2002, Bangalore Bio, a biotech congress organized by the state of Karnataka gathered the main players of the sector. The Karnataka Vision Group is also involved in India's main national event in the Field of Biotechnology: Bangalore Bio, organised each year in April in Bangalore.

[12] AIBA, 2000. Biotechnology Parks in the context of Indian Biotechnology Industry. An analysis of the sluggish Growth of Indian Biotechnology Industry. A plan for Remediation in the Context of Global Biotechnology. An Agenda for Action. *Report edited by AIBA in November 2000.*

The Confederation of Indian Industries (CII) is another institution involved in networking the Indian Biotech industry. The CII is in charge of industrial lobbying in all sectors, a specific deputy director, Dr Sandhya Tewari has been appointed to the biotechnology sector. The CII has recently a book on Opportunities in Biotechnology in India[13]. The confederation is also involved in the organisation of a national event about biotechnology called Biotech India 2003 in February 2003 in New Delhi.

Those profiles show the diversity of the different institutions involved in the networking and promotion of the Indian Biotech industry. Those profiles differ by their statute, and range of action. We can find government bodies at the central level (DBT) as well as the state level (Ministry of IT & BT, govt of Karnataka). We can find associations promoted by industrials such as the AIBA, which is specific to biotechnology, and the CII, which is a generalist confederation. We can also find autonomous bodies set up by governments such as the BCIL and the KBDC. Among those different entities, it is difficult to establish a clear repartition of tasks.
We can compare this situation to the one of the Information Technology. In this case, we also have dedicated government bodies at the central level (Ministry of Information Technology (MIT), and at the state level in the most dynamic states. The main difference lies in the existence of a recognise organisation representing the industry: the NASSCOM. This organisation takes in charge most of the roles mentioned earlier, i.e. gathering information about the industry, organising events, promoting the "India brand" abroad, proposing measures to be taken by the governments, etc…
The emergence of such a single representative body for the biotech industry would surely help to its development.

BT parks
The idea of BT parks is directly derived from the successful experience of the IT parks: those parks offer privileged conditions to the companies implanted within their location. Those advantages can take the form of good infrastructures for water and electrical supply, air treatment, etc… as well as special regulatory schemes[14]. From the point of view of the public power, the concentration of companies of a same type in a limited area allows to maximise the local externalities and to experiment more easily specific regulatory schemes. Therefore, more than a certain kind of public action, the settlement of a BT park is a way to enhance the efficiency of focused policies by gathering the companies of the targeted sector in a restricted geographical area.
Several projects of biotech parks have been launched by public authorities.
At the central level, the creation of biotechnology parks has been identified as the thrust area of pro-industry intervention for the DBT, whose action had been previously mainly directed towards education and research.
At the State level, the States of Andhra Pradesh, Karnataka, and Tamil Nadu, which have issued biotechnology policy papers, have included the creation of biotechnology parks in their agenda.

[13] Sandhya Tewari (Ed.), 2001, Opportunities in Biotechnology, Edited by CII.
[14] In the case of the IT, such areas have been created where the software exporting companies can benefit from tax holydays, duty exemption, process simplification, etc… the most widespread models are the one of the Special Economic Zones (SEZs) and Export Processing Zones (EPZs)

The biotech park of Hyderabad, in Andhra Pradesh presents the most advanced stage of realisation. The SP Biotech Park is a joint venture between Shapoorji Pallonji & Company Limited & the Government of Andhra Pradesh (11 % of the shares are owned by the govt. of AP, the government's contribution consists mainly in 140 Acres of Land conceded to the JV). The JV was set up in September 2001. The work started in March 2002 and the park is expected to be operational by October 2002. Almost 50% of the space is already booked.
One pharmaceutical company, Biological E., interviewed in Hyderabad has planned to settle in this biotech park. The company will create new infrastructure for vaccine production in the Hyderabad BT Park and perceives the infrastructure and the environment proposed by the Park as very convenient. It is important to mention that a BT park has to comply with certain characteristics, such as air treatment. These are not required for IT parks which mostly need good electricity supply, telephonic and physical connectivity. The cases of the Institute of Bioinformatics and Applied Biotechnology (IBAB) and of the genomics company Avesthagen illustrate this fact. The institute and the company both have settled in the buildings of the International Tech Park. The International Tech Park is a technologic park dedicated to companies involved in high tech activities located in the near suburbs of Bangalore. This location, though attractive for high tech companies and institutions, is not completely adapted to biotech activities. We can therefore notice the interest of biotech companies for parks dedicated to high technology taking into account their specific requirement.

1.4. Concluding remarks and recommendations

Comparison of the policy demands from the Information Technology and Biotechnology sectors.

While studying the policy statements made at various levels concerning the development of the Indian Biotech sector, one can notice the widespread ambition of reproducing the scheme that has allowed the Indian Software Industry to become a national success during the 90's.
It is argued that the Information Technology and the BT sector present similar characteristics. Both are a set of technologies with applications in various domains. But from the point of view of public-private interaction, Information Technology and Biotechnology present some important differences. Nevertheless, as the Information Technology industry as already reached an advanced stage of development in India, it is an interesting comparative example to study.

Let us describe briefly the main trends of public-private interactions in the field of Information Technology. The Indian software industry witnessed a tremendous growth during the last fifteen years. This growth was surely highly dependent from the reform of the licensing system initiated in 1991, but many public initiatives have enhanced this growth potential.
In terms of institutions, the public-private relation is highly oriented towards the bipolar organisations representing the central government and the industry in this field, namely, the department of information technology from the central ministry for communications and information technology, and the national association of software and services

company (NASSCOM). This channel of interaction has been the main force pushing towards pro-active policy making for several years, and many schemes have been implemented.

The highest demand for policy improvement from the information technology industry was:

- Public expenditure in infrastructure for the improvement of bandwidth, electricity supply, etc…
- Public expenditure in human resource development, that is an tremendous increase of the number of graduates able to join IT companies (BSc, MSc)
- Adaptation of the fiscal regulation to promote exports of IT services and products and to increase incentives on IT investment. For example, Special Economic Zones (SEZ) have been created, in which software exporting companies are allowed to operate with simplified procedures and tax holydays.

It seems that the specificity of biotechnology implies a different set of policy demands.

- The special regime of intellectual property applied to the food, chemical and pharmaceutical products by the Indian patent Act of 1970 puts India in a very singular position on the international biotechnology scene, given the importance of therapeutic application of the biotechnology
- Private biotechnology firms seem to be more demanding than IT firms in highly skilled scientists, i.e. PhDs or Higher level.
- Given the high politicisation of fields of application of biotechnology such as agriculture and health, the control procedures and the organisation of the public bodies in charge of these controls have a tremendous influence on the functioning of the biotechnology firms. Indeed, these elements determine the time and effort those companies have to invest in order the comply to the different standards and obtain the required approval.

Strength and weaknesses of the public environment of the Biotechnology

Generally, The public action in the field of biotechnology is characterised by the diversity of the agencies in charge of the different sides of this action: public expenditure, public initiative, and regulation. In India, the interest of the political sphere for the domestic development of biotechnology as a growth driver was initiated in the early 80's and many institutions have been set up in order to manage this development. The sector is now facing difficulties due to the complexity and the administrative of this institutional system. Nevertheless, we can say that after a period of experimentation, India is streamlining its institutional environment for biotechnology, as illustrated by growing success of the concept of "single window agency". The country already has strong assets for the development of a competitive and innovative industry with a countrywide network of research institutions. These institutions have a recognised academic level, bur the question is now to know how well these institutions are able to transfer their knowledge to the industry, either by institutional collaboration, or by the direct migration of scientists from the public to the private sector. The analysis of the interviews realised with Indian Companies presented in the next section will give us a clue about this.

The last element of the public environment that will have, of course, a dramatic influence on the development of the biotech industry in India, is the enforcement of the TRIPs India has to comply with within the gridline of the WTO. Even if the texts have been accepted by the Indian parliament, the players of the sector still have diverging view concerning the scenario of implementation.

Policy recommendations

For the Indian Public powers:

Clear Intellectual Property Protection Scenario: India is now at the crossroads between several models of development of its biotechnology-based industries. The future evolution will mainly depend on the intellectual property protection (IPP) regime that will emerge from the convergence with the WTO standards. We believe that while taking the precautions necessary to protect the health of its citizens by warranting an access to cheap drugs, India can and must send a clear signal to the domestic and foreign companies involved in biotechnology research. This signal must reassure these companies about the risk of intellectual piracy they are running while entering into research collaborations with Indian partners.

Coordination between the efforts of central and state governments: States governments such as the one of Andhra Pradesh, Karnataka and Tamil Nadu are moving very fast in order to make their state become an attractive location for biotechnology based industries. Nevertheless, these effort need to be combined to a national effort to promote all India as a privileged location for high-value-added activities in biotechnology. The focus should be on the international competition for attracting such activities rather than on a inter-states competition.

Concerning the efforts at the different levels toward the creation of “single window” agencies, the utility of these agencies would be dramatically if they could coordinate the relations of biotech companies with the central as well as state agencies.

Radical tax and duties exemptions enhancing the competitiveness of India-based private research: All should be made during the ten next years to make India as attractive as possible for biotech research activities. A fast and easy process of certification of research units should be set up. This certification should grant extensive tax holydays and total duty exemption for the import of research equipment.

These recommendations aim to enhance the efficiency of the policies currently formulated. The state and central policies that put a stress on the development of Bt parks and biotech venture funds have to be sustained.

For the Indian biotech community as a whole:

Creation of a single representative association: The Indian biotech community needs a single representative association comparable to what the NASSCOM is for the Information technologies. This body has to be totally independent from the political sphere. Moreover, beyond the activities of information gathering, promotion abroad, lobbying, and events organisation that the NASSCOM takes in charge for the IT sector. This association should gather the biotech companies as well as the public research centres willing to market their technology. This organisation should take in charge the co-

ordination between private and public research in order to direct the efforts of public research in the most valuable direction.

Focused strategies: The different business models emerging from the diffusion of biotechnology in India have different determinants of growth. We believe that a reasonable action directed toward the support of the growth of the biotechnology-based industry should identify clearly on which technico-economic dynamics based on the biotechnology the measures to be implemented are supposed to have an influence.

A.2. Analysis of the interviews: Interactions between public research institutions and private companies in the field of modern biotechnology.

The sources used for this analysis are the interviews realised with 50 Indian companies and institutes from April to September 2002. We identified the interactions occurring between the companies interviewed and public institutions. By interaction, we mean both bilateral interactions such as incubation, platform sharing, or collaborative research, and unilateral interactions such as the creation of a company by a former scientist from a public institution, or the hiring by private companies of scientists trained in public institutions. In the first case, the interaction demands a specific involvement (formal or informal) from both sides. In the second case, the interaction demands no specific agreement between the institutions.

The first step toward such an analysis was to collect all the cases of such interactions that had been mentioned during the interviews.

The table hereunder give the exhaustive list of collaborations mentioned during the interview on which this study is based. Only the collaboration between Indian Companies and Indian Institutes are mentioned. Mentioned collaborations involving Indian companies and foreign institution are listed in the annex. Those 53 interactions involve 19 different companies and 27 names of institutions were mentioned. The table gives an exhaustive list of these interactions listed by the name of the company involved. The reader can find the details about each collaboration in the interview proceedings of each company. The striking fact while looking at this table is the number of collaboration the companies are involved in. 13 companies out of the 19 companies mentioned here have more than one partner. We think that this fact reveals that companies and institutions are still learning how to work together.

Table 3. Private – Public collaborations mentioned in the interviews.

Private Company Involved	Public Partners
Avesthagen	NCBS
	University of Agricultural Science
	ICRISAT
Bangalore Genei	CCMB
	IBA - ICAR
Bharat	DBT – AIIMS – NIH - CDC Atlanta - Stanford
	ICGEB - AIIMS
	CBT
Bigtec	IMT
Biological E.	CCMB
	IISC
	ICGEB
	Christian Medical College
CDC Linux	CSIR project team

Genotypic	CBT
	IISc
	Madhurai University
IAHS	NRCPB
Ingenovis	IICT - CCMB
	CCMB
Monsanto	IISc
	TERI
Nicholas Piramal	CBT
Rallis	ICGEB
	IISc
	University of Madurai
Shanta	Osmania University
	CCMB
	IISc
	JNU
	BARC
	CCMB
	AIIMS
	NII
	IICB
	Anna University
	Tata Memorial Hospital
	NDRI
SP Biotech Park	IICT
	CCMB
	CDFD
Strand Genomics	IISc
TCS	CSIR project team
	CDFD
Themis	CDRI
	IIT
	CBT
Wockhardt	ICGEB
Xcyton	NIMHNS
	IISc
	NIMHNS
	ICGEB
	AIIMS

Several dynamics of technico-economic evolutions involving the use of modern biotechnology were identified. The one considered in this section are the development of Products such as Genetically Modified Organisms (GMO), Diagnostics, or recombinant therapeutic proteins, and the development of technological tools and platforms in the field of genomics and bioinformatics. It was noticed from the case study that the interaction between private companies and public research institutions are influenced both by the nature of the technico-economic dynamic the company is involved in and by

the stage of development of the company. That is why we first present the kind of interaction between the public research and companies in their earliest stage of development, and then what kind of partnerships are required in the case of more developed companies.

2.1. Interactions in the earliest stage of development

Research institutions as pools of entrepreneurs:

In such a highly technical field as biotechnology, as well as in the pharmaceutical sector, the managerial positions are often occupied by professionals with a long technical experience in this domain. Consequently, one can wonder if the public research institutions constitute a pool of potential project leaders and entrepreneur for the private sector, or if instead, most of the managers of the new Indian biotech firms come from the corporate world. Therefore, we have studied the background of the managers of the firms interviewed in order to see if many of them have migrated from public research institutions.

From the interviews, there are three cases of entrepreneurs having migrated directly from positions as scientists in Indian public institutes to found their company.

- Bangalore Genei (molecular biology research products manufacturer) was founded by its managing director Dr. Babu who was formerly a professor at the Tata institute of fundamental Research (TIFR) in Mumbai.
- Strand Genomics (bioinformatics company) was founded as a spin-off from the Indian Institute of Science (IISc), Bangalore by four professors in computer science from the Institute.
- Avra Research (a chemical contract research organisation based in Hyderabad) was founded by Dr. Avra Rao, former director of the Indian Institute of Chemical Technology (IICT), Hyderabad.

Some companies may also choose to hire a scientist in order to start a certain project. Given the specification given by the company about the objective of the project, this project leader can be consider as an entrepreneur if his range of action is wide enough.

Non resident Indians (NRI) choosing to come back to India also play a critical role in the current development of the industry.

Avesthagen (Genomics) was created by Dr. Viloo Morawal – Patel who did her PhD in Strasbourg (IBMP). Bhat Biotech (Diagnostics) was promoted by Dr. Bhat, a professor at U-Penn who moved back to India. So did Dr. Krishna who was a molecular biologist specialised in yeast in the US and moved back to India in 1996 to create Bharat Biotech (recombinant therapeutics). The two promoters of Genotypic Technologies (microarrays technology) have completed their PhD in Molecular Biology in the University of Madhurai and did their Post-Doc in Israel and the US before coming back to India.

As shown by the cases of biotech entrepreneurs from the TIFR, the IISc, and the IICT ,the presence of research institutions of excellent level has an influence on the company creation. Nevertheless, the social standard represented by a non-resident Indian with at least one part of her/his higher education (PhD or PostDoc) as well as eventually a successful beginning of carrier abroad seems to be a widespread model in the managerial levels of the Indian biotech companies. We have quoted all the examples of entrepreneurs

we have met having started their venture directly after and academic experience, but not only the head of these companies have a role in the development of these firms, the quality of the other scientists with roles of project leaders is also critical to the success of the venture. We deal with this case in the section about the interactions between public institutions and companies in later stage of the firms' development. The same effect of return of highly skilled Non Resident Indian (NRI) to their home country as well has an effect on the recruiting policy of the developing biotech companies.

When thinking of the much talked about problem of brain drain that India is supposed to be facing, one should take this element into account: it is a fact that many NRI remain eager to come back to their home country even after a very successful beginning of carrier abroad, and this back draft can be seen as the source of a flow of entrepreneurship combined with high technical competency in from industrialised countries towards India.
One might wonder if biotech professionals with experience from a certain public institution keep privileged relations with these institutions. The case of AvesthaGen gives us a clue. The promoter of the company, Dr Viloo Patel has kept relation with its former institution, her former supervisor now belongs to the scientific advisory board of the company, and the company has sent employees recruited in India with a masters degree to do their PhD in this institution. The scientific networks constituted abroad have been mentioned as an important asset by several companies, and those networks can also act as private financing networks when foreign academics invest in Indian companies founded by their former colleagues. For example, the bioinformatics company Strand Genomics founded by a group of former professors from the IISc has benefited from the private financial support of Scientists from Indian and foreign institutions such as the Indian Institute of Technology or Stanford. Another embodiment of the scientific networks that scientists bring with them when they enter a biotech company is the composition of the scientific advisory board. These boards are consultative bodies, which are asked about the technological strategy of the firm. Although it is hard to assess the real involvement of the board's member in the firm's strategy building, a board including internationally renowned scientists is a marketing argument frequently used by the Indian companies.

Incubation and Platform Sharing: flexible support for emerging firms

Apart from being a potential pool of entrepreneurs, public institutions can also play a critical role in the early days of a new biotech project by offering a shelter for the new born project. This interaction, called incubation is relatively loosely defined. It consists generally in the provision of a working space and the possibility for the incubated company to use some equipment from the incubator institution. Avesthagen and Genotypic (Genomics), Shanta (recombinant therapeutics) and XCyton (Peptide-based Diagnostics) have used this model of collaboration:
When the promoter of **Avesthagen**, Dr Patel came back to India with her PhD from Strasbourg in 1995, she wanted to build a bridge between the public and private sector in the field of biotechnology R&D. The NCBS sheltered her activities from 1995, and she started with grants, working as an independent researcher. In 98 Dr Patel received funds from the CEFIPRA. The next year she shifted to the University of Agricultural Sciences

and tried to convince the two institutes to start an incubator. Only in 99 did she decide to go fully private.
As for **Genotypic Technology**, the company can be considered as being still at the stage of incubation. Indeed, the only proprietary equipment of the company are computer equipments (Linux & PC) sheltered in the promoters home, and all the research in wet lab are carried out in the lab of the IISc Bangalore and University of Madhurai (from which the promoters have obtained their PhD), the company also use the robot from the CBT in Delhi to built its microarrays.
Xcyton was as well incubated in a public institution: the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore. Since then, the company has started a successful business of peptide-based diagnostics (cf. p. 27)
In the case of **Shanta**, the Incubation took a different dimension, with a higher scientific implication of the incubating institutions. Namely, the company was founded by an electrical engineer without in depth competency in molecular biology, in order to answer to the growing demand for an indigenous recombinant vaccine for hepatitis B. The development of this vaccine was initiated under the form of research program carried out in public institutions: in 92 a small lab in Osmania University was dedicated to the project. In 93 the research shifted to the Centre for cellular and molecular biology (CCMB), and only in 95 an autonomous private lab was settled. The production of the recombinant vaccine finally started in 97.

Those four cases show how the relation between public institutions and emerging companies can take place at a very early stage of a project. It also shows the diversity of the models of collaboration that can take place. Indeed, the case of Avesthagen, Genotypic and XCyton give an example of projects led by promoters with a highly specific competency, and who mainly need a logistic support and the access to some specific equipment. The partnership that takes place can be continued in the later stage of the development of the company under the form of a platform sharing. In the case of Shanta, the project is demand driven, and the incubation is a derived form of contract development.
The offer of incubation services is considered as a critical factor for the enhancement of the rhythm of company creation in the field of biotechnology. That is why the creation of an incubator is part of the various projects of Biotech Park in India (Bangalore, Chennai, Hyderabad…). In the case of Hyderabad, the incubator is being set up in collaboration by the biotech park - a joint venture between the state of Andhra Pradesh – and the Indian Institute of Chemical Technology (IICT).

2.2. Interactions at an advanced stage of development of the companies

A multitude of models exist for the interaction between a public institute with a certain technological competency, and a firm eager to use this competency. First, research institutions can take profit of a technology already developed by transferring or licensing it to the industry. The industry can also use the research capacity available in the research institutions through contract research or collaborative research. Institutions can also

support private companies by signing memorandum of understanding for competency sharing or by providing specific training to newly hired people from a certain company.

The difference between what will be called technology transfer, licensing, contract research, collaborative research, competency sharing agreement, training services is based on a few basic elements: the nature of the exchange, the precision of the contract defining this exchange, the entity taking the initiative of technology development. The case studies highlight that the form of competency trading is highly dependent from the technical level of the stakeholders and the repartition of this level can vary between two technological sub sectors.

Development of genetically modified organisms[15]: a privileged field for technology transfer

This kind of R&D involves a strong capability in plant tissue culture, and hybrid testing in greenhouse and field. These companies have developed research programs in order to develop a capability in genetic engineering, and they have small teams of scientists working on molecular biology in house. Nevertheless, the chance of coming up with a new gene are quite low in such kind of research, and in parallel to their internal competency building, those company are interested in acquiring interesting genes isolated by public institutions. When a research centre comes up with a gene interesting such a company, the preferred scheme of interaction will be a technology transfer with licensing: the technology will be transferred either under the form of information about the gene (sequence, access code, etc…) or the gene itself, cloned or already inserted in a vector.

Once the technology is transferred, the company will continue the process of insertion of the gene in the desired organism and in case of a successful commercial application, the institution would receive royalties.

Rallis and Indo-American Seeds are two Indian Seeds Company involved in conventional R&D in plant hybridation.

Indo American Seeds Company has had two such technology transfer from a research institute in Singapore and from the National Research Centre for Plant Biotechnology (NRCPB), a lab from the Indian Agricultural Research Institute (IARI), New Delhi.

[15] **Genetically modified Organisms: a primer**

Once a gene with interesting properties has been identified, it has to be inserted into the genetic patrimony of a vector. The vector is a simple organism such as a virus or bacteria. The gene is inserted in the sole circular chromosome (plasmid) of the vector via recombinant technology, that is, using enzymes to cut (restriction endonucleases) and paste (DNA ligase) fragments of DNA. Once the interesting gene is inserted in the desired location in the vector's chromosome, the vector is used to infect a culture medium. This culture medium is then used to grow the desired organism through the process of tissue culture: some cells of the organism are put in the culture medium, and if the composition of the culture medium and the conditions of culture are correct, the organism will grow with high chances to be infected by the vector. If infected, the organism will have chances to get the interesting gene inserted by the vector in its genetic patrimony and the new cells will constitute the desired Genetically Modified Organism. The last task is to identify and select the Organisms that have been actually modified in the desired way.

Indo-American Hybrid Seeds was also interested once in a gene for eggplant developed in JNU, New Delhi, but the transfer was not achieved because of time-related and financial constraints.
Rallis first technology transfer was made from a Dutch company, Bejo-Zader which was a commercial partner from the company, Bejo gave the gene to Rallis and Rallis worked on Bejo's parent lines. The collaboration stopped two years back, but this had more to do with the commercial side of the partnership. Since then, Rallis has approached the International Centre for Genetic Engineering and Biotechnology (ICGEB) Delhi, the institute provided genes with better characteristics than the one from Bejo to Rallis. Rallis paid a fixed price and ICGEB should receive royalties for a fixed amount of years in case of commercialisation.
Interestingly, the global major Monsanto is in a radically different position in terms of technology. The company has extensive research capabilities worldwide in genetic engineering. Among other projects the company has been working since the mid-90's on the improvement of expression of beta-carotene in Canola and in 1999 it announced it would share at no cost the gene transfer technology. The Tata Energy Research Institute (TERI) has then entered into collaboration with the company enhance the beta carotene concentration in the Indian mustard. The project is supported by the Michigan State University and aims at combating Vitamin A deficiency in the country. This collaboration brings to Monsanto a valuable publicity. Indeed, the company's action in favour of the development of GMO culture in India (cf. Monsanto interview proceeding – About the *bt* cotton in India) is much contested.

Bioinformatics: Research Institutions as competency pools.
In the case of companies entering the **bioinformatics** sector, the common trend is the demand from the companies' side for general competency in biology as their initial competency lies rather in information technology. Therefore they are keen on building flexible relations enabling them to tap in the competency pool provided by the institutes when required. This competency can be used for training. For example the new employees of the bioinformatics team of Tata Consulting Service (TCS) are trained at the Centre for DNA Fingerprinting and Diagnostics (CDFD) Hyderabad. Ocimum Bio-solutions, a bioinformatics company implanted in Hyderabad offering bioinformatics training uses teaching material developed specially by the Michigan Technological University (MTU). This competency can also be used in the development of a tool for which the institute can formulate the needs and conduct the testing. This model has been applied by Ingenovis in its collaborations with institutions such as Cambridge University, CCMB, or IICT. In the case of Bigtec, a bioinformatics company from Bangalore, a Memorandum of understanding has been signed with the Institute of Microbial Technology, Chandigarh for general competency sharing.

Diagnostics: different positions toward collaboration
The company XCyton, involved in the development of peptide-based diagnostics[16] has entered several partnerships with Indian institutions. The development of a diagnostic kit

[16] **Peptides and recombinant proteins: definition**
The proteins are produced naturally by the living cells through expression of a certain gene. Their chemical nature is a chain of amino-acids. Certain zones of this chain have certain metabolic roles. There are two

is composed of two main stages that can be handled separately: the first consists in identifying the short nucleic acid sequence that can be used to detect a certain disease, and the second phase consists in developing a commercially viable kit. In some cases the company has simply bought a sequence already developed, and in other cases it has collaborated with institutes during the work on the peptide sequence. Once the peptide sequence is identified, the company can undertake the kit development on its own, or in collaboration. The same kind of articulation between the isolation of a certain protein and its insertion in a kit can be found in the case of recombinant diagnostics. Bhat is a direct concurrent of XCyton using the recombinant technology in order to produce diagnostics instead of synthetic peptides. In the case of Bhat, the skills of the company's promoter - Dr. Bhat, former professor at University of Pennsylvania, USA – has enabled the company to develop its technology in-house.

Recombinant proteins: learning how to collaborate efficiently

The market opportunity for recombinant therapeutics manufactured in India is now well known and there is a large demand from all the local companies with connected competencies for the technology enabling them to produce such products. Nevertheless, it seems that the bridge between the technology developed at the lab scale in the public institutions and the industrial competencies of the firm is difficult to build. That is why companies such as the pharmaceutical giant Cipla have not been able to launch the production of recombinant products so far. If we put the development of a recombinant protein process in a nut shell, one needs to identify the coding gene, to clone it, and to insert it into the desired cell, which will reproduce itself. Then the industrial process of fermentation and purification must be set up. As it has been said, the main obstacle is rather in the stage of transition from the lab scale to the fermenter scale. The company having developed the required skills to undertake this scale-up have therefore built a valuable asset which enables them to collaborate with research institutes.

The examples of Bharat and Shanta illustrate this fact. Those two companies have been created with the explicit goal of providing an indigenous recombinant Hepatitis B vaccine for the Indian market. As mentioned earlier, Shanta's earliest stage of development took the form of a sponsored research program in the CCMB. In the case of Bharat, the skills of the promoter enabled him to start an independent research team. However, the two companies have made an extensive use of the competency available in the public institutes.

Shanta has collaborative programs with the IISc Bangalore, Jawaharlal Nehru University (JNU) Delhi, Bhabha Atomic Research Centre (BARC) Mumbai, Centre for Cellular and Molecular Biology, Hyderabad, All India Institute of Medical Sciences (AIIMS) New Delhi, National Institute of Immunology (NII) New Delhi, Indian Institute of Chemical Biology (IICB) Calcutta, Anna University Chennai, Tata Memorial Hospital Mumbai, National Dairy Research Institute (NDRI) Karnal, International Vaccine Institute, Korea.

The study of the ongoing collaborative projects of Bharat gives a concrete example of the role such a company can play in local as well as international public-private

---

different way to reproduce artificially these zones: one can modify genetically a living cell so that this cell express a protein with the wanted property (recombinant proteins), or one can do directly the chemical synthesis of a short chain of amino-acids (peptides) with the required property.

collaborations. Bharat is involved in two joint programs for the development of a rotavirus and a malarial vaccine and include both industrial and academic partners. Both projects are funded by the Bill Gates foundation (the first one through the Children Vaccination Program and the second one through the Malarial Vaccine Program). The joint program on rotavirus involves the DBT, AIIMS, NIH, CDC Atlanta, and the University of Stanford. Bharat is the commercial partner of the project. The company provides the Good Medical Practices (GMP) samples during the development studies. The project on malarial vaccine is carried out in collaboration with the ICGEB. The institute is in charge of cloning the gene and inserting it in bacteria in order to express the protein. Bharat will produce the GMP samples and the clinical trials will be carried out by AIIMS. The Intellectual Property Rights (IPR) will be transferred to Bharat.
Bharat is also involved in bilateral collaborations. A world wide patent has been filed by Bharat in October 99 on a vaccine against Lysostaphine. This project was initiated 3 years ago as collaboration with the Centre for Biochemical Technology (CBT), Delhi.
Another major player of the recombinant therapeutics market, the pharmaceutical giant Wockhardt also chose to enter into a partnership with a public research institution, the Trieste branch of the ICGEB in 93. The financial contribution from Wockhardt was supposed to be Rs. 50 M for a partnership of 5 years, the output was supposed to be the development of 3-4 products. The partnership was stopped after 3-4 years, because of the lack of results. When the partnership was interrupted, Wockhardt had already spent Rs. 20 M. Then, Wockhardt reoriented its strategy toward private-private technology transfer strategy and signed an agreement with the German Biotech Company Rhein Biotek. Wockhardt’s further trajectory of competency acquisition is detailed in part B. section 2.2.

Genomics: an emerging field

The main interactions between firms involved in genomics activities and research institutions were discussed in the section on collaboration at the earliest stage of development. The reason for this is that all these companies are considered to be at their very stage of emergence. Nevertheless, considering the impressive rate of creation of new companies in this field, one may wonder whether this dynamic will create a demand of collaboration toward public research institutes.
Avesthagen, which have achieved a first round of funding has heavily invested in order to build a comprehensive research platform, the same kind of investment is being done by companies benefiting from a strong corporate support such as Aurigene (backed by Dr Reddy's) and GVK bio (backed by the GVK group). Those companies clearly target the international market for research collaboration in drug discovery and plant improvement, with a model of technologic platform. In this context, the technology platform – combined to its lower cost of operating in India – is the main asset of the company, and the informal sharing of a platform with a public institution can be seen as too uncertain in such a context. For their recruitment, these companies take into account the fact that the best elements from the Indian academic system spend some years abroad. These companies count on the desire of these people with experience abroad to come back to India. Therefore, it seems that the group of companies emerging on a model based on international co-operation in genomics rely on the western countries both for their contracts and recruitment. One can wonder what kind of externalities these companies

will produce in India, especially in term of research support and orientation in the nearby institutions. Avesthagen, for example has adopted an intermediate strategy for its recruitment, it has selected outstanding elements directly at the masters grade in Indian institutions, and hired them with the promise of sending them to do their PhD abroad.
While the demand for collaboration with public institutes coming from well settled and focused genomics companies is hard to forecast, we can observe some case of ambitious collaboration in this field between some of the most reputed institutions and large pharmaceutical companies. Namely, Nicholas Piramal India Ltd. (NPIL) has entered into a collaboration with the Centre for Biochemical Technology (CBT) for the "genomed" project. The joint venture will conduct dedicated studies in various areas of genomics including pharmacogenomics, bioinformatics, functional genomics and proteomics. As for Biological E., it has launched a project for DNA based diagnostics in collaboration with the CCMB. This project started 18 months ago. The company intends to create a DNA microarray facility in the CCMB in order to screen existing drugs for new therapeutic uses.

Conclusion:
The separate study of public-private partnerships for each technical field allows us to understand what are the real determinants of the nature and efficiency of public-private collaborations in the field of biotechnology. First we can conclude that the very ability to manage the dialogue with a public partner is a valuable asset that has to be built. It has been observed that in the various technical fields, companies and public institutions are still learning how to work together. This can be seen with the multitude of different models of collaboration adopted. The examples also show how the mastering of these public-private interactions can be a strategic advantage. Companies such as Shanta, Bharat, or XCyton have developed sophisticated models of cooperation and already benefit from it through the launching of new products issued from these collaborations.

A.3. Analysis of the competency pool available in the public institutions

The case studies presented in the last section allow us to identify several public institutions taking an active role in the role of biotechnology at the industrial level in India. We distinguish five institutions. Each of these institutions is involved in more than four different collaborations.

Table 4 presented hereunder presents these institutions and the interactions mentioned during the interviews involving them.

Table 4. Institutions Identified as national centre of excellence

Name of the institution	Affiliation	Location	Interactions
Centre for Cellular and Molecular Biology (CCMB)	CSIR	Hyderabad	Bangalore Genei (Bangalore)
			Biological E. (Hyderabad)
			Ingenovis (Hyderabad)
			SP Biotech Park (Hyderabad)
Centre for Biochemical Technology (CBT)	CSIR	Delhi	Bharat (Hyderabad)
			Genotypic (Bangalore)
			Nicholas Piramal (Bombay)
			Themis (Bombay)
Indian Institute of Science (IISc)	UGC	Bangalore	Biological E, (Hyderabad)
			Genotypic (Bangalore)
			Monsanto (Bangalore)
			Rallis (Bangalore)
			Shanta (Hyderabad)
			Strand Genomics (Bangalore)
			Xcyton (Bangalore)
International Centre for Genetic Engineering and Biotechnology (ICGEB)	UNIDO	Delhi	Biological E, (Hyderabad)
			Rallis (Bangalore)
			Xcyton (Bangalore)
			Wockhardt (Mumbai)
			Bharat (Hyderabad), AIIMS (Delhi)
All India Institute of Medical Science (AIIMS)	ICMR	Delhi	Bharat (Hyderabad), DBT (Delhi), NIH (USA)
			Bharat (Hyderabad), ICGEB (Delhi)
			Shanta (Hyderabad)
			Xcyton (Bangalore)

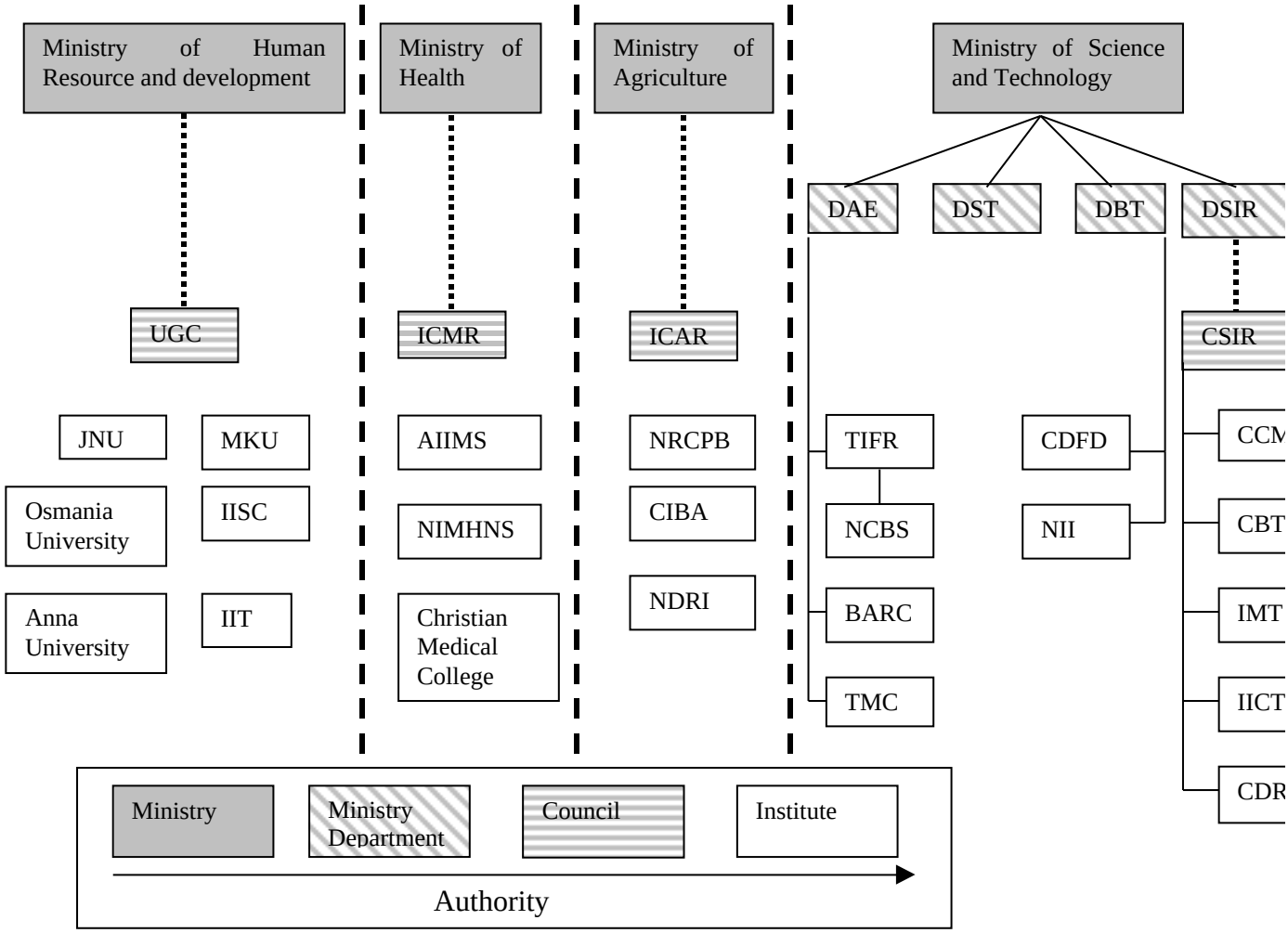
Beyond of these five nodal centres whose participation was mentioned in a large number of interactions, 22 other institutions were mentioned. These 22 institutions were mentioned in on or two collaborations. Table 5 shows the list of these other centres.

Table 5. Name and location of the other institutions mentioned in the Interviews.

Public	Private	Type of Interaction
Anna University, Tamil Nadu	Shanta	Collaborative research
Bhabha Atomic Research Centre (BARC), Mumbai	Shanta	Collaborative research
Centre for DNA Fingerprinting and	SP Biotech Park	Platform sharing
	TCS	Training
Central Drug Research Institute (CDRI), Lucknow	Themis	Contract Research
Christian Medical College	Biological E.	Collaborative research
Central Institute of Brackish Water Aquaculture (CIBA), Chennai	Bangalore Genei	Technology transfer
International Crops Research Institute for the Semi-Arid Tropics (ICRISAT)	Avesthagen	Collaborative research
Indian Institute of Chemical Biology (IICB), Calcutta	Shanta	Collaborative research
Indian Institute of Chemical Technology (IICT), Hyderabad	SP Biotech Park	Incubation
	Ingenovis	Collaborative research
Indian Institute of Technology (IIT)	Themis	Contract Research
Institute of Microbial Technology (IMT) Chandighar	Bigtec	MoU expertise sharing
Jawaharlal Nehru Universtiy (JNU), Delhi	Shanta	Collaborative research
Madurai Kamaraj University (MKU), Madurai	Genotypic	Platform sharing
	Rallis	Collaborative research
National Centre for biological Sciences (NCBS), Bangalore	Avesthagen	Incubation
National Diary Research Institute (NDRI), Karnal	Shanta	Collaborative research
National Institute of Immunology (NII), Delhi	Shanta	Collaborative research
National Institute of Mental Health And Neuro Sciences (NIMHANS), Bangalore,	Xcyton	Collaborative research
	Xcyton	Incubation
National Research Centre for Plant Biotechnology (NRCPB), Delhi	IAHS	Technology transfer
Osmania University, Hyderabad	Shanta	Incubation
Tata Memorial Centre (TMC), Mumbai	Shanta	Collaborative research
Tata Energy Research Institute, (TERI), Delhi	Monsanto	Collaborative research
University of Agricultural Science, Bangalore	Avesthagen	Incubation

This list cannot be considered as a comprehensive list of all the partnerships tied in this sector, nevertheless, it gives indications clear enough to validate the statute of the five first centres mentioned earlier as national centres of excellence.
At this stage one can have a look at the organisational affiliation of these different centres. This organisation is represented in chart 3.

Chart 3. Organisational affiliation of the main centres mentioned in the study:



This chart gives information about the organisational affiliation by ministry of the different public institutions that were mentioned. Each ministry has appointed a special agency to the management of the institutions under its supervision, the University Grant Commission (UGC) in the case of the Ministry of Human Resource and Development, the Indian Council for Medical Research (ICMR) in the case of the Ministry of Health, and the Indian Council for Agricultural Research (ICAR) under the Ministry of Agriculture. In the case of the ministry of Science and Technology, several departments have a role to play, of which the Department of Scientific and Industrial Research which has created the Council for Scientific and Industrial Research (CSIR).

One should notice that the different research institutions do have relations with other funding agency than their ministry. For example, the CCMB which is one of the laboratory of the CSIR, receives funds from other public agencies such as DBT, ICAR, DSIR, DST, etc.. but also from international cooperation programs such as the Imperial Cancer Research Fund (UK), the Volkswagen Foundation (Germany), The India Japan Science Council and the University of Ryukyus, Okinawa (Japan), The National Institutes of Health (USA), and the UNESCO. *Cf. Annex externally funded projects at CCMB.*
Some other institutes based in India are not directly under the supervision of any Indian Public Agency. For example the International Centre for Genetic Engineering and Biotechnology (ICGEB) is in fact an international organisation whose statutes were signed by 26 countries under the form of an international treaty in 1994. The Institution is structured in two components located in Trieste, Italy, and in New Delhi, India. The ICGEB is an autonomous, international, intergovernmental organisation supported by the United Nations Industrial Development Organisation (UNIDO). Some Indian institutes such as the Bose Institute[17] (Independent research institute of outstanding scientific level located in Kolkata) also work without any direct support from any Indian public agency. The revenues from these centres come from external project funding.

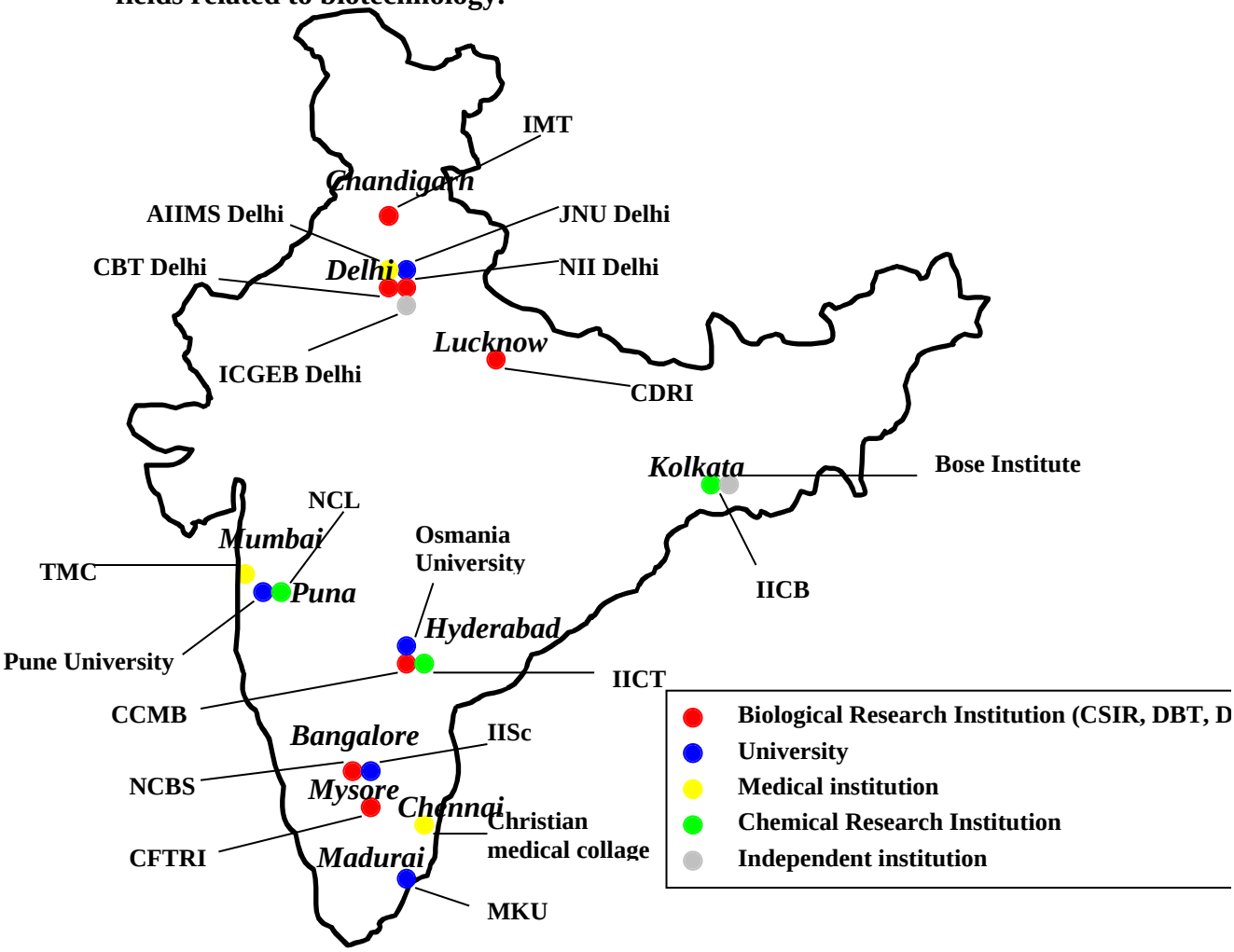
Looking specifically at the five centres defined in this study as centres of excellence, we can notice two main axes of differentiation between these centres : the location and the specialisation.
Concerning the location, the CCMB can be considered as the local pole of excellence in molecular biology in the area of Hyderabad. Similarly, the IISc can be considered as the pole of excellence for the area of Bangalore. Although we have not carried out interviews in the following institutes, the Institute of Microbial Technology (IMT) in Chandigarh, the Central Drug Research Institute (CDRI) in Lucknow, and the Indian Institute of Chemical Biology (IICB) in Calcutta, as well as the National Chemical Laboratory (NCL) in Pune or the department of Biotechnology from the Anna University in Chennai can also be identified as local pole of excellence in the field of biotechnology.
Nevertheless, the application of biotechnology demands the convergence of various different competencies. Consequently, out of the location, one can also expect a technical specialisation from the different centres. The All India Institutes of Medical Science (AIIMS) offers the example of one of these specialisation, indeed the AIIMS, as well as the Christian Medical College or the Tata Memorial Hospital are basically national centres of excellence in Medical Science, and they should become logically specialised partners in biotechnology research networks. As for the ICGEB, it is the leading centre in India in the field of applied recombinant technology. We can also give the example of specialisation in chemical technology related to the biotechnology. In this field, the Indian Institute of Chemical Technology in Hyderabad, or the National Chemical

[17] The Bose Institute is an independent and multidisciplinary institute of fundamental research, founded by and named after the world-renowned Indian scientist Acharya Jagadish Chandra Bose. Fields from Biology to Chemistry and Physics are studied in this institution. Although this institution was not mentioned in the interviews, it can be considered as one of the national centres of excellence in the various fields of biotechnology. The role of geographical multidisciplinary centre of excellence of the Bose Institute in the area of Kolkata can be compared to the role of the IISc in the area of Bangalore.

Laboratory in Pune are attractive partners for research network looking for applied competency in chemical synthesis for example.

This information is summarised in chart 4. which gives the geographic repartition of the main centres with competencies related to biotechnology in India.

Chart 4. Geographic repartition of the main research institutions mentioned in fields related to biotechnology.



A.4. Biotechnologies as a developmental model?

Biotechnology firms emerge on a close articulation between research and industry and combine Indian networks as well as international networks. They imply technological investment, which often calls for the comparison with Information Technologies (IT). Especially, the way IT have articulated to communication infrastructures and contributed to private-driven local development is exemplified for the BT sector. What is the status of Indian BT towards these questions? True, BT can have multiplicative effects, but impact of BT Parks, or impact on education are still to be measured. The comparison with It shall then be further detailed, for the type of assets and the direct local implications in

terms of demand for inputs are not the same in IT and BT. From these preliminary specifications we can better deal with some policy recommendations.

4.1. A comparison with the Information technologies: Assets, Multiplicative effects and externalities

BT have potential multiplicative effects and externalities either from one BT company to another (this is the role of BT Parks), or from the BT sector on the rest of the economy, namely, on education, on other industries, or on the infrastructure sector. The nature of their assets structures these.

Assets in BT vs. assets in IT

The main difference between the bulk of the ITs and the bulk of the BTs is that Biotechnologies are more capital intensive. Physical equipment, building specifications, are more structuring and represent a higher share in the initial investment. Similarly, if BTs are used in pharmaceutics or genomics, the level of technicity is immediately higher and therefore offer comparatively less learning-by-doing ways of climbing up the value chain. At the same time, the return on investments is less immediate on BTs, where the product cycle to meet initial cash-flow and further break-even points is more distant to the starting point of the enterprise. Though some companies build their models on services-derived revenues to sustain the product-building phase, this strategy is comparatively less evident for BTs than for ITs. First of all, it has to be a mixed strategy for BTs: they cannot take off if they start only with service without trying to build intellectual property. This is, however, feasible in the ITs. This is also less easy to find servicing outsourcing contracts, for the level of specialisation and of confidentiality is important.
Therefore, intellectual property assets have to matter for BTs, whereas IT firms can rely on body-shopping strategies only for quite a long time. The BT companies have at the same time to master a specific technology, while integrating externally (through partnerships, tie-ups and collaborations) many techniques, when the bulk of the IT firms can integrate internally different techniques, and make their specific advantage on a specific combination of these simpler techniques. Especially, compared to the IT sector, the high number of Ph-D level employees and the importance of the scientific advisory committees is striking in the biotechnology sector.

BT Parks

Further to the model of the IT sector, some pioneering States, among which Karnataka or Andhra Pradesh develop BT Parks. The rationale for IT Parks is to offer an infrastructure (the building), to facilitate the administrative procedures, as well as locating in the same areas industries that may have contractual relationships with each other (some supplying the others). If one look at the BT sector, the building infrastructure has to be much more strict (confined air, vacuum conditions, pressure conditions, temperature, and so on). These are generally specific to the companies and their type of activity. They further

prefer to keep the hand over the development, maintenance, and operation of these. That way, the BT Park essentially looses most of the functions of the IT Parks. Besides, the niche aspect and the high specificity of activities leads to really limit the potential collaboration within firms of the same BT Park. BT Parks, that way, can rather be analysed as an administrative facilitator and the BT industry is comparatively less keen on integrating them than the IT industry is to IT Parks. As such, they should not be neglected, for, being developed at the periphery of cities, they offer space to an industry that is eager to install laboratories, stocks or reagents or even fermenting capacities, that is, an industry more capital-intensive (and therefore space-demanding) than the IT. BT Parks can offer this facility, but then they should be analysed by the public powers as well as managed differently from the IT Parks. A softer structure, allowing specific equipment, or different kinds of building set-ups: that way, the first BT Park of Bangalore with its single principal high-rise building, may not attract the same success as 'Cyberabad' in Hyderabad, though with similar settings.

Education

The IT sector has boomed, and requests much more graduates and highly educated people than the public institutes can yearly train. The sector has therefore developed its own educational resources and actually created business models centred on education. For instance, some software development companies integrate educational capacities: they train students or graduates, acting as a private school, and select the best students to work with them. That way, they also test software developers as teachers. They ultimately manage to select good teachers by offering them industrial perspectives after a preliminary period of teaching. There are actual positive externalities between education and the IT activity. Other private groups even specialise in education, or distant education. Again, the BT sector is starting and does not show as of now the same evolutions as the IT sector. However, in that sector, and though some experiments like the IBAB try to develop BT training, the offer-demand gap seems to be even bigger in the BT sector. For that reason, the sector will have no other possibilities in the short run but to integrate young trainees or young students, and along with develop proper training programs. During the interviews, some interesting examples have emerged, of companies hiring MSc students for few years, then and following as well as supporting them during the completion of their Ph-D (either in India or abroad). Education will be a crucial input of the take-off of the BT sector. But it may as well be greatly supported by the industry itself. On that aspect, the comparison with IT is quite relevant.

Effect on other industries & Infrastructure

The IT industry has local spill-over effects on many sectors, for example building construction, catering, hotel industry, infrastructure. Given the possibility of body-shopping, once cost-advantages are present, the relative standardisation of techniques for the bulk of the sector allows a rapid growth; the impact on these sectors is therefore rapid as well as noticeable. Other local goods sectors are actually suppliers of the IT industry and grow at the same rhythm as the ITs do. The BT may of course require a similar

amount of supplies, but the slower pace of their development as well as the structurally low level of cash-flow in the initial years might bring a delay in noticing a similar effect.
As far as infrastructures are concerned, IT has definitely an impact on communication systems (not only internet cables but also telephonic facilities through technological linkages), being by nature a connected industry. On the contrary, BT companies do not need such elements, and cannot be expected to bring a similar change in the developmental models.

4.2. Discussion of the concentration of the BT sector in major Indian cities

This proactive State policies for the BT sector, also coupled with active policies for the IT sector and for large industrial investment raise larger considerations on its impact on the spatial patterns of Indian economic development and on the likely changing forms of the Indian urban hierarchy. It would require more in-depth studies at the State level as well as inter-State comparisons to build on this but few thoughts can be brought up.

The location of the Indian modern biotechnology sector provides interesting insights on the emerging metropolises in India. Various factors can explain the presence of BT industry in cities such as Mumbai, Delhi, Bangalore, Hyderabad and Chennai. Among them are the presence of better than average infrastructure, the presence of public research institutes and the facilities provided by State policies that aim at encouraging new sectors for development.
However, this location is certainly linked to the new forms of industrial organisation that are a requirement for the BT sector where the importance of networks is crucial for the innovation process. It confirms the importance of the “relation paradigm” enhanced by Veltz (1996) that emphasise that the metropolis is a more adequate location for innovation processes. This would partly explain the location of these companies in large Indian cities where there is an assurance to find adequate human resources and mostly adequate relationship that are key to innovation processes. The possibility of multiple interactions provided in a megacity, but also the links it offers with other poles of development (in India itself or abroad) explain this. The case of Aurigene is exemplary with a strong involvement in Bangalore as well as in the US, creating therefore various nodes in a network whose activation will be the key to the success of the company. It highlights the importance of the quality of the networks developed and the importance of coordination.

As demonstrated by Veltz, the globalisation process is con-substantial with the polarisation process where the horizontal relationships (between poles) are becoming more important that the vertical relationships (between the pole and its hinterland). It redefines therefore the notion of territory and explains the development of policies aiming to enhance the attractiveness of a region or even a city. This underlines on the other hand the strong role that the States can play. Apparently, from the BT sector, the Indian States emphasise more or less openly the role they expect their capital city to play. Bangalore is clearly mentioned as the heart of the Karnataka BT policy for instance. This

in many ways indicates a shift from previous industrial policies aiming at more regional balances. It might lead to a change in the urban hierarchy in India with the development of specialised clusters and large urban corridors (Maharashtra-Gujarat and the Southern corridor). As such, the BT sector is an interesting one as contrary to previous regional policies where industrial estates were mostly built far away from the main cities in order to promote a balanced regional development and to curb rural-urban migration, the new policies seem to favour an urban bias.

4.3. Recommendations for public action

The central Government

As early as the 80s, the Indian government considered the development of biotechnologies as an important sector for development. The prospects of being able to provide new life saving drugs as well as new types of plants appeared as crucial for objectives such as improvement of health conditions as well as food security. Consequently, the Central government devised a set of tools to support the development of the BT sector that are widely discussed in the core of the report.

First of all, actions and agencies were initiated to fund and enhance public research and to promote the development of human resource capacities through specialised degrees both in biotechnology and bio-informatic. The DBT (Department of Biotechnology) plays a central role and has supported a large number of research programmes. Many other institutions are also involved in the development of high level expertise and public research capacities. Clearly, the efforts in developing research are important but the leverage effect on the industrial development of BT products is not effective enough. Exchanges between researchers from the public and private sectors are limited and financial support/incentives are not able to encourage public scientists to launch business ventures. This could be facilitated by special schemes and by the possibilities for public researchers to shift temporarily or definitely to the private sector with adequate funds (this is also related to the increase of capital venture funds). However, the report underlines the fast ongoing process of public-private partnerships and its capacity building effect. One can assume that a few successful collaborations will surely act as a engine for further ones and will enable the development of a model of public-private collaborations in the field of BT.

Secondly, the government's role on the control procedures and drug approval system, even though essential, is considered as a hurdle to the sector growth due to complex and tedious procedures. Recently, the government is more aware of the negative impact of these procedures and there are efforts to simplify them (by the use of a single window agency system). In addition, the aim of the government is to develop an approval process at par with the American system, which underlines the ambitious strategy planned both by the government as well as by the industrialists.

Thirdly, other public initiatives have been developed to support and promote the sector, such as the participation in the funding of BT parks or the creation of entities such as BCIL (Biotechnology Consortium India Limited). Such entities also exist at the State level, which indicate the importance given to the BT by the State governments. It is early to assess whether the public investments in BT park will have a leverage effect but one can assume it will if one takes the example of the IT sector as a reference. However, funding of the sector is insufficient and there is a need to develop venture capital funds otherwise the initial efforts will not have a snow ball effect. From the industry point of view, a stronger association that can play a role of lobbying and relay with the public authorities is needed. The AIBA (All India Biotech Association) has not been able to play this role and has very little influence on government policies.

In addition, these efforts at the Central and State levels need to be better directed and enhanced if the BT sector has to follow a higher growth rate. The BT industry is an industry where established networks are a key factor for success. In many ways, the first one to identify the right partners and to establish satisfying collaborations will have a competitive advantage. It is therefore important to streamline the actions of the public bodies to ensure that these partnerships are efficient in order to accelerate the process of technology transfer as well as innovation. In addition, like for the IT sector, special incentive packages can be designed to favour the growth of the BT sector. In this regard, the special interest given to such proposals by specific States need to be looked at.

Finally, central to the development of the sector is the question of intellectual property rights. India is still perceived by many as a risky country regarding property rights and cannot therefore put forward its many advantages. The path taken to respect the TRIPS agreement should be a clear signal for international partners that India can be a fruitful partner in the BT sector.

The State policies

We would like here to look more precisely at the role of State policies in the field of BT. Indeed, the process of globalisation and liberalisation of the Indian economy has led to a stronger role of State policies in industrial location decisions. Andhra Pradesh, Gujarat, Karnataka, Maharashtra and Tamil Nadu are considered as the most reform oriented States and it is clear that these States plan to favour the BT industry. Delhi does not have a BT policy yet (though the process of devising a policy is ongoing), but the other States studied in this report (Maharashtra, Karnataka and Andhra Pradesh) have already devised BT policies. We shall include here the case of Tamil Nadu, where no survey was conducted, but that has a strategy regarding the BT sector and is also one of the most active States in devising attractive policies for new industries.

The aim of this section is simply to underline the common features of the BT policies. The State of Maharashtra's description of its comparative advantage by "its superior human resource, the excellence of its private and public institutions, the superb infrastructure, and a conducive business environment as well as the inherent strength of its industry. Equally important is the progressive and proactive government which is

prepared to go that 'extra mile' to make things happen." Reflects the focus given by all the States on partnerships, human resources and dedicated incentives.

Therefore, all these policies plan to offer tax holidays, capital subsidies and energy concessions (also allowing captive power generation). Each state has created specific institutions to facilitate procedures, ensure fast but efficient control procedures and to promote the development of the sector. In Maharashtra, 2 such institutions are created: the Maharashtra Biotechnology Board and the Maharashtra Biotechnology Commission; in Karnataka, the Karnataka Biotech Vision Group plays an advisory role to the governement.

The creation of specific development fund is on the agenda of all the four states in addition to policies to enhance the role of the capital venture funds. Interestingly, most of these funds are planned to be developped in partnerships with private partners. This indicates that the States consider their role as an enabler and a facilitator. The construction of BT parks is planned by all the States. The report alreadys suggests the positive externalities that the BT park in Hyderabad should provide. In Tamil Nadu, four BT parks and a Bioinformatics and Genomics Centre are planned to be developped near Chennai and they "will be the hub of the Biotechnology Enterprise Zone" (Tamil Nadu BT policy). This indicates that most of the States plan to indeed be a strong initiator of the development of clusters around the BT sector. In Tamil Nadu, it is called the BT entreprise zone, in Karnataka it will be the BT corridor that would extend from the Indian Institute of Science to the University and in Andhra Pradesh, this is the Genome Valley Project.

To facilitate the development of these "clusters" or "knowledge corridors", in addition to incentive packages, single window facilities will be provided to simplify licensing procedures and investments will be provided in developing adequate infrastructure for the BT specialised zones.

Part A - Conclusion

The development of biotechnology has been identified two decades ago as a priority by the Indian government. Since the early days of the building of a public action specific to this field, the complexity of the administrative system to be put in place has appeared. Indeed, the interactions of the biotechnology with democratic political structures are complex by nature. This is due to the application of these new technologies that question several values these structures are in charge of translating into rules. These may be the respect of intellectual property, the security of food and drugs, or the respect of bio-diversity. But these interactions are also due to the nature of Biotechnology as knowledge. Science and Technology as a whole are indeed at least partially public goods, and as such, the production of these goods has to be taken into charge by the public sector.

The first section has given an overview of the Indian System of control and promotion of the biotechnology. Concerning the control, the need for a simplification of the different

procedures has been recognised and efforts are being done in this direction. This evolution is already occurring with the development of “single window agencies” the state and central level, these agencies are conceived as simplified means of interaction with the administration for matters related to biotechnology ventures.

Concerning the development of science and technology in the public institutions, we have seen that the availability of technology and skilled people in the domestic institutions is a factor which helps new biotechnology to emerge in the private sector at different stages. A nationwide network of institution with outstanding academic level has been established. In all technical fields, companies with new projects are experimenting various type of collaborations, knowing that an efficient management of public-private collaboration may a be a key to the success of biotechnology ventures, as it has been shown by success stories such as the one of Shanta.

The public powers have also understood the implication of interactive exchanges, and are developing numerous projects of BT parks. This scheme has several advantage. Not only does it allow developing good quality infrastructure for a demanding industry such as biotechnology, but it also permits to take advantage of the geographical proximity of national centre of excellence to make the technological collaboration more intense, and to experiment easily special fiscal schemes.

Beyond these useful efforts, we think that several measures have to be taken rapidly for India to achieve its full potential on the global biotechnology scene. The IP scenario must be defined more clearly. Public action at the central and state level should be coordinated in order to provide a clear regulatory environment, and to avoid misallocation of funds. Radical tax and duty should be granted to units involved in research activities. Coordination should also be the main objective for the different institutions representing the industry. An organisation as independent and efficient as the NASSCOM should emerge. Finally, all these measures should identify clearly their target among the diversity of activities that can be considered as biotechnology.

Part B

B. Biogenerics - recombinant products

B.1. Market description

1.1. Definition of biogenerics, International and Indian context

The term biogenerics refers here to therapeutics products based on genetically engineered or recombinant technologies that are already on the market at least in some industrialised countries.

The two main classes of BT component entering the composition of these biogenerics therapeutics are recombinant proteins[18] and monoclonal antibodies[19]. A major advantage of utilising recombinant DNA (rDNA) technology is that proteins can be manufactured reproducibly in a highly pure form at an acceptable cost.

[18] **Recombinant Technology - Technical definition** : Recombinant technology uses enzymes to cut (restriction endonuclease) and paste (DNA ligase) fragment of DNA in order to make chimeric/recombinant DNA molecules. Typically, a DNA sequence of interest, called the insert is pasted together with a vector, a piece of DNA that enables the recombinant molecule to be replicated and harboured in an host organism. Among other applications, recombinant molecules are constructed for the purpose of cloning the DNA, that is, making a large number of copy of a single molecule.
Therefore, recombinant technology, by allowing obtaining the large quantities of single purified DNA species necessary for nucleotide sequence determination, constituted a critical path in the development of genomics.Recombinant DNA molecules have also found a critical role in the synthesis of proteins in host organisms like bacteria (Escherichia coli), yeast (S. cerevisiae), or mammalian cells. In this case, rDNA is engineered so that the host organism's DNA, RNA, and protein synthesis machinery act on the recombinant molecule to produce the protein encoded by the insert. Purified recombinant proteins are used in biomedical research, diagnostics, and therapeutics.

[19] **2. Monoclonal Antibody – Technical definition :** Humans (and mice) have the ability to make antibodies able to recognize (by binding to) virtually any antigenic determinant Not only does this provide the basis for protection against disease organisms, but it makes antibodies attractive candidates to target other types of molecules found in the body, such as receptors or other proteins present on the surface of normal cells as well as molecules present uniquely on the surface of cancer cells.
The response of the immune system to any antigen, even the simplest, is polyclonal. That is, the system manufactures antibodies of a great range of structures both in their binding regions as well as in their effectors regions. Even if one were to isolate a single antibody-secreting cell, and place it in culture, it would die out after a few generations because of the limited growth potential of all normal somatic cells.This problem was solved for mice in 1975 with a technique devised by Köhler and Milstein (for which they were awarded a Nobel Prize). An antibody-secreting Bcel like any other cell can become cancerous. The unchecked proliferation of such a cell is called a myeloma. Köhler and Milstein found a way to combine the unlimited growth potential of myeloma cells with the predetermined antibody specificity of normal immune spleen cells. They did this by literally fusing myeloma cells with antibody-secreting cells from an immunized mouse. The technique is called somatic cell hybridization. The result is a hybridoma. Currently marketed monoclonal antibody-based biopharmaceuticals are manufactured using both classic/conventional hybridoma and recombinant technologies. Monoclonal antibodies expressed by conventional murine or other rodent hybridomas, both by in vivo (ascites method) and in vitro culture in bioreactors, are, as expected, composed entirely of rodent/murine antibody sequences.
Monoclonal antibodies have already been introduced in human medicine for uses such as kidney transplant, leukaemia, and numerous prospects are studied in other cancer treatments.

As mentioned in the technical definition of recombinant technology, the recombinant proteins obtained may have various application. In this section we will focus on the therapeutics, this market is not the only one developing in India for application of recombinant technology, namely the market for diagnostics offers tremendous opportunities to the company able to apply the technologies mentioned earlier to the industrial production of antigens and antibodies to be inserted in diagnostic kits. Nevertheless, the dynamics of industrial reorganisation in the field of therapeutics and diagnostics present different technologic and regulatory determinants and have to be studied separately. We chose to study the market for therapeutics since it is the one gathering the largest number of contestants with the most diversified profiles. Moreover, with the alarming figures of diabetes cases in India, the production of recombinant proteins like human insulin is definitely a strategic domain of importance.

The first therapeutic protein produced through rDNA technology to be in the market, was Genentech's human insulin, introduced in 1982. The total amount of recombinant therapeutics molecules approved throughout the world is now around 30. In 2000, nearly 86 percent of the 77 biotechnology medicines approved by the FDA constitute recombinant human proteins. The approved products can be categorized into blood factors, hormones, growth factors, interferon, interleukins, vaccines, and other products.
The estimated worldwide sales of recombinant products were estimated at US$ 1.4 billion in 1990 and US$ 6.6 billion in 2000.
Over the next five years, more than $10 billion worth of products will come off patent.
Many treatments for diseases like Diabetes, Gaucher Disease, Hepatitis B&C, Sclerosis, Growth Hormone deficiency relying on biotechnology will face patent expiration between 2001 & 2005.

In 2001, 12 products out of the 30 latter approved products were approved for commercialisation in India. Those products are Hep B vaccine, Human Growth Hormone, interleukin, Granulocyte stimulating factor, granulocyte macrophage colony stimulating factor, alpha-interferon, beta-interferon, blood factor VIII and follicle stimulating hormone.
In India the market of approved recombinant therapeutics in 2001 was estimated to be about US$ 109 millions, which represented 3.2 % of the total Indian pharmaceutical market, and 1.6 % of the world market for recombinant therapeutics.
Shantha Biotech's launching of a locally produced recombinant Hepatitis B vaccine in 97 was the first introduction of a recombinant therapeutic protein developed by a domestic firm. It has forced down *SmithKleinBeecham's* selling price of$10 per dose down to 50 cents per dose, and has created a country wide awareness to the opportunities existing in this field. More than 10 Indian firms have drawn plans to produce other recombinant products in the 3 next years. Among others, the Indian market for recombinant insulin will see many firms compete in the next year. The interviews allowed us to observe that all the Indian companies with capabilities related with the production or the marketing of therapeutic recombinant proteins have at least actively studied the possibility of entering this market.

1.2. Recombinant proteins value chain

Development of new recombinant products

The general estimation of the cost of development of the first new recombinant proteins by U.S. companies during the mid 80's is generally estimated around US$ 250 million[20]. This cost can be estimated over US$ 500 millions. Nevertheless, Indian actors have a numerous opportunities available in the developing of technologies or products which have already been established elsewhere and whose intellectual property right period have expired.

Cost estimates of such developments in India have been realised by the Technology Information Forecasting and Assessment Council (TIFAC), under the Ministry of Science and Technology. These figures reflect the cost of developing a hybrid cell line that will express a certain protein. It is assumed that the sequence of the gene coding for the desired protein is already known. Then, the cost presented here is only the cost of successful insertion of this gene in a cell of a certain type. We can notice that this cost varies significantly from one type of cell to another. In most of case, the type of cell to be used is dictated by technical factors. Indeed some proteins can only be expressed in one certain type of cell.

Table 6. Estimated cost of development of recombinant cell lines.

Type of expression cell	Estimated cost	Specific costs entering in the estimation
Bacteria (E. coli)	0.1 to 0.2 US$ million	. molecular biology at the shake flask level . analysis and evaluation of target proteins by ELISA . finding the authenticity of polynucleotide sequence by PCR method
Yeast	0.2 to 0.6 US$ million	. Development of clone in lab scale . Standardization of the process in small fermenters . Isolation of protein from the yeast
Animal mammalian cell lines	0.4 to 1 US$ million	. Development and screening of clones . Analytical methods for testing the absence of opportunistic organisms

Source : TIFAC "recombinant DNA therapeutic products" January 2002.

These figures show that a reasonable investment may allow Indian firms to take the first step toward setting up a production line of recombinant products. Indeed, the cost

[20] TIFAC "recombinant DNA therapeutic products" TIFAC study, January 2002.

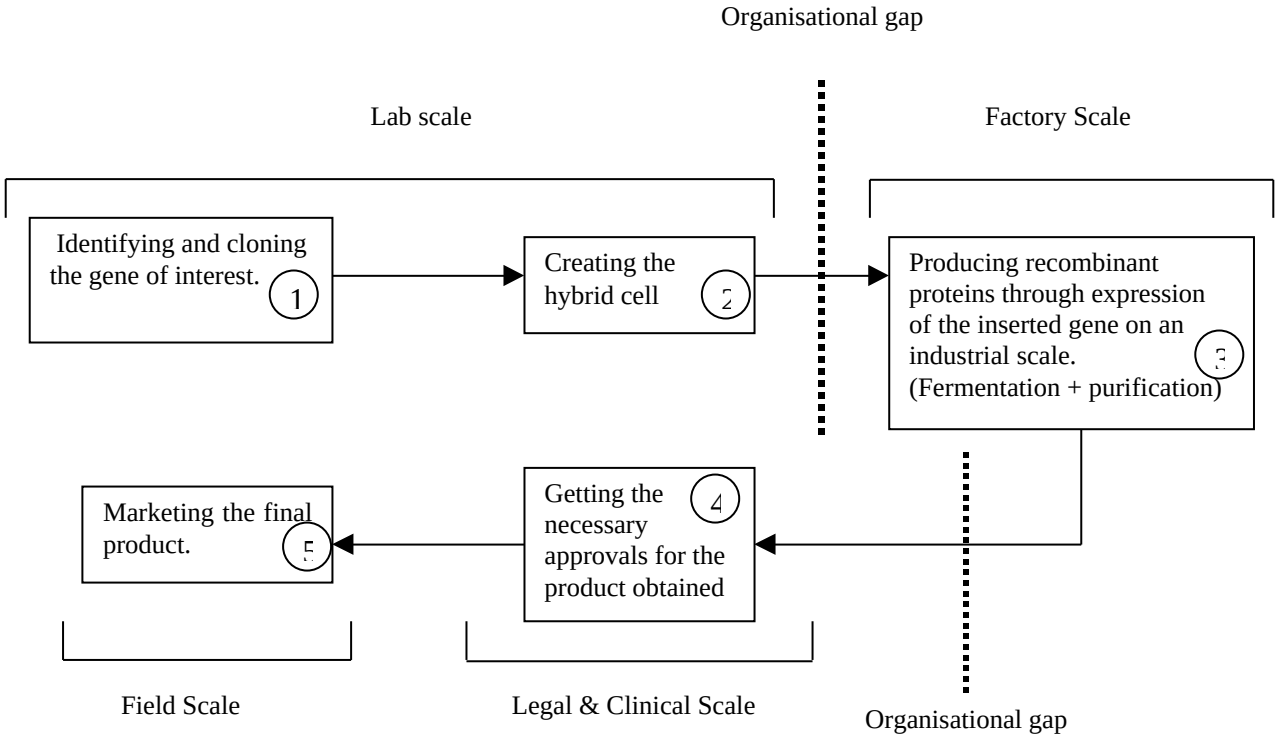
presented in Table 6. show that the entry barrier that represents the cost of development of an hybrid cell line is negligible compared to the initial cost of development of the recombinant product. Nevertheless, the achievement of the expression of a certain recombinant protein on a lab scale, whose cost is estimated in Table 6, does not allow in itself to undertake the commercial use of the technology, since an industrial scale-up is still to be done, and it has been observed from the result of the interview that this task requires very specific competency. In the next section we will describe all the complementary stages of the development chain.

Comprehensive value chain

Hereunder is presented a general scheme of the recombinant product development & marketing chain of a recombinant therapeutic protein.

This permits us to understand the articulation between the laboratory-scale development cost and the rest of the tasks entering the value chain. The first task (1 : Identifying and cloning the gene of interest) can be considered as basic or fundamental research. This kind of research can be conducted either by public institutions or by companies with the required resources to set up a research team dedicated to this kind of prospective research. The second task (2 : creating the hybrid cell) is more of a technical stage, nevertheless it is a highly specific technology, and only scientists with a post graduate education in genetic engineering are able to take charge of such a task. These kinds of profiles can be found either in the public research institutes where this kind of tasks may be part of a PhD work, or in private companies with young scientists who have worked on cell hybridising during their academic training. The main organisational gap in the value chain is situated between the second and the third task (3: Industrial scale up). Indeed, while the task (2) pertains to the domain of genetic engineering, the task (3) is more related to technical competencies in fermentation. These competencies are not specific to the production of recombinant proteins, since it can be applied as well to natural cells, to produce natural proteins through fermentation of these cells, for example this process has been used for many years for the production of industrial enzymes. The latter stage of the process, that is the purification of the content of the fermentation product in order to extract the protein of interest, is directly connected to the general competency in fermentation of natural or hybrid cells. Another organisational gap is found after the task (3). that relies on competencies in biochemistry and process engineering (common to all processes of protein production through fermentation). As for the fourth (4 : legal filing for product approval) and fifth stage (5 : marketing) of the value chain, the capabilities required for these tasks are determined by the nature of therapeutics of the final product, therefore, they will be found more easily in companies already involved in the development and marketing of therapeutic products. This constitutes the second organisational gap between the stage (3) pertaining to the field of biochemistry and the stage (4) and (5) specific to therapeutic value chains.

Chart 5. Lab-to-market value chain for a therapeutic recombinant protein.



1.3. Market description

Main products

Table 7 presents the main recombinant products on the market, as well as their indication, their mean of expression and their first date of approval. The classification used in the first column takes into account the metabolic nature of the product. This nature is logically correlated with the therapeutic indication. This table shows the diversity of the therapeutic areas in which recombinant products are positioned. Some of these areas such as diabetes treatment, and Hepatitis B. Vaccination are of strategic importance for the Indian health policy. Another striking element of this table is the date of approval of these products. Given these date of approval, it can be seen that most of those main products currently on the market will fall into the public domain in the next years[21]. If we consider that the products were patented before the starting of the clinical trials, even in the case of the 20 year protection granted by the TRIPs agreements, the products that received their first approval in the early 90's will fall in the public domain before or short after the

[21] Date of approval and duration of the patent: A distinction has to be made between the starting date for the duration of a patent on a given drug and the date of approval of the drug by the Drug Control Authority, but the date of acceptation of the patent filing by the Patent Authority. Indeed, if the approval is needed to put a certain product on the market, the product can be copied by a competitor before this date, and the data published when the new drug application is filed to the drug control authority increases the risk of copying. Therefore, companies have to patent their product early enough to prevent their competitors from copying, and as late as possible in order to enjoy the longer period of patent protection after the approval.

deadline of 2005 fixed for the enforcement of the TRIPs agreement by developing countries.

Table 7. Main recombinant therapeutics on the market.

Product class	Product	Indication	Expression Cell (type of cell)	Year of first approval
Blood factors				
	Factor VIII	Haemophilia type A	Chinese Hamster Ovary Cell (CHO cell) (mammalian cell)	1992
	Streptokinase	Acute myocardial infarction	E. coli (bacteria)	1990
	Tissue plasminogene activator	Acute myocardial infarction	CHO cells, E. coli	1987
Hormones				
	Insulin	Diabetes mellitus	E. coli	1982
	Erythropoietin	Anaemia	Mammalian cell line	1989
	Human growth hormones	HGH deficiency in children	E. coli	1985
Growth Factors				
	Granulocyte Colony stimulating factor & Granulocyte macrophage colony stimulating factor	Mammalian cell line	E.coli	1991
Interferon				
	alpha-interferon	Leukaemia, Hepatitis B&C, cancers	E. coli	1986
	beta-interferon	Sclerosis	CHO cells, E. coli	1993
	gamma-interferon	Chronic granulomatous disease	E. coli	1990
Interleukins				
	Interleukin 2	Renal cell carcinoma	E. coli	1992
Vaccines				
	Hepatitis B vaccine	Hepatitis B prevention	S. cerevisiae (Yeast)	1986

Global market

Table 8 gives figures about global sales of recombinant products until 2000, and a projection of these sales in 2005. It can be noticed that the six products with the largest sales are either already produced or in advanced stage of development by Indian companies. In order to give an Idea of the opportunities offered by the markets for those products, we can mention the criterion globally accepted to define a “blockbuster drug”, which are sales over $ 1 billion. Given the size of Indian companies, an efficient positioning as global providers of biogenerics would represent a tremendous opportunity of growth for them.

The projection for 2005, based on estimates by global market research agencies, reflects a dynamic growth of the market for existing products, which should nearly double, and a massive overall development thanks to the entry of new products. Thus, by entering the market for recombinant Hepatitis B vaccine, Insulin, alpha-interferon, or Granulocyte Colony Stimulating Factor (GCSF), Indian pharmaceuticals do not only enter a large and fast growing market, but they also acquire competency in a technical field that has not yet delivered all its promises.

Table 8. Global sales of recombinant therapeutics (US$ millions)

Product Name	Year					
	1990	1995	1997	1999	2000	2005
EPO	225	776	1212	1535	1703	3337
alpha-interferon	182	582	673	837	946	1939
Insulin	310	655	673	816	918	1720
G-CSF & GM-CSF	19	194	586	746	823	1542
Growth hormone	221	492	444	5469	592	1011
Hepatitis B vaccine	124	233	299	380	421	987
Monoclonal Ab based products	19	155	216	294	329	674
Factor VIII	136	465	300	306	310	581
TPA	163	78	82	61	115	215
Streptokinase	N.A.	N.A.	31	35	39	122
Interleukin 2	N.A.	N.A.	34	46	51	105
gamma-interferon	N.A.	N.A.	30	35	39	80
Follicle stimulating hormone	N.A.	N.A.	20	26	29	59
beta-interferon	N.A.	N.A.	24	28	31	57
Others	39	105	153	301	377	705
Total	1439	3812	4778	5992	6743	13134
New products being introduced	0	0	0	0	0	32959
Grand Total	1439	3812	4778	5992	6743	46093

Source: TIFAC "recombinant DNA therapeutic products" January 2002.

Indian Market

The recombinant products market has been led so far by imports of established global brands and marketing of the products either by local subsidiaries (*SmithKline Beecham (SKB), Novo*), or through marketing arrangements as in the case of *Nicholas Piramal* and *Roche*.

This trend is changing thanks to the massive entry of local competitors with a critical cost advantage.

When *Shantha* first introduced its locally developed recombinant Hepatitis B vaccine, it has forced down *SKB's* local selling price of $10 per dose down to 50 cents per dose. The market of recombinant Hep. B vaccine now counts four local players: *Shanta*, *Bharat*, *Panacea* and *Wockhardt*.

Other approvals have recently obtained by these companies: *Wockhardt* commercialises EPO since the beginning of 2002, and *Shanta* has obtained the same year the first approval for a locally developed interferon-alpha.

Other companies plan to enter the market in the three next years, and a fierce local competition can be expected in the two next years in the market for human insulin.

Table 9 gives an estimate of the Indian market for recombinant therapeutics and a projection for 2005. These figures, provided by the TIFAC, imply that the markets for these products are growing at a rate of 15% per annum in the country.

While considering these figures, one has to consider the fact that the potential demand for those products in India is highly dependent from the price levels of these therapeutics, as India's health system is not so developed, and many poor populations that would need treatments based on these products simply cannot afford them.

Namely, these figures are estimated by the TIFAC to represent only about 15-20% of the total requirement.

Table 9. Indian market for recombinant therapeutics (US$ millions)

Product Name	Year		
	1997	2000	2005
Insulin	7.1	16.7	26.9
Streptokinase	3.1	52.7	9.0
Erythropoietin	2.0	4.1	6.5
Hepatitis B	30.6	45.9	92.3
Human Growth Hormone	1.0	2.3	3.7
Granulocyte colony stimulating factor	4.1	15.3	24.7
alpha-interferon	12.2	16.3	26.5
gamma-interferon	N.C.	0.1	0.2
blood factor VIII	N.C.	0.2	0.3
FSH	N.C.	3.1	4.9
TPA	N.C.	N.C.	N.C.
Total	60.2	109.3	195.4

Source : TIFAC "recombinant DNA therapeutic products" January 2002.

1.4. Influence of the public policy on the environment and the strategies of firms

General facts about the public environment of biotechnology in India have been discussed in part A. This section details the elements of the Indian and global public environment of biotechnologies which have a specific influence on the biogenerics sector.

Generics status for biopharmaceuticals[22]

The explosion of the new drug development costs in the last years is known to be caused mainly to the cost of clinical trials that any new therapeutics has to go through in order to get the necessary clearance to be put on the market.

Regarding this fact, the legal aspect of the definition of biogenerics is critical to the strategy of potential new comer in the market of conventional biotherapeutics.

Indeed there is a controversy still going on about the feasibility of generic products issued from biotechnology.

Whereas chemical identity between short molecules can be achieved with the assay technologies currently available, this becomes much more difficult, and - to some experts point of view – impossible when the identity has to be proven between two macromolecules as the one produced through recombinant technologies.

[22] Ref: ABN-AMRO Generic Biologics: the next frontier. *ABN-AMRO Paper*

This controversy is of course evolving thanks to the development of more refined production and assays techniques (bioinformatics, microarray technology, pharmacogenomics, spectroscopy, and chromatography).

On the field there are some clear signs of evolution towards the acceptance of "generics" status given to recombinant product, as it is shown by the cases of Biogen's Avonex®, Shalala's generic version of Serono's Pergonal®, Transkaryotic Therapies' equivalent version of Amgen's Epogen®.
In this case the FDA has recognised the equivalence between two products issued from different cell lines, but whose functional characteristics were proved to be similar enough to the one of the original product to consider the new product as a generic version of the existing product.

Technology development in public institutions
If several Indian public research institutes have the skills to achieve recombinant proteins expression on a lab scale, they lack of the scale-up competency necessary to transfer this technology on an industrial scale. Considering that the firms potentially interested by a technology transfer do not have this scale up skill neither, this explains why the gap between the institutes and the industry is hard to fill. This corresponds to the first organisational gap represented in Chart 5. In the next section, we will discuss which of the different Indian companies entering the market have the capabilities enabling to fill efficiently this gap.

Although the industrial results aren't here yet, there are collaborations between Indian industries and public institutes as it is shown in this table given in the TIFAC study "recombinant DNA products".

Table 10. Public-Private collaborations for the development of recombinant products in India.

Product	Institution	Industrial Partner
Streptokinase	Institute of Microbial Technology (IMTECH) Chandigarh.	. Cadila . Bharat Biotech
Follicle stimulating hormone	Indian Institute of Science, Bangalore	. Cadila
Human growth hormone	Indian Institute of Science, Bangalore	. Shantha Biotechnics
Hepatitis B vaccine	M.S. University of Baroda ICGEB, New Delhi	. Biological E. Ltd.
Epidermal growth factor	Centre for biotechnology, New Delhi M.S. University of Baroda, Baroda	. Bharat Biotech . Biological E.

Source : TIFAC "recombinant DNA therapeutic products" January 2002.

Status of recombinant products

The *pharmaceutical policy 2002*[23] has reviewed in depth the last policy issued in this field: the *Drug Policy 1896.* Studying the new text allows us to see the strategic importance of the sector of recombinant therapeutic proteins. Indeed, the new regulation has introduced a new segregation between chemical drugs and biotech drugs.
Industrial licensing for the manufacture of all drugs and pharmaceuticals has been abolished except for bulk drugs produced by the use of recombinant DNA technology, bulk drugs requiring in-vivo use of nucleic acids, and specific cell/tissue targeted formulations.
Automatic approval for Foreign Technology Agreements is being given in the case of all bulk drugs, their intermediates and formulations except those produced by the use of recombinant DNA technology, for which the procedure prescribed by the Government would be followed.
The abolition of industrial licensing was the main element of the general liberal reforms initiated in India in 1991. It has removed an heavy burden from the entrepreneurs by setting them free from the painstaking administrative process any industrial project had to go through before being implemented. The late abolition of this system concerning the pharmaceutical ventures shows the strategic position of this sector. Maintaining the industrial licensing system for the manufacturing of recombinant products is a mean for the government to keep control on the nature of the firms entering this market, imposing for example conditions about minimum domestic ownership shares.

Intellectual property
The evolution of Indian system of Intellectual property protection is described in Part A, section 1.3.1. The striking fact is the shifting from a very loose regime of intellectual property protection in which only process patents are granted on drugs, to a regime in compliance with the WTO standards with a 20 years period of protection on processes as well as products themselves. India will have to enforce the amendments required by the TRIPs agreement before the 1st of January 2005.
Nevertheless, this legal evolution goes along with the expiration – before the deadline of 2005 – of many recombinant products representing a market worth of more than US$ 10 billions.

This may lead to two different strategies:

- Indian firms could choose to focus on the generic markets, knowing that thanks to the patent expirations, they could target the global market for this class of products
- On the other hand, these companies could respond to the global harmonisation of patent protection by adopting a research-based strategy, developing new products to address the global market and relying on intellectual property.

Of course these strategies rely on the assumption of a strict enforcement of patent protection in India, but the compulsory licensing provision, for example, offers numerous different interpretations.
For example, Cipla's CEO, Dr. Hamied – famous for his aggressive commercial strategy in the field of generic tri-therapies - thinks that considering the number of people needing a treatment for diseases like Anaemia or AIDS in the country, India could be declared as

[23] http://www.nppaindia.nic.in/may-2002/policy-02.html

in a state of medical emergency. Legally, this could allow actors like Cipla to be granted licences for manufacturing certain drugs at a price decided by the Indian authorities without the agreement of the patent owner.
The interviews of companies with projects of therapeutic recombinant proteins already implemented, i.e.: Shanta, Bharat & Wockhardt, shows that even in the case of "generic" products, the litigations are an important criterion of decision. Indeed, the western companies whose patents expire can find a way to file patents protecting their product for a longer time. As a result of the complexity of the legal system, the determinant factor in the globalization strategies of the Indian players is the cost of the litigations rather than fixed rules determined in the domestic or global texts. The cost of the litigations is itself determined by the ability to pay of the companies trying to protect their market, and the strategic importance of this market that will determine their willing to invest in legal procedures in order to prevent generics to compete with their products.

Price control
Drugs price control goes through the registration of each drug in the Drugs Price Control Order (DPCO). The schedule of the DPCO of 1995 lists 76 bulk drugs, out of which the only protein is Insulin. Although this listing regarded natural insulin, the new recombinant insulin enters in this legal framework.
Nevertheless, in the absence of listing, the price of the 11 other recombinant proteins are not controlled.

Conclusion
The striking elements of the public environment related to the bio-generics market are:

The market of US$ 10 billion for bio-generics that represents a very attractive target for Indian players with proved cost efficiency. This market being unrestricted by the compliance with the WTO agreement on Intellectual Property Rights (TRIPs).

Technology is available in the public institute, but efficient collaboration proves to be difficult to set up, these organizational difficulties will be detailed in the next section.

Bio-generics have been recognized as a strategic field by the Authorities and the production of such products in India is still subject to the licensing system, which can be a way of preventing foreign companies to take profit of the cost advantage provided by a domestic production.

The drug approval system is being reformed in order to accelerate the approval process and to converge towards the international standards set up by the International Conference on Harmonization (ICH).

Except for the Insulin, the price of the recombinant products marketed in India is not controlled.

B.2. Indian companies' strategies to enter the bio-generics market

2.1. Categorisation of the actors and stylized facts

Profiles of the potential entrants

Four profiles of companies who can be potential players in this market have been identified

Those profiles are presented in Table 11, they refer to the initial positioning of the firms. It is assumed that those different positioning confer various assets that may be considered as relevant for the new activity.

Table 11.Profiles of the Indian potential entrants on the market for recombinant therapeutics.

Profiles	Companies interviewed
Indian Integrated Pharmaceuticals Company (IIPC)	Wockhardt ***Cipla*** ***USV*** ***Ranbaxy*** ***Dr Reddy's*** ***Biological E.***
Diagnostic reagents & vaccines manufacturers	***Bharat Serums & Vaccines*** ***Yashraj*** ***Artemis Biotech*** ***Bhat Biotech***
Enzyme manufacturers	***Advanced biochemicals*** ***Biocon*** ***Bangalore Genei***
Dedicated start-ups	***Shanta Biotechnics*** ***Bharat Biotech***

Those profiles are stylized facts, and the classification of some companies in one category or another may be subject to discussion.

For example, Biological E. had an activity of vaccine manufacturing as well as drug formulation and marketing, thus it could be considered as belonging to the first as well as the second categories, the choice for the classification was operated considering the strategy actually adopted by the company.

We will analyse how the initial capabilities of firms can influence their strategy of competency acquisition, and its final positioning on the value chain.

The main relevant capabilities for the development of an activity in the value chain of therapeutic recombinant proteins are:

R&D capabilities in molecular biology and genetic engineering.
R&D capabilities in biochemistry and process engineering.
Technological know how in fermentation and protein purification.
Technological know how in drug formulation.
Legal capabilities for drug approval filing.
Marketing skills in a certain therapeutic area.

We assume that the strategies of the new entrants are strongly determined either by the presence of some of these capabilities thanks to other activities of the firm, or by a precise plan to acquire or to tie up with a partner with the complementary capabilities.
Interviews' analysis provides us data to attempt to describe these strategies of entry with stylized facts regarding the strategies of technological competency acquisition on the one hand, and the strategies of commercialization of the different firms interviewed on the other hand.

Stylised facts about the strategies of entry.
The main strategies observed for technology acquisition can be classified as follows:

- **In house R&D:**
  - Basic R&D
  - Process scale-up R&D
- **Collaboration with a public institute:**
  - Project funding
  - Incubation
  - Platform sharing
- **Technology transfer:**
  - A technology transfer can be defined by the precision of the contract. In this case, the contract defines precisely what the transferring part has to bring (cell line, scale up, support) and when the transfer ends.
- **Joint Venture:**
  - A joint venture (50/50 is the general case) is a well defined financial structure allowing flexibility in the inputs of each parts, considering that each part has the same interest in the venture.

For a given company involved in the production of recombinant products, there are several characteristics defining its marketing strategy:

- **Bulk compound / finished products:** the company may choose to market the purified protein as a component bought by other companies formulating the final drug.
- **Comprehensive marketing / Distribution Agreement:** In the case of finished products the company may choose between marketing itself its product and using the marketing force of an integrated pharmaceutical company. This "pharmaceutical marketing force" constitutes an important asset in the pharmaceutical value chain, it is composed of a comprehensive network of representatives in close relation with every medical actor in the country, this can represent between 500 and 1200 people for a country like India.
- **Geographical range :**
  - In the case of a Bulk Compound marketing strategy, the choice will be made between selling this compound to Local Pharmaceuticals Companies or Foreign Pharmaceuticals Companies.
  - In the case of a finished product the choice will be between addressing the Indian market and targeting the global market.

2.2. Strategies of entry in function of the initial profile.

2.2.1. Indian Integrated Pharmaceutical Companies

Main assets: marketing and legal work force, knowledge of the market, funds available for new projects.

The Indian pharmaceutical companies are known to have outstanding in house competencies in chemical analysis synthesis and process engineering, but those competencies are hardly of any use while trying to set up the Industrial production of recombinant proteins *(cf. interview Cipla).* Nevertheless those companies' marketing network and their experience in the field of chemical generics is a relevant asset.

Moreover, some of these companies have had the opportunity to get a marketing know-how of this field through marketing agreement for the distribution of recombinant products for foreign companies. (USV, Nicholas Piramal)

The Integrated Pharmaceutical Companies' expertise in formulation, drug delivery, legal matters, and their marketing network are valuable assets for the entry in the market of therapeutic recombinant proteins. Since the skills necessary to complete the preceding stage of the value chain (development of the hybrid cell line and the industrial scale up of the fermentation and purification process) are costly to acquire, technology transfer partnerships seem to be the more reasonable way. We will see what kind of strategies the companies interviewed has adopted.

Competency acquisition:

- ***Cipla***: The company has identified the production of recombinant therapeutics as a thrust area but has not yet achieved any technology acquisition (basic technology and industrial scale-up).The company's head thinks that he needs a comprehensive technology transfer, and an in-house leader able to manage the project. He does not think that the Indian public institutes have the competencies to be good partners, they may have the competency for shake-flask expression, but they lack the scale-up skills. He is not satisfied with the project from other foreign companies that have been submitted to him so far. Either the project was not detailed enough, or the financial involvement required from *Cipla* was too important. Dr. Hamied thinks that a J.V. is the better form of partnership for this kind of project, since it ensures a market involvement from both parts.

- ***Wockhardt*** : Biotechnology have been identified by the chairman has a core development path since the early 90's and since then, *Wockhardt* has experienced many different strategies of competency acquisition.
  - Collaboration with a public institute: a collaboration was initiated with the Italian branch of ICGEB in Trieste concerning joint research on recombinant products (Hep-B Vaccine, EPO, Human Insulin…) but this collaboration was stopped because of the lack of results.
  - Some trials were done in house to develop a recombinant Hep-B Vaccine.
  - By 1995 an efficient research base was set in house and the first BT product launched was a biopesticide (1997).

- Corporate collaboration: *Wockhardt Rhein Biopharm Ltd*, A 50/50 Joint-Venture was set up in 1996 with *Rhein Biotech GmbH*, for development and manufacturing of Recombinant Bio-pharmaceuticals. This collaboration has met success with the successful introduction of a recombinant Hepatitis B vaccine Biovac-B. Due to conflict of interest, *Wockhardt* has bought *Rhein*'s shares and now controls 100% of the venture. Nevertheless technology transfer agreements have been signed with Rhein.
- By 1999 *Wockhardt* had an in house expertise in genetic engineering
- *Wockhardt* is now developing its in-house technical base in its BT-dedicated R&D centre in Aurangabad.

· ***USV***: The company has some licensing agreement to sell recombinant products in India, and is engaged in BT R&D concerning the production of recombinant peptides & proteins. It plans to launch the production of Hep B vaccine, EPO, and Human Insulin in the two next years.
- USV has signed licensing agreement concerning streptokines, interferon alpha-beta, and Muromonob (recombinant product) with *Heber* biotech and *Cimab* (Cuban companies).
- It set up its own BT R&D team in 1999 with a team of 10 to 12 scientists.

· ***Ranbaxy***: Production of Protein therapeutics is not part of *Ranbaxy*'s BT strategy. Ranbaxy has established a J.V. with Eli Lily for the marketing in India of the Swiss company's recombinant insulin.

· ***Dr reddy's:*** Dr Reddy's is the first company in India to develop a molecule from the molecular biology stage to production. GRASTIM (generic name: filgrastim), the human Granulocyte Colony Stimulating Factor (hG-CSF), is a recombinant protein used in chemotherapy-induced neutropenia and in bone marrow transplantation. The biogenerics project started in 98, The first molecule was obtained in 3 years. No collaboration was used, all the research being carried out in house.

· ***Biological E:*** Biological E. R&D strategy is strongly oriented toward the funding of both applied and basic research in public institutions. Among other projects B.E. is developing a recombinant Hep B vaccine in collaboration with the IISc Bangalore. BE licensed the technology from IISc; IISc used a particular yeast to express the surface antigen, they delivered the project on lab scale (gave the clones). BE then improved the expression and brought the product to clinical trials.

The case of Cipla illustrates the first organizational gap mentioned in the description of the value chain. It shows the difficulty that a firm with capabilities relevant for the latest stage of the value chain like Cipla will face while looking for a partner able to transfer the technology it lacks to implement the production.

The case of Wockhardt confirms the difficulty of a technological collaboration between a research institute and a private company. The collaboration with another company may be an interesting alternative as shown by the examples of collaborations between Wockhardt and the German company Rhein Biotech, and between USV and the Cuban company Cimab. This kind of collaboration may be a way for the Indian companies willing to acquire a technology, to deal with interlocutors more aware of the corporate imperatives than in the case of collaboration with a purely public institute. The learning may be done, not only through a technology transfer agreement, but also through a simple

licensing agreement. In this case, as illustrated by USV's strategy, the distributing company increases the efficiency of its marketing force in the specific field of therapeutic recombinant proteins. Coming back to the technology acquisition through collaboration with public institutions, it can be assumed that both parties are learning how to collaborate more efficiently with each other. Indeed, the ICGEB, whose collaboration with Wockhardt in the early days of the interest for therapeutic recombinant proteins did not prove successful is now involved in several private-public partnership, and Biological E. has set up several ambitious programs in collaboration with the IISc.

Marketing strategy:

The IIPCs logically position themselves as providers of finished goods, and use their domestic marketing force to address the local market. Concerning the expansion strategy the progression from the local market toward the global market seems to be the classical business plan. :

- ***Cipla***: Cipla's strategy is to become a global leader in generic pharmaceuticals thanks its cost advantage.
- ***Wockhardt****:* Wockhardt has set an agenda for its globalization based on the different procedures of clearance applicable in certain types of countries. The scheduled progression is organized as follows.

1. Take the same product as existing in some countries (S.E. Asia, Eastern Europe, Latin America)
2. Enter a second type of countries where the registration might take 1.5 to 2 years (Hungary, Poland)
3. Target Europe & Canada
4. Get into the U.S. market (risks of expensive litigation)

Wockhardt sees the biogenerics products as the vector to make the company global.

Today, 33% of Lockhart's turnover comes from export, and this share is expected to rise to 50% in 2005.

- ***USV***: The company plans to get into the market of therapeutic recombinant proteins as an integrated manufacturer and distributor, its current role of distributor in India for its Cuban partners Heber and Cimab is seen by the company as a way to get a better knowledge of the market in order to build a more efficient integrated strategy.
- ***Dr reddy's:*** A specific field force dedicated to the BT products is being set up. As far as the Granulocyte Colony Stimulating Factor is concerned, the marketing of this drug used for the treatment of cancer is taken in charge by the field force dedicated to this specific therapeutic area (40 people in the Oncology field force)
- ***Biological E:*** The company has adopted a ***s***trategy for globalisation in three phases
  - South East Asia
  - Africa
  - Eastern Europe

  The determinant of this strategy is the time required for approval but also the role of public health institutions in the countries. Indeed, getting a market for a public program needs less investment than developing a private market. In the case of large scale health programs

The Indian pharmaceutical companies have built a very valuable asset with their respective marketing network in India. Therefore, they are partners of choice for foreign companies willing to address the Indian market for therapeutic recombinant proteins, which offers tremendous prospects. Moreover, the production of those products in India has proved to be very cost effective and the Indian Pharmaceutical Companies are positioning themselves as competitive global providers of bio-generics in the came way as they are already considered as major player in the field of chemical generics.

2.2.2. Diagnostics reagent & vaccines manufacturers

Main assets : acquisition of technical know-how through the production of recombinant products with diagnostics application, international network of customers in the health care sector, compliance with the international standards of quality. The adoption of rDNA-based products is a logical evolution for this kind of companies. Most of the products they marketed can now be obtained both by conventional way and through recombinant or monoclonal technologies. While the conventional process involves the extraction of the antigens or antibodies from natural sources, and their purification, the modern technologies allow producing the same kind of compounds through the expression of genetically modified and cloned DNA. The recombinant products, on a long term basis, are also less costly, and their adoption is a natural evolution for the diagnostics reagents and vaccines manufacturers.

The production of recombinant products for diagnostics application does not require the same investments in testing than the one required for the commercialisation of products with therapeutics use, since the products used in diagnostics do not enter in contact with the patient metabolism. Once they have mastered the use of recombinant technology for the production of products with diagnostics application, they can use the acquired know how in order to shift to the production of recombinant proteins with therapeutics application..

Strategy for technology acquisition

- ***Bharat Serum and Vaccines:*** The company is already a global provider of natural reagents for diagnostics and vaccines. It has drawn ambitious plans for the production of recombinant products and monoclonal antibodies for diagnostics kits, and has already planned the production of recombinant therapeutics. Concerning the technology acquisition, it has set up an internal R&D team and has several tie up with foreign partners for technology transfer.
- ***Yashraj***: *Yashraj* has strong in-house competencies in molecular biology and recombinant technologies and plans to produce recombinant products in the three next years. The competency acquisition was realized by hiring young scientist with a strong background in modern biotechnologies techniques. Although *Yashraj* envisages developing the new product independently, the scientists think that a technology transfer (cell line, target identification) could help them to save some time.
- ***Accurex***: *Accurex* is involved in kits development. Therefore, the company is a consumer of recombinant enzymes as raw materials for its diagnostics kits. The shifting from the use of natural enzymes to recombinant enzymes doesn't require any adaptation of the process. Nevertheless, the company has plans to develop more

integrated and high value activities, the company is looking for ties up with universities to develop new products in immunoturbimetry. They first plan to import such products in order to understand the market (within a year), and then import antibodies and manufacture the products. They could manufacture monoclonal antibodies in house in 2 to 3 years (the help from a university would be useful).

- ***Artemis Biotech***: *Themis* is prospecting the possibilities of technological transfer for the production of EPO, Human Growth Hormones, alpha-interferon, and plant hormones. *Themis* has established contact with biotech firms in China, Argentina and Italy. What *Themis* expects from a potential partner is: quality of the technology (cell lines as well as the production facilities), knowledge of the business, as well as financial resources. The first contacts were established one year ago and the negotiations are still going on. Dr; Patel is still not completely confident in the technology proposed by the potential partners.
- ***Bhat Biotech****:* Dr. Bhat was a professor at U-Penn. He moved back to India in 1994 and decided to settle a business in his field of competency. Bhat is the only company in India to produce antigen-based diagnostics. The future prospects of the company are expanding the diagnostics product line and getting in the production of recombinant therapeutics.
  The chairman competency is a strong asset for the technology development. For a new cell line in order to produce recombinant therapeutics, the assessed need would be: 1 year of R&D, involving 3 scientists paid 10-15000 Rs/months
  It took him 6 months to develop the technology for the expression of the antigens used in the diagnostics, produced in bacteria.

The sector of diagnostics is in itself a major field of application of the modern biotechnology. We consider here only the relevant assets the different companies interviewed and belonging to this group may have to enter the market for therapeutic recombinant proteins. Considering the assets relevant for the earliest stage of the value chain, i.e. the lab scale development, we can notice that companies like Bhat Biotech and Yashraj are well armed to implement efficiently new productions of recombinant products thanks to the presence in their team of a little number of scientists with the very specific skills necessary to conduct the operations of research and development. Regarding the stage of industrial production, the know-how acquired through the production of reagents or vaccines through manipulation of natural products is a capability that can be reinvested efficiently in a process using hybrid cells fermentation.
Compared to pharmaceutical companies with experience only in synthetic chemistry, we can therefore say that the players of this category have a slighter organizational gap to fill in order to enter the market for therapeutic recombinant products.

Commercial strategy

Although the companies interviewed have several projects of recombinant therapeutics, and even products in advanced stages of development (bioequivalence assessment) no such product has been put on the market yet, and no information is available about the strategy of distribution that these actors would adopt. Nevertheless, we can already notice that the marketing and legal forces necessary for the direct introduction of such products on the market are specific assets that most of these companies do not possess, contrary to

the one belonging to the group of Integrated Pharmaceutical Companies. In the case of the entry of such a company in the market, it would have, either to develop its own marketing force dedicated to the new line of product, or to sell its products to another company in charge of the distribution.

2.2.3. Enzymes manufacturers

Main assets: acquisition of technical know-how through the production of recombinant products with non-therapeutic applications, expertise in fermentation process.
As in the case of the latter class of companies, the recombinant technologies have introduced cost-effective production process that can be substituted to the conventional processes based on natural products.
These actors benefit from an initial competency in conventional fermentation that can be reinvested in the industrial scale-up of recombinant DNA expression.

Competency acquisition:

- ***Advanced Biochemicals***: Advanced biochemical has begun to integrate the modern biotechnology in its production process by 1991.
  - Development of in house competency through the hiring of experienced professionals: due to a bad choice of project people (from public companies like Hindustan Antibiotics Limited.) the company found itself in a difficult financial situation in 1995 (10 M US$ were “lost” at the starting of the project). Finally, the in house competency for recombinant enzymes production could be developed
  - Acquisition of cell lines through corporate collaboration: 0.4 M US $ for the acquisition of 7 cell lines from a south Korean Company.
  - Acquisition of cell lines through a loose collaboration with a Japanese university: 0.6M US$ funding and 7 cell lines obtained.
  - In house development of cell lines: 2 to 3 M US$ have been invested during the ten last years in process development and molecular biology. 2 cell lines have been developed in-house.
- ***Biocon:*** In the field of generic pharmaceuticals, Biocon has built some strong entry barriers thanks to competency in: Solid state fermentation, submerged fermentation Chemical synthesis.
  Concerning the recombinant proteins Biocon has entered into a J.V. with Shanta for the production of Insulin. The two companies conduct independent R&D activities. Biocon will be in charge of the production and will sell the protein to Shanta. Shanta will then take care of the formulation and the final product should be sold by the J.V.
- ***Bangalore Genei:*** Bangalore Genei produces enzymes and related reagents for genetic engineering research. The company is already in talks with Indian pharmaceutical companies for the production of recombinant therapeutics, but no concrete agreement has been reached.

The companies belonging to this group have developed a valuable asset which is their technical know-how in fermentation and downstream processes. This corresponds to the third stage of the value chain described in chart 5, and several articulations with the upstream activity of R&D are observed. Advanced Biochemicals is exploring

possibilities of partnerships with foreign companies and institutes from East Asia. Biocon has set up its own R&D force and has built partnerships with a major player of the market. As for Bangalore Genei, the company is waiting for agreement with a downstream partner but its in house R&D capabilities should enable the company to achieve the upstream development.

Marketing strategy:

- ***Biocon***: Biocon has set up a JV with Shanta for the development, production and commercialization of Human Insulin. Biocon will be in charge of the production and will sell the protein to Shanta. Shanta will then take care of the formulation and the final product should be sold by the J.V. (interaction with the first refusal agreement signed between Shanta and Pfizer.). This agreement is motivated by the fact that Shanta has no such large fermenters (2000L) as Biocon has, and production on a smaller scale would not be economically viable.

The case of Biocon shows clearly the critical importance of the know-how of companies such as the one described in this section. The ability to scale up an industrial process of fermentation and purification for the production of recombinant proteins is a key competency that has to be articulated with the upstream technology and the downstream marketing and legal forces to complete the value chain. The case of Biocon signing a JV agreement with the Indian pioneer of the therapeutic recombinant proteins Shanta shows how valuable is the technology that Biocon masters thanks to its experience of industrial enzymes manufacturer. The valuation of this technology should also offer good perspective to Bangalore Genei. In the case of Advanced Biochemical, the absence of initiative in the domain of therapeutics is justified by the lack of knowledge of the legal matters specific to this domain and the financial difficulties the company has just achieved to overcome.

2.2.4. Dedicated start-ups

Main assets: clear & focused strategy, specialised and efficient technical management, network of technical cooperation.

The two companies representative of this class were promoted in the mid 90's with the clear objective of providing a cheap substitute to the recombinant Hepatitis B vaccine then provided through import from MNC pharma majors like *SmithKline Beecham*.

While Shanta was initially incubated in public institutions (Osmania University and CCMB, Hyderabad), Bharat developed its first product with a team of 8 scientists headed by the promoter of the company.

Technology acquisition

- ***Shanta Biotechnics***: Shanta is involved in the development, manufacture and marketing of therapeutics obtained through recombinant technology and monoclonal antibodies. The Managing director identified the need for local production of recombinant Hep-B Vaccine in the early 90's. In 92 a small lab in the Osmania University was dedicated to the project. In CCMB the research shifted to the CCMB, where Dr. Prasad headed the research team. In 95, Shanta settled its own lab with 10-

12 scientists. Shanvac, the first Indian recombinant therapeutic protein was put on the market in 1997. The development of Shanvac was achieved by Shanta's own team. Nevertheless, Shanta has several collaborative research program ongoing with public institutions such as :

- IISc for Human Growth Hormones.
- JNU for Streptokinase.
- BARC (Mumbai) for a fruit based Hep B Vaccine.

All these partnerships were initiated two years ago.

· ***Bharat Biotech:*** Dr. Krishna was a molecular biologist specialised in yeast in the US. He decided to come back to India in 1996 and wanted to start a business. He started Bharat Biotech at the end of 1996. It took 2 years to develop the Hep B vaccine. The research team was composed of 8 people headed by Dr. Ella. A pilot plant was set up at the end of 96. In 1999 the product was launched. It took a total of 2 years to get the DCGI's approval (phase II & III studies had to be carried out on 500 patients). In 97, the company started developing streptokinase. This product is now in phase III trials. The main technological obstacle was folding and stabilisation of the protein, since the protein size is very different in the case of streptokinase. The reason why the Streptokinase took more time to be brought to the market was the financial constraint. Given the funds available, the focus was on developing the revenues from the sell of the Hep B vaccine. The Hep B vaccine has been on the market since 99. The next products to be launched are the recombinant Streptokinase and a conventional vaccine for Typhoid. The other products under development are Epidermal Growth Factor (produced in E. Coli) and Insulin (produced in E. Coli).

The case of these two companies shows how well-managed collaborations with Indian public institutes may enable new entrants with no settled capabilities to build the needed capabilities to enter successfully the market.

Commercial strategy

· ***Shanta Biotechnics:*** Shanta has a co-marketing agreement with Pfizer. Pfizer has a first-refusal right on the distribution of each of Shanta's products. Currently, Pfizer is distributing 50% of Shanta's Hep B Vaccine under its own brand. Pfizer's field staff in India is composed of 900 people, nevertheless Shanta wanted to get into the marketing stage because of the effect of the brand on the rest of the business. The marketing began in September 97. Shanta first covered the western and southern part of India with 60 people, then after 18 months the company covered the northern and eastern part with 60 other people.

· ***Bharat Biotech:*** Bharat has its own marketing force of 140 people. The company has developed an efficient logistic chain with private partners (the main technological obstacle consists in respecting the cold chain). Bharat is already selling in Latin America (1/2 M $), and is waiting approval for South Africa. The company needs more funds to address the other Asian markets.

The strategies of these two companies shows the importance of the asset that a field-force dedicated to the distribution of therapeutics on the Indian market represent: in terms of people, this field force represents 120 to 140 people. Setting up such a marketing network represents a considerable investment for young companies such as the one mentioned in this section. Nevertheless, it has been shown by the example of the chemical drug market that the margin is mainly situated on the side of the pharmaceutical companies taking in charge the formulation and distribution of drugs rather of the bulk drug manufacturer's side. This fact explains the effort done by the two manufacturers of recombinant proteins in order to set up their own marketing capability in India.

2.3. Conclusion

In the latest sections, we have seen that the three first groups of companies, through their respective initial activities are embedded with capabilities that can be invested usefully in a new activity in bio-generics. In the case of the Integrated Pharmaceutical Companies this asset is the legal and marketing capabilities. In the case of the diagnostic reagent and vaccine manufacturers, the expertise in the downstream processing of natural proteins can be reinvested without cost in the processing of recombinant proteins. In the case of enzymes manufacturers, the expertise in fermentation is also a strong asset that can be valuated through the production of high-value recombinant proteins. In the case of the fourth group of companies, named dedicated start-up, all the capabilities had to be acquired and the success of the venture relied on the quality of the management of this competency development.

Concerning the industry organization, we can first conclude that the Indian market for bio-generics will become more and more competitive in next years with the entry of several firms from different origins. Potential leaders of the market seem to belong to all the four groups mentioned in this section. Indeed, Wochardt (IIPC), Shanta, and Bharat (dedicated start-up) are already well positioned on the market, and the entry of large players such as Biocon (Enzyme manufacturer) and Bharat Serum (Diagnostic reagent and vaccines manufacturer) is already planned. Apart from the Shanta-Biocon J.V., the preferred strategy seems to rely on an integrated model with discrete technology transfer agreements. Concerning the technology transfer, the ability of both private companies and public institutions to collaborate within the gridline of a technological partnership seems to be increasing.

Concerning the role of the Indian bio-generics producer in the global market, the agreement of first refusal signed between Shanta and the global major Pfizer - well known to be the pharmaceutical company with the largest R&D budget world wide – shows that Indian players should be considered as serious competitors by the global major.

C. Drug development

C.1. Introduction

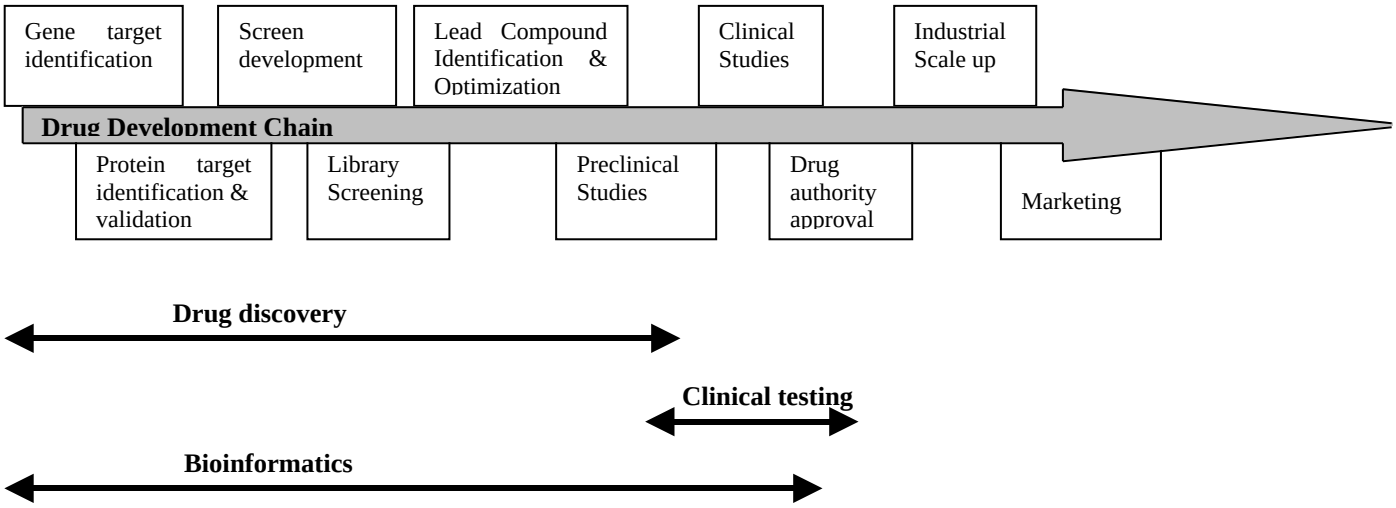
The new drugs issued each year always target more singular diseases with more restricted market, and the complexity of the compounds developed thanks to biotechnology increases the cost of testing. Therefore, if the global pharmaceuticals companies want to maintain their rate of return, each opportunity of cost saving must be taken into account.
India has been considered for the last 25 years as a risky country by pharmaceuticals companies because of the reviewing of the patent act in 1976 restricting the patent protection to the processes. This allowed - along with an exceptional local competency in reverse engineering – to build a strong local pharmaceutical industry, now recognized as a global player in the generics markets.
Therefore, India has not been the place for any large-scale international co-operation in the pharmaceutical sector so far.
Nevertheless, many elements allow predicting an evolution toward a development of this kind of international collaborations.

- India's representatives have recently voted the amendment of the patent act, in order to include the compulsory provisions required by the TRIPS agreement from WTO. This means that on January the 1st 2005, the product patents will have to be respected in India.
- The assimilation of a biotech-based process requires far more competency than the copying of existing chemical best-sellers drugs. Therefore, an unwanted diffusion of technology has less chances to occur through local informal channels.
- In case of technical piracy, the only potential markets for the copy are unprotected markets. In the case of chemical best-sellers drugs, the Indian market offered enough opportunities to motivate reverse engineering. But in the case of the drugs currently developed by the biotech companies, the market in India would be negligible, considering the therapeutic targets of these new drugs that are often more restricted, and the cost of developing the market for a new drug.

There are now several small-size companies in India that have been created with business models based on partnerships in fields related to the manipulation of genetic information. All these companies do not only focus the sector of drug development. Namely companies like Avesthagen and Metahelix focus on plant genome knowledge application. Nevertheless we chose to organise our description of the sector around an analysis of the drug development process and its organisation.

Here is a segmentation of the value chain that can allow us to position the main types of business models.

Chart 6. "Concept to market" : the comprehensive drug technical development and marketing Chain



The "concept to market" chain provides us information about the positioning of the companies on the development chain. This segmentation is based on the technical progression of the drug development and does not provide an actual vertical segmentation of the value chain. For example, bioinformatics acts as an input in several activities located along the drug development technical chain, but is not necessarily inserted in this chain as a central stage. One bioinformatics company can therefore be considered as an upstream partner on the value chain for several other companies situated in different segments of the drug development technical chain.

Although this segmentation is commonly used, the technical evolution in the field of drug development produces constant reorganisations. Having to consider complex and fast evolving models of co-operation, we cannot avoid defining in depth what are the characteristics of a certain model, that is, basically, the type of technologies involved and the type of contracts used by the company.
As we will see further, the companies belonging to the "drug discovery" category do not form a homogenous population. Neither can they be discriminated following an one-dimensional positioning on the drug development chain. In fact the category of

bioinformatics and clinical trial are the only ones for which a strict – though restrictive – definition can be provided.

In the following section, we give a technical introduction to the complex and fast evolving structure of the drug development chain. Then we discuss the different business models that can be identified along this chain.

1.1.1. BT-based drug development: technical introduction.

The new trends in drug discovery, namely, the focus on genomics drug discovery and development relies on the belief that stages of disease and its progression are caused by a sequence of changes in the expression levels of genes[24] and the activities of specific proteins and pathways in affected cells.

Genomics is broadly defined as the study of an organism's genome including the location, structure, sequence, regulation, and function of its genes. The worldwide effort to increase the knowledge was embodied in the Human Genome Project.

The **Human Genome Project** (HGP) is an international research program designed to construct detailed genetic and physical maps of the human genome, to determine the complete nucleotide sequence of human DNA, to localize the estimated 30.000-40,000 genes within the human genome, and to perform similar analyses on the genomes of several other organisms used extensively in research laboratories as model systems.

A first draft sequence of the Human Genome was disclosed in February 2001 and the sequencing is still going on with a goal of providing a more refined result in 2003. However, the results already available have a critical impact on the drug discovery by

[24] The **genome** of a certain type of organism defines the comprehensive sequence of nucleotide pairs constituting its DNA material. DNA can be arranged in a single circular chromosome (in prokaryotes organisms) or in several linear chromosomes (in eukaryotes organisms), each of which is segmented into discrete informational units referred to as genes.
Each gene, in turn, contains within its DNA the specific instructions to produce a protein, that is, the actual coding of the protein sequence (the exon), and information about the conditions of this expression.
During gene expression, different cellular elements come together to produce the protein. This process occurs through an intermediate molecule called messenger RNA (mRNA) whose sole purpose is to communicate by means of translation, the information in the genetic code of the gene into the structural and functional elements that specify the protein.

While each cell of the body contains all of the roughly 30,000 to 40,000 human genes, only a small percentage of those genes are simultaneously active in any cell. The particular genes that are active, or expressed, determine which proteins will be made. The degree to which a gene is expressed determines the quantity of the corresponding protein. These proteins in turn determine a cell's structure and function, whether, for instance, it will be a brain cell, a lung cell, or a blood cell. Gene expression also reflects how the cell is functioning and how it is responding to its environment. For example, certain genes will be more or less active in a diseased cell than in a healthy cell of the same type. These differences provide valuable clues about which genes, and therefore which proteins, are involved in a disease pathway. By finding compounds that affect these over- or under-expressed genes and proteins, researchers can develop innovative drugs that prevent or treat the disease.

providing a huge amount of data relevant to target identification. Therefore many experts claim that the biotech industry has entered the "**postgenomic era**".
The challenge is now to use the amount of data available to make the next step toward new drug discovery that is to explore how DNA and proteins work with each other and the environment to create complex, dynamic living systems. This is what is usually called **functional genomics.**

Since proteins are the way the genes influence the environment, the study of the proteins present in the cell, that is, its **proteome** is logically an important part of functional genomics. A protein's chemistry and behaviour are specified by the gene sequence but also by the number and identities of other proteins made in the same cell at the same time and with which it associates and reacts. Studies to explore protein structure and activities, known as **proteomics**, will be the focus of much future research. The main techniques used for proteomics are: 2D-Gel Electrophoresis (used for separation), Mass Spectrometry (used for identification, quantification, and characterization), and Protein Chips (emerging and high throughput technology).

Nevertheless functional genomics does not only encompass proteomics but also:

Transcriptomics involves large-scale analysis of messenger RNAs transcribed from active genes to follow when, where, and under what conditions genes are expressed, this analysis involves the use of oligonucleotide and cDNA **microarray** chips.
Comparative genomics--analyzing DNA sequence patterns of humans and well-studied model organisms side-by-side-has become one of the most powerful strategies for identifying human genes and interpreting their function.
Structural genomics consists in generating the 3-D structures of one or more proteins from each protein family, thus offering clues to function and biological targets for drug design.
Knockout studies consist in inactivating genes in living organisms and monitoring any changes that could reveal their functions.

The general process for genomic based discovery program is organised as follows:
Target identification consists in isolating the molecules or pathways responsible for, or associated with a certain disease. Once a gene is identified as being related to a certain disease (functional genomics), the action of this gene has to be studied in depth by studying the transcriptome and proteome. These studies provide a list of candidate target, which have to be validated.
During **target validation** stages, functional genomics technologies are used to evaluate whether or not the protein would make a good target for therapeutic intervention.
Then **drug screens** are developed to detect whether or not a potential drug candidate can effect a specified change in a disease-related target gene. During this stage of development, targets are developed into **assays** and are subsequently screened in an iterative process with small molecule libraries to identify drug **leads**. Leads are short chemical molecules from the libraries that have been tested, and for which an interaction with the target has been observed.

The number of chemical entities in the libraries is amplified by the **combinatorial chemistry** techniques.
The automated technologies allow to screen the target through a large number of small molecules from the **chemical library**, these technologies are called **High Throughput Screening**, the fastest technologies, called Ultra High Throughput Screening, can accelerate the screening to greater than 100000 test per Day.
The screening indicates a certain number of lead compounds from the chemical library that made a hit on the assay. This constitutes the **lead identification** stage. These leads compounds are reviewed considering their properties (like bioavailability, pharmacokinetics, toxicity, specificity), they are then optimised thanks to medical chemistry and combinatorial chemistry. This constitutes the **lead optimisation** stage. This phase, as well as the following phase of the drug development can also be carried out more efficiently thanks to the new techniques emerging from the genome knowledge. Indeed, **pharmacogenomics**, by relating drug response to genetic markers, allows adopting more relevant methods of selection during the lead development.
If this optimisation allows the final lead candidates to match the conditions, this lead compound will then start the process of **preclinical trials**. Those are laboratory and animal studies designed to test the mechanisms, safety, and efficacy of a therapeutic intervention, before the first test on humans. The lead is tested in-vitro on cell lines for effectiveness, and in live animals in order to test the toxicity and validate the pharmacological activity.

Once this process of drug discovery is completed, in the case of validation of the lead by the preclinical trials, an investigational drug application is filled and if accepted, allows the developer to start clinical trials.
Those trials are organised in three phases:
At the stage of the **Phase 1 trials,** the drug is tested on a small group of healthy volunteers. These studies aim at determining the metabolism and pharmacological actions of drugs in humans. It allows to identify the side effects that can occur following an increase of the doses, and to assess the effectiveness.
The **Phase II trials** aims at assessing the effectiveness of the drug for a particular indication in patients affected by the disease under study, and determining the short term side effects and risks of the treatment.
The **phase III trials** are conducted once a preliminary evidence of the drug effectiveness has been obtained. They are intended to gather additional information allowing assessing the long term benefit-risk ratio of the drug. These studies take several years and involve a large number of patients and constitute the most expensive part of the drug development.

One question that can arise at this point is: which of these activities have to be considered as biotechnology activity?
Technically speaking, the tasks entering in the fields of biotechnology as we defined it are the one involving an in depth knowledge of the structure and mechanisms of expression of the genome. We could try to carry out the painstaking study of which knowledge of the genome is involved at each stage. Nevertheless, while performing an economic study of the development of a certain economic sector – the so-called

"biotechnology" sector, each type of activity which is affected by the overall development of biotechnology has to be studied. Namely, even if the building of software tools used as input for biotechnology research did not involved any knowledge about molecular biology (which does not seem to be the case anyway) neglecting the development of the field would be meaningless within the gridline of an economic analysis. Some other type of activities, which do not imply obviously the use of the modern tools of biotechnology, have also to be considered while studying the sector. For example, chemical research is a critical element of the drug development chain, which importance has not been reduced by the apparition of the new tools of biotechnology. The development of chemical libraries through combinatorial chemistry, or the development of theoretical libraries in-silico[25] is hardly separable from either biotechnology or bioinformatics.

The next section proposes tools to analyse the nature of the different business models emerging on the drug development chain.

[25] The term “in-silico” refers to its analogues “in-vitro” and “in-vivo”. These terms can be used referring to biological experiments. When an experiment is carried out in a living organism, it is an “in-vivo” experiment. When carried out in an artificial medium, it is called “in-vitro”. Finally, when the axperiment is simulated on a computer, it is called “in-silico”. The term “silico” refers to the silicon used in the computer chips. In the same way, an “in-silico” library will be a computer listing of hypothetical molecules used in computer simulations.

1.1.2. Categorisation of the business models

In this section we will try to set the base for the definition of standard business models in the biotech-based drug development chain. The term of business model was mentioned in the introduction of this report. It was explained that we have observed that the spreading of biotechnology is linked with profound changes in the organization of existing firms, or with the apparition of new firms with original business models. The elements constituting the base for the definition of the business model of a given firm were said to be the value chain the firm gets involved in, the stages of this value chain the firm takes in charge, and the kind of contracts it signs, those contracts defining the tasks of the firms as well as its type of revenues.

General Characteristics of a business model

In the case of a company involved in a chain of research and development in the medical sector, the identification of the business model requires the definition of several classes of characteristics that can be determined in the following order.

- **End use products** – to one end use product is associated one value chain with several stages.
- **Central development stages** – in the process of developing a new drug with the tools provided by the biotechnology, a stabilised sequence of stages seems to have emerged, which is common to every research programs. Identifying the achievement of which of these central development stages the work of a certain company contributes can be used to locate the business model vertically on the value chain.
- **Exchangeable goods –** The nature of the inputs and outputs actually exchanged by the company with its partners.
- **Assets** - The nature of the assets on which the company bases its model of value creation.

End use products

Therapeutics, Vaccines, Gene therapy, or diagnostics can be considered as end use products. The down-stream value chain does not involve the application of in depth competency in the range of technology defining the sector. The end use product also be characterised by its therapeutic application, the main therapeutic areas being : Oncology/Haematology, Metabolic/Endocrinology, Immunology/Inflammatory, Central Nervous System, Infectious Disease, Cardiology. (Source LEK)

Central development stages

Genomics, Proteomics, Pharmacogenomics, as well as sub-categorisations of the latter terms like functional genomics or functional proteomics only refer to the application of a certain range of techniques at a loosely defined stage of the drug development stage. If it is useful to understand what these terms refer to because of their widespread use, they cannot be substituted - in the case of an analysis in term of industrial economics – to the precise terms referring to the different stages of the technical chain.

The identified central stages are so far:

- Sequencing

- Mapping
- Gene targets identification
- Protein targets identification
- Protein target validation
- Lead identification
- Lead optimisation
- Preclinical testing
- Clinical testing

Those different stages are defined by their inputs and outputs:
The inputs can be:
Informational input products (database, outputs from up-stream stage).
Technical input products (chemical library, outputs from the up stream stage).
Technical equipment (HTPS, DNA chips)
Application of scientific knowledge (Molecular biology, combinatorial chemistry, medical chemistry)
Computational & Knowledge management work (bioinformatics, cheminformatics).

Some examples of outputs are:
Sequencing: sequence of chromosomes
Mapping: knowledge about the position of genes in the DNA sequence
Gene target identification: List of genes potentially responsible for a certain disease.
Protein target identification: List of genes potentially responsible for the disease.
Protein target validation: Identification of the protein most likely to be responsible for a certain disease.
Lead identification: List of chemical compounds with an action on the protein.
Lead optimisation: Identification of the chemical compound with the best characteristics for a therapeutic use (availability of the compound in industrial quantities, possible interactions with other drugs, duration of the presence of the compound in the organism).
Preclinical testing: Predictive information about the potential risk for the patients.
Clinical testing: Statistical data about the response of patients to the drug (efficiency, risk for health, risk of interaction with other drugs).

These inputs and outputs can be categorised to really understand the nature of these goods (products/services), (informational/technical)).

Exchangeable goods
Informational product: Spot contract, well defined object of the exchange.
- DNA sequences + information on these sequences (gene)
- SNP databases.
- Target
- Lead
- Virtual Library

Informational services: Takes information as an input to deliver information in a more valuable form.

- Some kind of computational services (Data analysis, Protein 3-D modelling)

Technical product:

- Technical equipment (High ThroughPut Screening equipment, Diagnostic equipment)
- Process inputs (chemical library).

Technical services: Provided a certain technical process input, returns a valuable good (other technical input or informational product). Characterised by the status of the input: black box

- Service oriented exploitation of a certain equipment (PCR: DNA as an input, amplified DNA as an output, Analysis: compound as an input, information as an output).

Assets:

- Scientific knowledge base (molecular biology, combinatorial chemistry, medical chemistry, informatics…)
- Technical equipment.
- Technical know-how.

All the categories mentioned earlier may seem exhaustive but rely in fact on an assumption of defined contracts.
We will see that most of the contracts between the companies are very loosely defined. This can be explained by the impossibility to forecast the exchange of information (feedback) needed between the different partners during the project. We will then present in which cases the ability of the contracting parties to determine each party's responsibility allows to us to witness the emergence of business models described with the tools developed in this section.

Definition of business models in the case of relatively complete contracts: bioinformatics and clinical research organisation.

At this stage, we can explain why we considered however that it is possible to define the activities of bioinformatics and clinical testing.
These two activities can be defined technically:

> Bioinformatics consists in developing software tools for management and treatment of biological information.
>
> Clinical trials consist in managing the well defined process of testing of a drug candidate. (cf. chart 2. p. 21 : FDA drug approval process)

Even if such definitions are consistent, their utility is only verified if we can actually observe companies emerging with such kind of models. Indeed, the process of developing a drug cannot be considered as linear and as in any technical development process, feedback loops are a critical to the optimisation of this process.
In the case of clinical trials and bioinformatics, we can assume that the amount of information sharing between the entities involved in those activities and ways of interactions are defined precisely enough to allow the subcontracting of those activities. This assumption comes from the observation of business models focused on one of these activities.

Apart from these models we did not observe the emergence of other general models based on a technical positioning.

At this stage, we can already analyze how these models can be explained with the tools formulated in the latest chapter.

A project of bioinformatics can be considered as composed of two phases which are the definition of the needs, and the operational development (in French: maîtrise d'ouvrage et maîtrise d'oeuvre).
In the case of bioinformatics, the first phase of conception requires a practical knowledge of research in molecular biology, while the second phase requires knowledge in mathematics, data management, and software development. The intensity of the feedback needed during the conception, linked to the ability of the user to define their needs, will determine if the development of the bioinformatic tools should be integrated or not by the potential users. On the other hand, the complexity of the programs and the need for established methodologies of software development - available in the established software companies - will push toward an integration of the bioinformatics activities by the established IT companies.
Several tasks require tools for which the specifications of the tools are defined precisely enough to allow the conception of generic tools sold as products.

In the case of clinical trials, the input is a drug candidate to be tested, and the main assets are:

- The ability to recruit patients for the testing and to carry out the testing correctly, which is based on the system of patient recruitment, and the network of clinics established by the company in charge of the clinical testing.
- The ability to manage the correct filing of the applications, this is based on legal skills, and knowledge of the administration.

The specificity of these assets to a certain kind of drugs is also critical, since it determines in how many different value chains one company should take part.

The concrete cases of Indian firms falling into these two categories will be studied later, but we can already use the example of these two business models in order to recapitulate the articulation between the business models and the ability of the contracting parties to sign relatively complete contracts. In the case of models of outsourced development of bioinformatics tools or management of clinical trials, the material and informational goods exchanged during the execution of the contract can be defined at the signature of the text.
We assume that it is in the opposite situation, that is, a situation of uncertainness about the exchange, that actual collaborations will take place. We consider that the very characteristic trait of collaborative work is the uncertainty of the different parties concerning the exchanges that will effectively take place during the collaboration. Given a certain objective, the partners work together in order to achieve it and revise the terms of the collaboration while progressing in the realisation.
In such a case of incompleteness, two different modes of incentives can be imagined. The first one is based on the repartition between the different actors of the incentives provided

by intellectual property rights. Such repartitions of the property rights used as a tool to provide efficient incentives in a situation of asymmetric information have been studied by the theorist of the firm applying the approach named the property rights approach. The second tool of incentives relies on the principle of multi-period games. In the case of a principal-agent[26] relation between two partners involved in research collaboration, the principal may choose to remunerate its partner on a milestone base. By doing so, the principal establishes a game with several periods in which the agent's optimal strategy is collaboration.

Other types of business models

The most common dichotomy used to define the business models of biotech companies is based on the opposition between **platform-based** models and **product-based** models. A company with a platform-based model uses a certain technological platform as an asset in order to provide mainly services, whereas product a company following a product-based logic focuses on the development and selling of a certain product. The second logic is supposed to present higher risks and highest rewards

In the case of the Indian players of the drug development chain, this dichotomy does not prove to be applicable, since all the company operate a mixing of the two logic in order to generate cash flow rapidly with a platform logic while pursuing a long term objective with a product-based logic. Since most of the companies operate this mitigation of the risk and rewards ratio, we preferred to establish a dichotomy based rather on the initial impetus for the emergence of the company.

Indeed, among the companies interviewed, a distinction can be established between **Technology driven** companies and **Opportunity driven companies.**

Technology driven companies start with a specific technological competency, and the will to develop revenue models based on this competency. Opportunity driven companies are created with the general goal of taking advantage of India's cost effectiveness to take part in the drug development chain.

This distinction may seem similar to the latter one, the technology driven companies being supposed to adopt product-based strategies while the opportunity driven companies would rather focus on platform-based models. But the interviews carried out shows that, while the need for rapid generation of cash flow is an incentive for all kinds of companies to propose services with various level of value added from their first days of operation, they all aim at the same goal, which is, accessing intellectual property on the final drug.

Combination of several business models

One other characteristic of the Indian companies interviewed is the multi-project aspect of their activities, indeed, only a few companies are really focused on developing a

[26] The economic study of principal-agent was introduced by Jensen and Meckling in their seminal article of 1976. What is now called "the Agency Theory" in Industrial Economics arises from the behavioural study of employer-contractor or employer-employee interactions characterised by asymmetries of information. The central question is how to get the agent (employee or contractor) to act in the best interests of the principal (employer).

certain product or offering a certain service, and most of them are involved in different stages of the drug development chain, and sometimes in different sectors.

Therefore, it is hard to define easily the companies who do not correspond to the two models detailed earlier of bioinformatics tool developer and clinical research organisation.
Some example of corporate strategy are revealing about the multitude of logics that can coexist in the field of drug development. The examples of Dr Reddy's and Biocon are especially interesting. Indeed these companies have created several entities, each of them corresponding to a different strategy.
The pharmaceutical company Dr Reddy's is involved in the development of recombinant DNA based products and has an internal program of BT-based drug targets discovery. It has also set up a bioinformatics company named Molecular Connections, and a contract research company named Aurigene, involved in chemical and biological research for drug discovery.
As for Biocon, this company whose core activity is the manufacturing of industrial enzymes, has set up a contract research subsidiary named Syngene, and a Clinical Research Organisation named Clinigene.
One can wonder if these logics are really independent, and if the competencies acquired by the subsidiaries involved in research collaborations with international partners could be reinvested by the group in internal R&D on a model of integrated drug discovery. It is hard to forecast now what will be the actual nature of the interactions between those contract research subsidiaries and their mother company, nevertheless at least on the short term, the mother companies claim not to have any intention of interfering with their subsidiaries. This means that no technologic information should circulate between the company in charge of contract research and the mother company involved in its own research. Therefore, the setting up of such contract research activities is claimed to be only an interesting investment in a promising business model, and not a collaborative strategy of competency acquisition.
If we accept the effective separation between those different entities, we can read the strategies of the Biocon and Dr Reddy's group as the parallel and separate trial of different business models. This shows that no models as been identified as the best base for competency acquisition, and that companies that are determined to find a way to the building of a biotechnology competency can follow many different paths.

General Questioning

On a larger scale the long term organisation of the drug discovery chain remains unclear: a very fashionable assumption is nowadays the one of an evolution of this organisation toward what is called a "virtual pharma"[27], that is, stabilised research networks taking the place formerly occupied by the integrated pharmaceutical companies and collaborating to feed common drug pipelines[28]. This assumption is comforted by the current rate of apparition of new companies aiming at inserting themselves in the constituting R&D

[27] Devlin A.J., 2001 The concept of virtual pharma companies" *Drug Discovery Today Vol 6.*
Walters G.E., 2001, Virtual Pharmaceutical Development : Case Study *Fulcrum Pharma*
[28] "pipeline" is a consulting expression used to designate the set of drug candidate that a pharmaceutical company has developed and that are going through the time consuming clinical trials.

networks. Nevertheless, the shape the ties of these networks will take in the future is still hard to forecast. We have mentioned the ambition widespread among the new companies to access to intellectual property. The management of the repartition of intellectual property among the discovery chain will surely be a challenge for the stakeholder of the constituting networks, and we can wonder if the organisation will be achieved with a decentralised co-ordination or if a new movement of vertical integration will appear once the technological paths are stabilised. The cases of successful pioneer biotech companies like Amgen that have built integrated capabilities argues in favour of this assumption. In this case, the technological chock of modern biotechnology would have produced a Schumpeterian movement of creative destruction within an unchanged model of organisation, integrated biopharmaceutical company simply taking the place of the pharmaceutical companies.
As it is shown in the following sections, the dynamic of development of biotechnology in India is not only the consequence of a technical evolution. It is also deeply dependent on the overall movement of globalisation of research and development, and one may wonder which place exactly the Indian companies will occupy in the international research and development networks.

The next sections show which business models the Indian companies interviewed have adopted so far. We will first describe the companies established with models based on collaboration in the general field of genomics and proteomics, then we will describe the companies that can be considered as developing activities on the model of bioinformatics tools provider and clinical research organisation.

C.2. Genomics-proteomics

In this section, the companies are differentiated following their conditions of emergence, on the first hand, one can find opportunity driven companies, and on the second hand technology-driven companies. No qualitative judging is associated with those terms, since they are only related with the conditions of emergence and not to the later functioning of the companies dealt with. An opportunity-driven logic can be considered as essentially demand-driven. Namely, the companies developed under this model are developed to offer a cost advantage on identified bottlenecks of the drug development chain. In the same way, a technology-driven logic can be described as supply-driven, the first focus being to build a comprehensive platform around a certain technology.

2.1. Opportunity-driven companies

The emergence of the companies considered as "opportunity driven" is supposed to be directly linked to the perception of an important opportunity for contract research activity in drug discovery. This is opposed to a “technology driven” trajectory which model is the building of a comprehensive technological platform in order to exploit the mastering of a certain technology.
It has been noticed that the companies belonging to the first group are financially backed by a large industrial group.

2.1.1. Condition of emergence

Here is a list of the companies identified as belonging to this group and their backing institution.

Table 12. Opportunity-driven companies in genomics and proteomics.

Name of the company	Affiliation.
Aurigene	Dr Reddy's (pharmaceutical)
Genenquest	Nicholas Piramal (Pharmaceutical)
Chembiotec*	The Chaterjee group (Oil, High Tech)
GVKbio	GVK group (Power, Hotels, Infrastructure)
Questar*	Gland Pharma (Pharmaceutical)
Reliance Life Science	Reliance group. (Fabric, Chemicals, Oil)
Syngene	Biocon (industrial enzymes)

**no interviews were carried out with these companies. The information used comes from the respective web pages.*

The strategy of these companies are not homogeneous, nevertheless, two main logics can be distinguished:

- A *prospective logic*, applied by Reliance Life Science and Genenquest, which can be characterised by an initial focus on competency building by independent research.
- A *contracting logic* which focus on the rapid signing of research contract with foreign companies. Aurigene, GVKbio, and Syngene can be considered as following this logic.

No matter which one of these two logic is followed by the company, the need for cash flow generation, and the implication of learning by doing mitigates the difference between the two ways of progression on a longer term.

2.1.2. Positioning

Except Genenquest, which has focused on the building of a Single Nucleotide Polymorphisms (SNP) database for certain kinds of disease, the companies belonging to this group offer a broad range of services?
If these companies respect their recruitment objective for the next 3 years, they should become giants, comparing their scheduled size to the critical size of a research team in molecular biology (around ten people). For example Aurigene is completing the building of a research facility designed for 200 scientists, and Reliance Life Science is investing 20 M $ in the building of a new R&D campus, as for GVKbio, the company already employs 75 scientists and this number should double before the end of next year.

This size should allow these companies to establish technical platform enabling them to cover nearly all the field of drug discovery, from genomics to lead development and preclinical testing.
Nevertheless, some thrust areas can already be identified.

One trend that can be observed is the offering of chemical research services. Indeed, Aurigene, Chembiotec, GVKbio, and Syngene claim to have a strong competency in the different fields of chemistry directly related to drug discovery, that is: synthetic and process research, medical chemistry, and combinatorial chemistry.
The cost efficiency of chemical research led in India has already been proven by the success of the Indian pharmaceutical industry. Moreover, the model of chemical contract research led in India for foreign firms is already established. Syngene was created in 1995 on this model and several companies and institutes have already achieved successful partnerships in chemical Research.
Among them are companies like Rubamin, IOCL, Strides Arcolab, Hikal Chemicals, Denisco, Avra Research, and public institutes like the IICT Hyderabad, or NCL Pune.

The other trend is the development of competency in proteomics, especially computational proteomics. Namely, Aurigene, Chembiotek, GVKbio and Questar are positioning themselves on this domain.
The border between services in computational proteomics and bioinformatics is not clear, but we chose in this report to consider as only bioinformatics activities the providing of computer solutions applied to biotechnology, and not only the use of computer tools to perform such analysis.

2.2. Technology driven companies

This group of companies is even less homogeneous than the first group. Nevertheless it can be easily differentiated from the first group by the financial conditions of emergence. While the first group of companies benefits from at least an initial support from the group they belong to, the company belonging to the second kind originated from the initiative of scientists who had to look for external funding and support to launch their activity.

Here are the three companies that have been identified as belonging to this group and their core technology.

Table 13. Technology driven in genomics and proteomics

Company Name	Core Technology
Avesthagen	Plant Genomics
Metahelix	Plant Genomics
Genotypic	Microarrays

2.2.1. Conditions of emergence

These three companies have been created by scientists or professionals in order to implement a certain research program directly linked with the promoters' initial field of competency.

Avesthagen was set up by Dr. Viloo Morawal – Patell, who did her PhD in Strasbourg (IBMP) under the direction of Jacques Henri Weil. She was working on mitochondrial genomics.

When Dr Patell came to India in 1995, she wanted to build a bridge between the public and private sector in the field of biotechnology R&D.

Genotypic was promoted by M.C. Raja and Sudha Rao, a couple of doctorates in molecular biology. The promoter have done PostDocs in Israel and US, and they wanted to come back to India and to start a business, taking advantage of the lower cost of operating in India.

Metahelix was created in Bangalore by 5 scientists with professional experience in the field of biotechnology, of which 3 were formerly associated with Monsanto.

The financial condition of emergence of the three different companies is quite different and is closely linked to their investment policy, and the link of the company with public institutions.

In the case of **Avesthagen,** the company initially benefited from the shelter of institutions like the NCBS and university for agricultural sciences, then it organised a first round of venture funding in order to set up an extensive proprietary platform.

The case of **Genotypic** gives an other example of support provided by public institutions to emerging companies, indeed Genotypic has only invested Rs. 25 Lakes so far (from personal savings), but the company uses extensively the lab of molecular biology of the IISc Bangalore and the microarrays robot of the CBT Delhi.

As for **Metahelix**, the company benefited from the financial support of an Angel Investor[29] who injected 1,5 M $ with long term objectives.
The 5 founders have 75% of the shares and the angel investor has 25%.

2.2.2. Positioning

Those companies' positioning is relatively focused compared to the first group of companies. Namely, Avesthagen and Metahelix have developed a strong competency in plant genomics, as for Genotypic, the central competency is microarrays.
Nevertheless, we can see that, while taken into account the specificity of their competency, these companies are involved in a range of activities offering them different risk-revenues ratio.
The offering of basic services like analytical studies, or testing assures the lowest risk-revenue ratio.
A medium risk-revenue ratio is assured by initiatives like the building of databases, or development of biomarkers. The value added in this case will depend on the originality of the project.
The discovery of a drug target, or even the development of a drug or a diagnostic presents the highest ratio.
Each of them in its own field, the three companies are proposing contracts presenting low and medium risk-revenue ration and are conducting in parallel more ambitious research.

2.3. Competency building strategy

In this field, the main entry barrier is the scientific skills of the project leaders and their collaborators. Most of the scientists occupying managing positions in these companies have done at least their PhD or post doc abroad (USA, Israel, and France).
It is a well known fact that the best element of the Indian superior education choose to go abroad to complete their studies, and the Indian companies willing to attract these elements have to cope with this fact. The fact is that this brain drain is not an irreversible migration, many of the students achieving successful studies and carriers abroad are still willing, after many years abroad, to go back to India. This is well illustrated by the case of the managers that we mentioned earlier, and this allow us to assume that the Indian professional coming back to India after a successful carrier abroad bring back with them an entrepreneurial spirit which can be interpreted as a critical factor in the emergence of the biotech industry we are studying.

Understanding this process, Aurigene focuses its recruitment efforts towards non resident Indians (NRI) willing to go back to India, its office in Boston being an important asset for this recruitment strategy. This office will also allow the company to attract high profile professionals not willing to work in India.
Avesthagen has also elaborated a recruitment strategy taking the migration factor into account. The company have hired several masters from leading institutions in India, taking the engagement of sending them to complete their PhD in western institutions.

[29] Angel Investors are private venture capitalists. They invest in emerging projects under the form of a capital participation, with a view to making a profit when exiting the capital of the company once maturity has been achieved.

2.4. Conclusion

To conclude on this section about genomics and proteomics, we can first say that there is an impressive volume of activity going on in India in order to build an export-oriented industry of cutting hedge biotech research. The future of these research capabilities will be highly dependent from the trust that India as a whole will inspire in the next years to these companies' potential partners abroad.

Concerning the strategies of these firms, we have presented two profiles related to their conditions of emergence. While considering the companies belonging to these two groups, we can notice that all these firms are still looking for defined technological and business positioning. The opportunity driven companies that target the bottleneck identified in the drug development chain can choose to integrate connected competencies such as clinical trials management or chemical research to their portfolio. As for the technology driven companies, their technological platforms allow them to propose various types of goods or services. The common point is the conciliation between the constraint of rapid cash flow generation that all these companies have to cope with, and the will to access to the intellectual property. The general business model that emerges from this group of companies is based on the development of an internal competency thanks to contract research, and the parallel pursuing of more ambitious research thanks to the cash flow generated by contract research.

C.3. Bioinformatics

3.1. General Statements

Definition

Bioinformatics is defined as the application of computer technology to the management of biological information. The rapid development of bioinformatics as a discipline has been propelled by the explosion of information coming out of the Human Genome Project (HGP). The HGP's information management challenge involves tracking the sequencing of the entire human genome - approximately three billion base pairs of DNA that make up our 23 pairs of chromosomes - and the precise mapping of the 100,000 or so genes that are interspersed on these chromosomes. The amount of public DNA sequence data doubles every 12-14 months and will increase even more dramatically in the coming years.

We will describe the technical applications of informatics for biotechnology. Nevertheless we can already restrict the range of bioinformatics understood as a business sector. Indeed, if the explosion of the amount of data available and the very nature of biotechnology implies the use of advanced informatics. We will only consider as bioinformatics, the development of technologies - namely algorithms and methodologies – to be applied in the computational treatment of biological data.

Applications

Informatics and sequencing & mapping:

The automated sequencing technologies are only able to sequence short fragments of DNA. During the sequencing of an entire genome, a large amount of DNA fragments are sequenced, and the different sequences are correlated thanks to Sequence Tagged Sites (STS) acting as landmarks. This demands an enormous amount of single character comparisons in order to locate those STS. Therefore, the complete sequencing of a bacteria's genome may require $2*10^{14}$ single characters comparison.

Informatics and functional genomics:

A painstaking work of data mining and statistical analysis is also to be done when the whole genome has been sequenced and mapped, in order to understand the internal logic of the genome and its influence on the different functions of the organism.

Informatics and microarrays:

Microarrays, or DNA chips is a developing, high throughput technique allowing to study the DNA material and its level of expression. The design of the microarrays, and the interpretation of the results imply the use of sophisticated algorithms.

Informatics and proteomics:

In the case of proteomics, the essential role of important computational capacities is to go beyond the sequence of the proteins in order to study their 3D structures, the knowledge of the 3D geometry of the proteins is critical to study their activity and data analysis on linear sequence is the only way to achieve it.

These applications provide an overview of the flow of data that will have to be managed in the next years but bioinformatics will in fact have a role to play in all the stages of the drug development cycle, from the target identification, with the application to genomics and proteomics, to the clinical trials thanks to the application of informatics to pharmacogenomics.

As we mentioned it earlier, bioinformatics does not consist simply in the use of a computer to achieve the latter mentioned task. It should rather be defined as the development of user-friendly tools that will be used in those different areas. The typical offer of a bioinformatics company would therefore be composed of software products or computing services, rather than of databases.

Related fields

From an computational point of view, the three main type of bioinformatics application can be defined by their technological content. Along with the classical skills necessary to build a robust and user friendly software there are basically three kind of specific skills used in the development of a biotechnology application :

- **Statistical analysis** (based on multivariate analysis, neural computing, etc…)
- **Molecular modelling** (based on computational geometry).
- **Data management**

Especially in the health care sector, we can observe the development of application of computational sciences to drug development using the same kind of skills.
Many IT consulting firms already propose solutions for the management of medical data. A good management of clinical data during a phase of clinical trial for example, is critical to the respect of the deadline, and has a huge economic impact. This sector is already well developed and it is usually referred to as **Health Care IT**.
Indeed the recent advances in medical and combinational chemistry also provide a flow of data that can be used for rational drug design. These applications, called **cheminformatics** are closely related to bioinformatics and offer the same kind of prospects.

Opportunity for India

Although bioinformatics has been a critical element of the advances made so far in the fields of genomics and proteomics, its role is taking know an even greater importance.

The Consortium of Indian Industries (CII) has estimated the global turnover of the bioinformatics industry of $ 2 billion in 2001 and a predicted market of $60 billion by 2005. Identifying an objective of a 5% global market share for the Indian industry, the CII presents bioinformatics has a good candidate to be the opportunity of growth for India in the next decade like Software outsourcing was during the 90s.

Here are the reasons why India should have a role to play in this industry:
The development of the Indian Software industry has provided the country with:

- An increased awareness of the growth opportunities in high tech outsourcing.

- The evolution of the regulatory bodies in order to facilitate the expansion of the sector.
- The development of bandwidth and other infrastructures required by IT enabled services.
- The development of an extensive skilled manpower base in informatics.
- An India inc. Brand recognizing for the quality of the services provided by the local industry.

The development of the local Biotech sector brings:

- Public bodies with a clear mission to make Indian Biotech industry a success story similar to the IT industry.
- Public initiatives specifically directly towards bioinformatics as a part of the Central Biotech policy. (Biotechnology Information System sponsored by the DBT, academic programs of bioinformatics)
- A strong academic knowledge in the public institutes in the fields of biology.
- Industry leaders eager to seize the opportunity the bioinformatics may offer.
- A general enthusiasm towards all the biotech-related fields.

3.2. Entry strategies

Profile of the Indian companies entering the market

The opportunities mentioned earlier have already attracted several players with different background strategies, we will try to give a first grid of analysis of the sector.
The companies entering the sectors can be differentiated following three main criteria : The financial-organisational backing, the technology used, and the business model.

Here is a list of the companies taken into account for this study :

Table 14. Bioinformatics companies in India

Company	Financial / Organisational Backing	Business model
Avesthagen	Biotech company	services + databases
Astrazeneca	Pharmaceutical company	in-house
Bigtec	Private	Solution
CDC Linux	High Performance Hardware	Hardware + Integration
DSQ Biotech	IT + Biotech	
GVK Biotech	Biotech company	Training + Services
Ingenovis	IT Company (I-Labs)	Products
Jubilant Biosys	Chemicals (Jubilant)	
Kshema technologies	BI division IT Company	
Landsky solutions	Private	Products + Services + databases
Mahindra - British Telecom	BI division of an IT Company	
Metahelix	Biotech company	services + databases
Molecular connections	Pharmaceutical company Dr Reddy's	Projects
Monsanto	Biotech company	In-house
Ocimum biosolutions	Pharmaceutical company Saraca Group	Products

PrayogNet Computing	Private	
Questar Bioinformatics	Pharma company Gland Pharma	
Reliance Life Science	Biotech company	
Satyam	BI division of an IT Company	
Strand Genomics	Private Spinn of from IISc	Products
Spectramind	BI division off an IT Company	
Syngene	Biotech company	Services
SysArris	BI division of an IT Company	
TCS	BI division of an IT Company	CSIR Joint Program
Wipro	BI division of an IT Company	

Financial & organisational backing

The financial-organisational backing criteria refers to the condition of emergence of the bioinformatics and the way it got the money, the people and the technology it needed for its start.

Here are the main trends that we can observe concerning the influence of this criterion on the conditions of emergence of the bioinformatics project.

· **Bioinformatics division of an Indian IT company:**

We call IT companies the companies offering either outsourcing services, software products and solutions, or IT enabled services (cf. Digital India, CERNA 2001)

This trend encompasses 10 companies out of the 27 considered for the study. (DSQ Biotech, Ingenovis, Kshema technologies, Mahindra British Telecom, Satyam, Spectramind, SysArris, TCS, Wipro).

The basic business logic in this case is a logic of diversification. Compared to other domains of software, bioinformatics is characterised by its high value added and is an attractive area of diversification for the main players that have emerged from the fast growth of the IT sector in India during the fifteen last years.

However, the technology is specific enough to impose the hiring of experienced professionals in the field of biology. The asset of such bioinformatics initiating from an IT company lies in the methodology of software development available from the other departments, and in the brand asset. The brand is not only an asset within the marketing phase, but also within the critical phase of hiring. A name such as TCS or Wipro can attract several thousands of applications.

· **Bioinformatics division or in house department of a pharmaceutical company.**

(AstraZeneca, Ocimum, Molecular Connection, Questar).

In the case of pharmaceutical company, the entry into the bioinformatics sector can be part of very different strategy. A pharmaceutical company like AstraZeneca can choose to set up its own bioinformatics department, adopting a strategy of vertical integration. But setting up a bioinformatics company as an independent subsidiary like it is the case of Dr Reddy's with Molecular Connection can also be a simple strategy of investment in a fast growing sector, motivated by the initial knowledge of the sector and the growth prospects. In the case of Ocimum biosolutions, the backing pharmaceutical company, the

Saraca group, expect from its bioinformatics venture a future synergy, enabling the group to build an internal integrated drug discovery chain.

· **Spinn-off (Metahelix, Strand Genomics)**

Certain companies, thanks to the profile of their promoters, have been able to raise private and venture capital in order to launch a bioinformatics venture. Such companies are Strand Genomics whose managing team is essentially composed of former computer scientists from the IISc, or Metahelix, headed by several former managers from Monsanto.

· **Biotech companies**.

Since bioinformatics is a constitutive element of BT-based drug discovery, any company in this sector has strong skills allowing it to offer bioinformatics services, especially if, as it is the case of the new Indian player of this sector like Avesthagen, Syngene, Reliance, or GVKbio, they can take advantage from a geographical cost advantage.

Business models

Since most of the Indian players in the sector have started their activity recently, is difficult to analyse their business model on the basis of past contracts. Nevertheless it is possible to give a gridline for the analysis and some general trends. In the same way than in the classical IT sectors, the business model of the firms can be defined by the kind of contract they offer. Namely, bioinformatics can adopt the following kind of model:

- Integration: The company provides its customers with a ready-to-use and coherent computing system composed of hardware and software. The company offering integration services can be also involved in providing some components of the final system.
- Computing services: The company takes information under a certain form and return it in a more valuable form.
- Solution: A solution contract implies the delivery by a company of a tailored product answering the specific needs of the customer.
- Product: While some company offer standard products (i.e. software), most of the companies offer, along with the basic product, services in integration and customisation.
- Intellectual Property Development: Although the development of a bioinformatic tools does not constitute a central stage of the drug development chain, the specificity and the value added by a certain tool can be allow the access to intellectual property applied on the final product (therapeutic or agricultural) Intellectual property relevant to the final product is the best way for a bioinformatics company to access to high returns.

At the stage of emergence, the business model is strongly determined by the financial constraints of the bioinformatics firms. Whereas firms with a strong corporate backing can allow themselves to adopt a long term strategy of competency building, small independent firms must cope with the requirement of external funding, i.e. rapid generation of cash flow.

Namely, companies like Tata Consulting Services (TCS) or Reliance Life Science (RLS) belong to the first type. TCS current activity is based on its taking part in a joint CSIR project for the development of an Indian comprehensive package of bioinformatics software. This project deadline being April 2004, it allows the company to develop a coherent team with a relatively long term objective. As for RLS, the large number of other biotech activities the company is involved in allows it bioinformatics team to start as an internal support unity with a view to become a full fledged commercial division on a longer term.
On the other hand, companies relying on an external source of funding such as Bigtec, or Ocimum Biosolutions have to take into account the need for fast cash flow generation, and have to include in their initial offer low return offers such as services, or as in the case of Bigtec, software marketing for an other firm.
The long term of any of these firms is however to have access to the highest level of the value chain, that is intellectual property. The access of bioinformatics firm to intellectual property on the final product is difficult to assess, and should depend of the structure of the market. If we assist to the emergence of a common competitive market for comprehensive software packages, the possibility to access to the intellectual property should be low. However, if the market presents itself rather under the form of several niche market with low competition and a strong need for customisation, the bioinformatics firms aspiration to intellectual property should be fulfilled.

Partnerships strategies

During this phase of emergence, the newly formed bioinformatics team need a strong backing in fundamental life science. This can be achieved by hiring high profile professionals or academics, but it seems that private-public co-operation constitute an attracting way for companies without initial skills in life science, to have a scientific support. These co-operations can take the form of a public institute offering training to newly hired IT-people having to solve life-sciences related problems, as it is the case with the co-operation between TCS and CDFD. The institute can also take part in the product development, during the first phase of the development by expressing needs, or in the last phase, by testing the software. One example of this kind of co-operation is provided by the partnership between Ingenovis and CCMB.
In the case of bioinformatics training, an institute can provide the teaching material to be dispensed in a private training centre as it is the case of Ocimum and GVK.

3.3. Public initiatives

Capacity building

Biotechnology Information System.

As mentioned earlier, bioinformatics have benefited from a proactive policy from the central government. The DBT has developed a nation wide network called Biotechnology Information System. a bioinformatics programme, envisaged as a distributed database and network organisation, was launched during 1986-87. Ten Distributed Information Centres (DICs) and an Apex Centre at the Department of Biotechnology, and 46 Sub-Distributed Information Centres, located in universities and research institutes are

engaged in this task. The network has been equipped with modern computers and communication system and employs 150 people.
Ten DICs have been established with the task of providing discipline-oriented information to all institutions belonging to the branch as well as other institutions and individual users interested in particular subject related to Biotechnology. These are listed below :

- Genetic engineering
  - Indian Institute of Science, Bangalore
  - Madurai Kamaraj University, Madurai
  - Bose Institute, Calcutta
  - Jawaharlal Nehru University, New Delhi.
- Animal cell culture and virology.
  - University of Poona, Pune.
- Plant tissue culture, photosynthesis and plant molecular biology.
  - Indian Agricultural Research Institute, New Delhi.
- Oncogenes, reproduction physiology, cell transformation, nucleic acid and protein sequences.
  - Centre for Cellular & Molecular Biology, Hyderabad.
- Immunology.
  - National Institute of Immunology, New Delhi.
- Protein modelling and protein engineering.
  - Institute of Microbial Technology, Chandigarh.
- Neuro-informatics.
  - National Brain Research Centre, Gurgaon

Although, the utility of a specific physical network for bioinformatic resource has naturally decreased with the emergence of the internet, the organisational network constituted remains the base for the DBT's policy of development of bioinformatics in the country, especially in terms of human resource development. Indeed the DBT has encouraged the development of bioinformatics degrees in the research institutions and universities hosting the Distributed Information Centres.

Development of a domestic suit of bioinformatic tools.

The Development of Versatile Portable Software Suit for Bioinformatics Applications (DVPSSBA), implemented by the CSIR is part of the New Millennium Indian Technology Leadership Initiative. Within this project, private companies, namely TCS (in charge of the software development) and CDC Linux (in charge of the Hardware development), collaborate with institutes like CBT (Delhi), CDFD (Hyderabad), IISc Bangalore, University of Pune, NIPER, IMTech Chandigarh, etc… (a total of 14 public institutions).
This project was funded in April 2002 and should be completed in April 2004. The output of this project should be a set of software applications covering the main fields of bioinformatics, this software suit would be made available at a low cost for Indian public research institutions.

Human resource development

DBT has initiated a long-term academic course in Bioinformatics leading to the award of an advanced diploma in bioinformatics. The course is being conducted by Madurai Kamaraj University, Madurai, Pune University, Pune, Jawaharlal Nehru University, Delhi, and Calcutta University.
Several other bioinformatics programs have been developed, for example in CBT Delhi, or in the Department of Biotechnology - Sindhu Mahavidyalaya University where an undergraduate level for B.Sc. is offered.
The creation of the IBAB is another project showing the will of the public sector to develop human resource development facilities in the field of bioinformatics. The IBAB is a training institute delivering postgraduate degrees in bioinformatics. The project was initiated by the Karnataka Vision Group, following the model of IIIT.

Companies launching a bioinformatics project will be able in the following years to pick in a growing pool of specifically trained graduates in bioinformatics. However, they have already built strategies to develop their own human resources. The simplest strategy is to recruit IT people as well as life science professional, and to rely on their ability to build a coherent team. The competency of people with one of the two backgrounds can also be increased thanks to short courses provided either by public institute (CDFD or IBAB), either by the company itself. Indeed, providing professional training in bioinformatics seems to be a strategy of choice to train and select future team members, this strategy has been adopted by GVK, Ocimum, Bigtec and Landsky Solutions for example.

Table 15. Indian training centres in bioinformatics

Companies offering training programs	**Location**
Ocimum Biosolutions	Hyderabad
Landsky Solutions	Hyderabad
GVK	Hyderabad
Global bioinformatics	Hyderabad
NGGT infotek	Bangalore
Suprada Softech	Dharavar
Veetech Infoline	Bangalore
Manvish InfoTech	Bangalore
Degrees in bioinformatics developed within Indian universities	
University of Pune	Pune
JNU	Delhi
Department of Biotechnology Sindhu Mahavidyalaya	
Madurai Kamaraj University	Madurai
IIT Hyderabad	Hyderabad
IIT Kharagpur	Kharagpur
Sikkim Manipal University India	Manipal
Mysore University	Mysore
Others institutions offering training in bioinformatics	
IBAB	Bangalore

BII	Delhi
ICGEB	Delhi
Institute of Bioinformatics	Bangalore
CDFD	Hyderabad

C.4. Clinical trials

The management of clinical trials can not be considered in itself as an economic application of biotechnology. Nevertheless, as we will show, the clinical trials are the most expensive stage of the drug development chain and India possesses resources that should allow the country offering clinical research services at a very competitive cost. We consider that monitoring the evolution of the companies based in India with a model of Clinical Research Organisation should be a good way to measure the actual openness of the international research networks to the participation of countries such as India.

4.1. Impetus

The tufts Centre for Study of Drug Development has announced in November 30, 2001 that the average cost to develop a new prescription drug is $802 million. This announcement updates a similar study done by the same centre in 1987 when the new drug development cost was estimated to be $ 231 million.
According to the centre's director of economic analysis, the main reason behind this rising is the rising of clinical trial costs.
This can be explained both by the difficulty in recruiting patient, and in the increased focus –thanks to the development of biotech based drug discovery – on developing drugs to treat chronic and degenerative diseases.

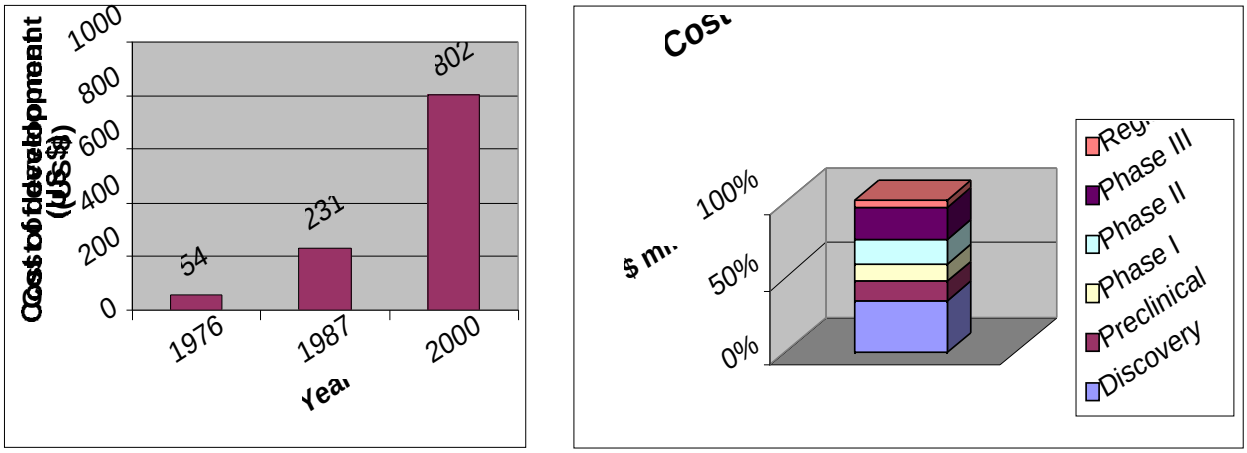


Chart 7. Evolution and structure of the cost of development of new drugs.

Source : Tufts Centre for the Study of Drug Development, 2001 Source : Serono, 2000

Therefore, reducing clinical trials costs is becoming a compulsory strategic move for most pharmaceuticals companies. The new tools of bioinformatics and pharmacogenomics do provide opportunities for reducing those cost, but one of the main

prospects in this field is in outsourcing the clinical trials in country where patients are more available and R&D cost lower.
With its enormous patient pool benefiting from an exceptional biodiversity, along with a long tradition of excellence in Medicine sciences, India is definitely in a good position to become a major player in this new form of outsourcing. The main constraint to this evolution is the convergence of the Indian clinical test procedures toward the international standards, but after years of sluggish evolution, the government is taking proactive measures with the clear goal of making the Indian standards converge towards the US-FDA standards.

4.2. India's response

Several companies have already taken the initiative to develop an activity of contract-driven clinical trials in India. For example the global major Quintiles has already settled three centres in the country and some Indian companies having activities in Biotech and pharmaceuticals have launched their own division for contract clinical trials. Indeed, the enzyme manufacturer Biocon has set up a new subsidiary, Clinigene to conduct clinical research under contract, so did the pharmaceutical companies Nicholas Piramal with its subsidiary WellQuest, and Ranbaxy with SRL Ranbaxy. Siro Research was founded in 1995 as a clinical research organisation. Catalyst Clinical Services is another clinical research organisation settled in India. All these companies are looking for large scale contracts with foreign partners and they are working on their practices in order to comply with the international standards such has the Good Clinical Practices (GCPs) defined by the International Conference on Harmonisation (ICH).
On the regulatory side, the process of convergence of the Indian institutions in charge of the control of the clinical trials carried out in India - the Drug Controller General of India (DGCI) under the tutorship of the Central Drugs Standard Control Organisation (CDSCO) – toward the international standards has been already initiated.

C.5. Integrated drug discovery

Although this chapter mainly deals with non-integrated insertions in the drug development chain, it is useful to consider the strategies of the Indian Integrated Pharmaceutical Companies (IIPCs) concerning BT-Based new drug development.
Here is a diagram that presents the strategies of IIPCs concerning the biotechnologies, taking into account both their strategies in biogenerics and BT-based drug discovery.

The quantities used to represent the companies on the diagram are a combination of the following factors :

Biogenerics :
- Turnover of licensed bio therapeutics.
- Investment in technology transfer.
- Funding of public research.
- Investment in in-house industrial scale-up R&D.
- Investment in in-house basic R&D (molecular biology / shake-flask scale expression).

· Turnover in proper recombinant products.

BT-based drug discovery :

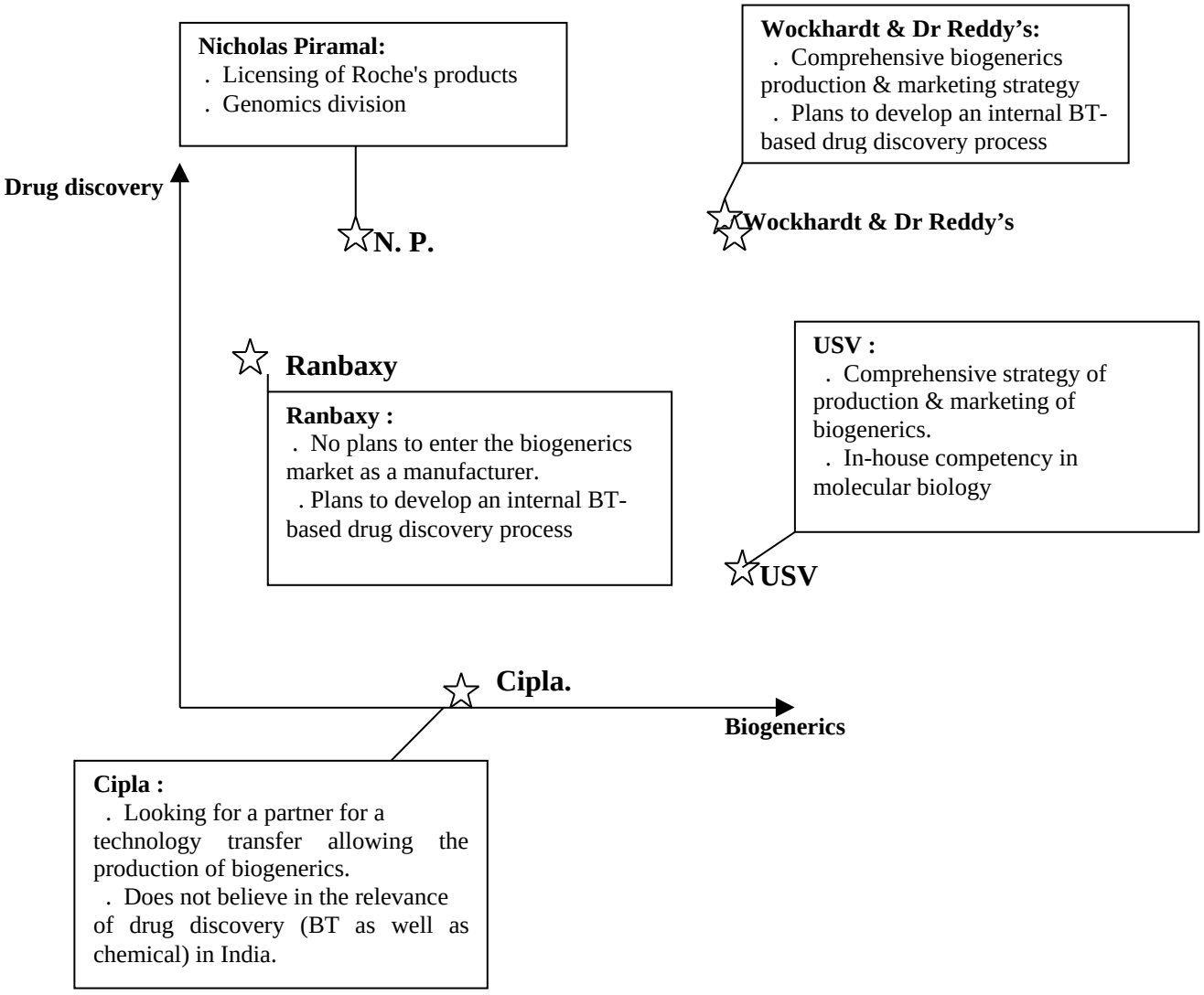
· Investment in in-house R&D.
  - Proprietary investments
  - Human resources
  - Use of external services

· External acquisition of technology.
· Revenue from knowledge sharing.

Graphic representation of the interviewed firms strategy :

The position on the axis reflects the evaluation of the strategic importance of each parameter for each firm, based on their current market characteristics, and results from the interview.

Chart 8. Biotech Strategies of Indian Pharmaceutical companies.



The diagram shows the diversity of the strategies adopted by the pharmaceutical companies interviewed. One can wonder if those strategies will converge in the future. While trying to answer, we have to take into account the fact that aside from the integration of biotechnology, the Indian pharmaceutical firms will also have to cope with the challenges of globalisation. Therefore the technological paths followed by the companies will be articulated with their geographic strategy of entry in new markets, as well as their policy of international alliance making.

Conclusion générale

Les biotechnologies ont été identifiées par les pouvoirs publics indiens comme un axe de développement stratégique depuis une vingtaine d'année. Cela c'est traduit par le développement de nombreuses institutions publiques de promotion, de contrôle, et de recherche pour encadrer et stimuler la croissance de ce secteur. Mais c'est seulement au cours des dernières années avec le développement de l'activité privée dans ce domaine que les biotechnologies font parler d'elles et apparaissent comme un nouveau secteur à forte valeur ajoutée pouvant participer pleinement au développement de l'économie indienne.

Pour étudier cette évolution, nous avons choisi de ne nous intéresser qu'aux biotechnologies issues des développements les plus récents des sciences du vivant, c'est-à-dire le génie génétique et la biologie moléculaire. Parmi les différentes applications de ces technologies, nous avons sélectionné celles qui impliquent de manière active le plus grand nombre de firmes indiennes. Ce choix n'a pas pu être fait de manière objective en considérant des données sectorielles regroupées au niveau national. La raison en est simple : ces données ne sont pas encore disponibles. Ce choix découle donc d'un effort d'identification préalable qui a montré que l'essentiel de l'activité industrielle dans le secteur des biotechnologies modernes en Inde est concentré autour des applications à la santé et à l'agriculture. En se penchant sur les domaines d'activités caractérisés par l'application des nouvelles biotechnologies aux secteurs précédents en Inde, on peut identifier plusieurs types de dynamiques. La première observation à faire est le lien direct entre ces dynamiques et les conditions internationales et locales. En effet, les principaux déterminants de ces dynamiques (techniques disponibles, débouchés, et concurrence) sont pris en compte par les entreprises indiennes au niveau national et international, et ce dès l'élaboration de leur stratégie d'entrée dans ces nouveaux domaines d'activité. Ce rapport prend le parti de considérer chaque dynamique de manière indépendante et d'exposer dans chaque cas les caractéristiques des stratégies d'entrée des différentes firmes indiennes ainsi que les outils à la disposition des pouvoirs publics pour appuyer les entreprises dans le développement de leur projet.

Quatres dynamiques stylisées peuvent être distinguées :

(i) L'acquisition et/ou le développement par des entreprises indiennes de capacités de production de protéines recombinantes tombées dans le domaine public (biogénériques).

(ii) Le développement au sein d'institutions indiennes, publiques ou privées, de variétés de végétaux génétiquement modifiées (OGM).

(iii) Le développement en Inde de capacité de recherche dans les biotechnologies de pointe – et de manière connexe dans les différentes étapes de la chaîne de développement du médicament - et la mise à disposition de cette capacité sur un marché international de la recherche sous contrat.

(iv) Le développement d'outils informatiques et la proposition de services informatiques dans le cadre du traitement des données du vivant par des entreprises indiennes.

Comme nous l'avons dit, les facteurs déterminants de ces dynamiques indiennes interviennent à la fois sur le plan local et sur le plan international. Ces facteurs sont essentiellement articulés autour de la technologie. Ils concernent en effet la disponibilité

concrète de cette technologie, la disponibilité et le coût des ressources humaines, matérielles, et financières nécessaires à sa mise en oeuvre, ainsi que le cadre légal de son utilisation.

En ce qui concerne les techniques disponibles, l'étude est l'occasion d'étudier les formes concrètes que prend le transfert technologique. La question qui se pose est : comment une entreprise indienne peut mettre en œuvre une technologie donnée ? Si la science fondamentale peut être considérée grossièrement comme composée d'énoncés codifiés rendus publics par les scientifiques à l'origine des progrès scientifiques, la maîtrise d'une technologie et sa mise en œuvre industrielle impliquent des processus d'apprentissage qui dépassant le simple transfert d'information codifiée. L'interaction joue donc un rôle primordial dans ce processus.
Nous nous sommes penchés sur ces phénomènes d'interactions à partir des entretiens menés avec les entreprises indiennes afin d'identifier leurs stratégies d'intégration des nouvelles biotechnologies, et en particulier la place des relations avec les instituts indiens. Il en ressort que plusieurs entreprises indiennes ont recours aux collaborations avec des instituts locaux pour développer leurs capacités. Cependant l'efficacité de ces collaborations demande une certaine expérience qui est encore en train d'être développée. Les entreprises indiennes ont d'ailleurs des alternatives à ce type de collaboration pour développer leurs capacités et certaines n'hésitent pas à avoir recours à des partenaires étrangers dans leur stratégie d'acquisition de compétence. Par ailleurs, ce qui caractérise la collaboration par rapport à d'autres types d'interactions commerciales, c'est l'incapacité des acteurs qui entrent en collaboration à formuler ex-ante les termes exacts de cette collaboration lors de la signature des contrats qui régissent ces interactions.
Dans le cas des interactions entre entreprises et instituts indiens, on a pu ainsi distinguer deux périodes dans le développement du projet au cours desquelles les interactions prennent des formes différentes. Dans la phase d'amorçage d'un projet, l'interaction peut intervenir par le passage d'un scientifique d'un institut à un poste de chef de projet, ou de manager dans une entreprise. Des formes de partenariats plus ou moins formels peuvent également être mises en œuvre sur des modèles d'incubation ou de partage de plateforme technologique. Lorsque le projet se développe et que l'entreprise devient mieux capable d'identifier ses besoins les relations peuvent évoluer vers de la recherche sous contrat ou du transfert de technologie.
Comme nous l'avons mentionné, une grande part des initiatives dans le secteur sont appuyées sur des entreprises existantes possédant des compétences connexes. Ces compétences existantes au niveau des entreprises mères ont une influence très importante sur les stratégies d'intégration de la technologie. Dans le cas de la dynamique (i) – biogénériques, à coté d'entreprises lancées directement sur ce créneau, on voit un intérêt important des entreprises pharmaceutiques, des producteurs d'enzymes industrielles, et des producteurs de produits biologiques tels que les vaccins ou les réactifs de diagnostiques. Dans le cas de la dynamique (ii)-OGM, ce sont logiquement des entreprises déjà impliquées dans l'hybridation conventionnelle des plantes qui se lancent dans ce type de projet.

En ce qui concerne la disponibilité des ressources nécessaires à la mise en œuvre des biotechnologies modernes au niveau de l'Inde, on peut noter le rôle primordial des

ressources humaines dans l'ambition indienne. Le système d'éducation supérieure scientifique a en effet montré son aptitude à former des informaticiens capables d'être compétitifs sur le plan international. Afin que le scénario des technologies de l'information se répète dans les biotechnologies, l'Inde compte sur le réseau dense de départements universitaires et d'instituts spécialisés développés par différentes instances (DBT, CSIR, ICMR…), ainsi que sur la création plus récente de diplômes spécialisés au niveau du Masters of Science.
Si la disponibilité de scientifiques compétents en Inde est un facteur déterminant, on ne peut pas négliger l'existence d'un marché de plus en plus mondialisé du travail. Ainsi, les entreprises de biotechnologie qui recrutent de nombreux docteurs doivent prendre en compte le fait qu'une part importante des meilleurs étudiants indiens considèrent une expérience à l'étranger comme un passage obligé dans leur carrière.
Mais les ressources humaines ne sont pas les seules ressources nécessaires au type d'activité que l'Inde souhaite développer sur son territoire. En effet, pour se développer, un secteur innovant comme celui des biotechnologies modernes a besoin d'infrastructures adéquates et surtout de financement. La grande majorité des projets étudiés lors de l'enquête ont bénéficié de l'investissement d'entreprises privées avec des activités plus ou moins connexes au projet développé. Mais les pouvoirs publics travaillent activement à l'amélioration de cet aspect de l'environnement. Au niveau du gouvernement central aussi bien qu'au niveau des états les plus avancés dans la promotion de leur espace en tant que terre d'accueil privilégiée pour les biotechnologies, le besoin de développer la disponibilité de financement sous la forme de capital-risque a été pris en compte et des initiatives ont été lancées afin de répondre à ce besoin.
Pour répondre aux attentes très spécifiques des entreprises de biotechnologies en terme d'infrastructure, plusieurs projets de « biotech parks » sont mis en route. Le plus avancé d'entre eux à Hyderabad accueille déjà ses premières entreprises. Ce schéma particulier n'est pas seulement un moyen économique de développer des infrastructures spécifiques. Plus généralement, la concentration d'entreprises du même secteur est une situation favorable à la construction de liens privilégiés avec des pôles technologiques similaires à l'étranger, et du point de vue des pouvoirs publics, cela fournit un terrain propice aux différentes expérimentations institutionnelles et en terme de régulation qui ont lieu lors du développement d'un secteur comme celui des biotechnologies.

Le développement des projets de biotechnologie est en effet largement influencé par le cadre légal. L'aspect le plus important de ce cadre est le régime de protection de la propriété intellectuelle. La restriction de la protection de la propriété intellectuelle (PPI) aux procédés dans les secteurs chimiques alimentaires et pharmaceutiques à partir de 1970 a permis entre autre le développement d'une industrie pharmaceutique qui est aujourd'hui un acteur important sur le marché international des biogénériques. Mais la place des entreprises indiennes dans les réseaux internationaux de recherche ne pourra être déterminée que lorsque le scénario de convergence du régime de PPI indien vers les standard de l'OMC sera clairement fixé. Il est de la responsabilité des autorités indiennes de fixer le plus tôt possible un cadre clair en terme de PPI pour le développement de la recherche indienne en biotech. Mais les pouvoirs publics peuvent influencer la croissance du secteur avec plusieurs autres outils. Des efforts sont réalisés au niveau central et au niveau des états pour établir une voie unique d'interaction entre les entreprises et

l'administration (Single Window Agency), et pour simplifier et accélérer les différentes procédures de contrôle et autorisation. Par ailleurs, le choix peut être fait comme pour cela a été le cas pour faciliter le développement des activités dans le technologies de l'information de définir un cadre fiscal et douanier spécifique pour les biotechnologies. Ces mesures seront d'autant plus faciles à mettre en œuvre que les entreprises concernées seront concentrées dans des BT Parks.

Pour ce qui est des débouchés, on observe également l'intervention de facteurs locaux et internationaux. Le développement de biogénériques indiens a pour motivation première l'offre sur le marché indien de médicaments à des coûts très inférieurs à ceux pratiqués par les entreprises importatrices. Néanmoins, les entreprises indiennes qui se lancent sur le secteur ont pour ambition affichée de se positionner à terme sur le marché mondial des biogénériques. Le cas des OGM, avec l'implantation du leader mondial Monsanto à Bangalore et le partenariat noué avec l'Indien Mahyco pour le développement du *bt*-coton - premier OGM autorisé en Inde après de nombreuses controverses – montre que le marché indien peut également attirer des entreprises étrangères. Si le marché du secteur pharmaceutique indien représente encore un risque de copie trop important pour que l'on voit les grandes entreprises pharmaceutiques mondiales investir en masse en Inde, la modification du régime de PPI devrait entraîner à terme des modifications dans ces stratégies. Enfin dans le cas de la recherche sous contrat et du développement d'outils de bioinformatique, la stratégie d'entrée des firmes indiennes est directement tournée vers l'international, les échanges intra-nationaux étant appelés à s'intensifier avec l'approfondissement des compétences de ces différentes entreprises.

General conclusion

General conclusion

The area of biotechnology has been identified by the Indian Administration as an area of strategic development since the past twenty years or so. This was accompanied by the mooting of various public institutions for promotion, monitoring and research in order to determine the scope of this sector and for stimulating its growth. However, it is only during the last few years, with the advent of private players in this field, that biotechnology has come into the news and appears to be a new and heavily value added sector that will be able to fully contribute to the growth of Indian economy.

In order to study this evolution, we have chosen to take up only biotechnologies that have originated from the most recent developments in life sciences, namely genetic engineering and molecular biology. Among the various applications of these technologies, we have selected those which are of the utmost active concern to the largest number of Indian firms. This choice could not be made in an objective manner by considering sector-wise data at a national level. The reason for the same is simple: these data are still not available. This choice has therefore been made possible owing to earlier efforts of identification which pointed out the fact that most of industrial activity in the biotechnologies sector in India is concentrated around health and agriculture related applications.

If one were to look into the fields of activity characterized by the application of new biotechnologies to industrial sectors in India, one can identify several types of dynamics. The first observation made concerns the direct link between these dynamics and international and local conditions. In fact, the main determinants of these dynamics (available techniques, openings, and competition) are taken into account by Indian companies at the national and the international level, and this holds true right from the time their strategy of entry into these new areas of activity are worked out. This report will take up each of these dynamics in an independent manner and strive to bring out, in each of these cases, the strategies of entry adopted by various Indian companies as well as the tools at the disposal of public authorities for supporting these companies in the elaboration of their project.

Four typical dynamics may be highlighted:

(i) Acquisition and/or development of production capacities of recombinant proteins by Indian companies which have come under the public domain (biogeneric).

(ii) Development of varieties of genetically modified plant species (GMO) within Indian institutions both public and private.

(iii) Development in India of research capacities in state-of-the-art biotechnologies – and that too in a related manner in the different stages of the development chain of medicines – and making this capacity available in an international research market under contract.

(iv) Development of data-processing tools and the offering of computer services within the framework of processing of life science data by Indian companies.

The determining factors of these Indian dynamics intervene on a local as well as international plane. These factors are essentially established around technology. They actually pertain to the concrete availability of this technology, availability and cost of

human, material and financial resources required for its implementation, as well as the legal frame-work linked to its usage.

As far as the available techniques are concerned, this study gives an opportunity to analyze the concrete forms that technological transfer takes. The question that comes to the mind is: how can an Indian company go about implementing a given technology? If fundamental science can be crudely considered as being made up of codified utterances made public by scientists who are at the origin of scientific advances, the mastering of a technology and its industrial implementation involve learning processes which go far beyond just a simple transfer of codified information. Interaction therefore plays a crucial role in this process.
We studied these phenomena of interactions from interviews conducted with Indian companies in order to identify the strategies adopted by them for integrating new biotechnologies, and in particular, the role of their relations with Indian institutes. What comes out of these studies is that several Indian companies have recourse to collaborations with local institutes for developing their capacities. However the effectiveness of these collaborations requires a certain amount of experience which is still in the process of being developed. Indian companies moreover have other alternatives to this type of collaboration for developing their capacities and some of them do not show any hesitation in taking recourse to Foreign partners in the context of their strategy for acquiring expertise. Furthermore, what characterizes these collaborations as compared to other types of business interactions lies in the incapability of the players who enter into them to formulate the exact terms of these collaborations which will govern these interactions ex-ante at the time of entering into a contract.
In the case of interactions between Indian companies and institutes, we could thus determine two stages in the development of projects during which interactions take on different shapes. In the beginning phase of a project, interaction can take place by way of the transfer of a scientist of a given institute to the post of project head, or manager in a company. More or less formal partnership arrangements may also be set in place based on incubation period models or sharing of technological platforms. Once the project progresses and the company finds itself better placed to identify its requirements, the relations can evolve towards research under contract or technology transfer.
As we had mentioned, a great share of the initiatives in this sector rests on existing companies that possess related expertise. These competences that exist at the level of the parent companies have a far reaching importance on the strategies of integration of technology. First, in the case of (i) – biogeneric dynamics, besides the companies launched directly in this segment, we can observe the pronounced interest from pharmaceutical companies, manufacturers of industrial enzymes, and manufacturers of biological products such as vaccinations or diagnostic reagents. In the case of (ii)-GMO dynamics, it is logically those companies that are already involved in conventional hybridization of plants which get launched into these kinds of projects.

As far as the availability of resources required for the implementation of modern biotechnologies in the Indian context is concerned, we can notice the preponderant role of human resources in this Indian ambition. The scientific higher education system has indeed demonstrated its ability to train computer specialists who are capable of being

competitive on the international level. In order to see a repeat of the performance of the information technology scene in the field of biotechnologies, India is counting upon the dense network of university departments and specialized institutes that have been developed by various authorities (DBT, CSIR, ICMR…), as well as on the creation of specialized degrees at the level of the Masters of Science programs.
If the availability of skilled scientists in India comes forth as being a determining factor, we cannot ignore the existence of a more and more globalized work market. Therefore, biotechnology companies that recruit a number of doctors must keep in mind the fact that a considerable portion of the best of Indian students consider acquiring experience abroad as being a definite step in their career.
However, human resources are not the only resources that are required for the type of activity that India wishes to develop on its territory. In fact, in order to develop fully, an innovative sector such as the sector of modern biotechnologies needs a sufficient quantity of infrastructure and especially financial backing. Almost all the projects that were studied during the investigation had received investments from private companies having activities that were more or less related to the project being developed. But public authorities are actively working towards an improvement in this aspect of the environment. Both at the level of the central government and that of the states that are most advanced in promoting their area as the most favoured welcoming area in so far as biotechnologies are concerned, the need to develop availability of finances in the form of venture capital has been taken into account and initiatives have been floated in order to respond to this need.
In order to respond to the highly specific requirements of biotechnology related firms by way of infrastructure, several " biotech parks " projects have been set into motion. The most advanced amongst them in Hyderabad has already welcomed into its folds its first set of companies. This specific scheme is not only an economic means to develop specific infrastructures. More generally speaking, a concentration of companies of the same sector is a situation that is favourable to building privileged links with similar technological poles abroad, and from the view point of public authorities, this gives them an area that is conducive to institutional experiments as well as in terms of regulations that have to be set into place during the development of a sector such as the biotechnologies sector.

Development of biotechnology related projects is in fact greatly influenced by the legal frame-work. The most important aspect of this frame-work is the system of protection of intellectual property. The restriction of the intellectual property protection(IPP) to processes in the chemical, food and pharmaceutical sectors from 1970 onwards paved the way for, among other things, the development of a pharmaceutical industry which has become an important player today in the international generic drugs market. However the place of Indian companies in the international research networks will become clear only when the scene of convergence of the Indian PIP system with WTO norms will be clearly established. It is the responsibility of Indian authorities to fix a clear frame-work by way of PIP at their earliest for the sake of development of Indian research in biotech. However public authorities can bring about a growth in the sector with several other tools. There have been endeavours at both the central and the state level for establishing a single channel of interaction between companies and the administration (Single Window

Agency), and for simplifying and accelerating the various procedures of monitoring and authorization. Moreover, a choice can be made just as in the case of activities in the field of information technologies in order to facilitate their development of setting into place a fiscal and customs frame-work specifically for the field of biotechnologies. It will be all the more easy to implement these measures if the relevant companies were to be concentrated in the BT Parks.

As far as markets are concerned, we once again notice the coming into play of local and international factors. The first and foremost motivation for the development of Indian biogenerics is to supply medicines to the Indian market at far lower costs than what were being levied by importing companies. However, the Indian companies that are hitching on to this sector have very clear ambitions of positioning themselves at the end of the day in the world biogenerics market. The case in point of GMOs, with the implantation of the world leader Monsanto in Bangalore and the partnership worked out with the Indian company Mahyco for the development of bt-coton – the first GMO authorized in India after a lot of controversy – demonstrates that the Indian market can also attract Foreign companies. If the Indian pharmaceutical sector market still represents a rather considerable risk of duplication that would seem to foreclose the chances of mass investment in India by leading international pharmaceutical companies, the modification of the PIP system should bring about changes in these strategies at length. Finally, in the case of research under contract and the development of bio-informatics tools, the strategy of entry adopted by Indian companies is directly oriented towards the international scene, intra-national exchanges being likely to intensify with the deepening of these different companies' expertise.

ANNEXES

References

AIBA, 2000. Biotechnology Parks in the context of Indian Biotechnology Industry. A analysis of the sluggish Growth of Indian Biotechnology Industry. A plan for Remediation in the Context of Global Biotechnology. An Agenda For Action. Report edited by the AIBA in November 2000.

Bomsel O., Ruet J., 2001. Digital India. CERNA report.

Callon M. Forray D. 1997 Nouvelle économie de la science ou socio économie de la recherche scientifique? Revue d'économie industrielle, n°79 pp. 13-32

Charurvedi S., 2002. Status and Development of Biotechnology in India: An Analytical Overview. RIS Discussion Papers.

Chaturvedi S., 2002. Agricultural Biotechnology and new trends in IPR regime. Challenges before developing countries. Economic and political Weekly, 30 March 2002.

Dasgupta P., David P.A. 1994 "The new economics of science" Research Policy, Vol. 23, pp. 487-521

Ernst & Young, 2001. Convergence, the biotechnology industry report.
Ernst & Young, 2002. Beyond borders, the biotechnology industry report. *Report edited by E&Y in 2002.*

Fink C., 2000 How stronger patent protection in India might affect the behaviour of transnational pharmaceuticals Industries. *The World Bank Working Papers, Development Research Group*

Hamdouch A, Depret M-H, 2000. L'économie des "nouvelles biotech". *Biofutur 200. Mai 2000*

Hamdouch A, Depret M-H, 2000. Pharmacie et biotech : l'ère des réseaux. *Biofutur 203. Septembre 2000*

Hamdouch A, Depret M-H, 2001. La nouvelle économie industrielle de la pharmacie. *Editions Elsevier, Juillet 2001.*

Hamilton W.F., 2001. The biotechnology revolution : lessons for technology management research and practice. *Int. Journal of Biotechnology, Vol 3., Nos. 1/2, 2001.*

Jensen M.C., Meckling W.H., 1976. Theory of the firm: Managerial behaviour, agency costs and ownership structure. *Journal of Financial Economics.*

LEK Consulting – France Biotech, 2002. Discovery Alliances. *Ppt.Presentation France Biotech March 2002.*

OECD 1998, National Innovation Systems, *OECD Paper*

Ramani S.V., 2001. Who is interested in biotech? R&D strategies, knowledge base and market sales of Indian biopharmaceuticals firms. *Research policy 1300 (2001) 1-18*

Ramani S.V., Venkataramani M.S., 2001. Rising to the technological challenge: possibilities for integration of biotechnology in the Indian pharmaceutical industry. Int. *Journal of Biotechnology, Vol 3., Nos. 1/2, 2001*.

Raugel P.-J., 1999. Stratégie des sociétés de biotechnologies dans le monde et émergence de la société entrepreneuriale. *in Biotechnologie (R. Sciban ed.), Tech&Doc Paris, pp. 977-999*

Ravishankar A., Archak A., 2000. Intellectual Property Rights and Agricultural Technology. Interplay and Implications for India. *Economic and Political Weekly 1 July 2000.*

Richardson G.B., 1972. The organisation of the industry *Economic Journal, Vol. 82, n° 327, pp. 883-896*

Rosenberg N. 1990 Why do firms do basic research (with their own money)?, *Research Policy, Vol. 19, pp.165-174*

Stiglitz, Joseph E. 1977 "Theory of Local Public Goods" *in Martin S. Feldstein and Robert P. Inman eds. The Economics of Public Services. New Yorki: Hastled Press.*

TIFAC 2002, Recombinant DNA Products, *TIFAC Report*

WTO, 1994. TRIPS : Agreement on trade-related aspects of intellectual property rights. *Annex 1C of the Marrakesh Agreement Establishing the world Trade Organization, 15 April 1994.*

Glossary

Amino acid

The fundamental building blocks of a protein molecule. A protein is composed of a chain of hundreds or thousands of amino acids. Our bodies can synthesize most of the amino acids. However, eight amino acids (called "essential amino acids") must be obtained from food.

Antibody

A **protein** produced in response to the presence of a specific antigen.

Antigen

A foreign substance that elicits the production of antibodies.

Anti-sense technology

The use of an RNA molecule to block gene expression by interfering with protein production. This technique is used commercially in tomatoes to slow ripening for better shipping and longer shelf life.

Assay

A method for determining the presence or quantity of a component.

Bioassay

A method of determining the effect of a compound by quantifying its effect on living organisms or their component parts.

Biological molecules

Large, complex molecules, such as proteins, nucleic acids, lipids and carbohydrates, that are produced only by living organisms. Biological molecules are often referred to as macromolecules or biopolymers.

Cell

The smallest structural unit of living organisms that is able to grow and reproduce independently.

Cell culture

A technique for growing cells under laboratory conditions.

Cell fusion

The formation of a hybrid cell produced by fusing two different cells.

Chromosome

Components in a cell that contain genetic information. Each chromosome contains numerous genes. Chromosomes occur in pairs: one obtained from the mother; the other from the father. Chromosomes of different pairs are often visibly different from each other (see also DNA).

Clone

A cell or collection of cells containing identical genetic material. Clones are produced from a single parent cell.

DNA (deoxyribonucleic acid)

The chemical molecule that is the basic genetic material found in all cells. DNA is inherited. Because DNA is a very long, thin molecule, it is packaged into units called chromosomes. DNA belongs to a class of biological molecules called nucleic acids.

DNA fingerprinting (or DNA typing)

A technique for identifying individual organisms based upon the uniqueness of their DNA pattern. The technique has applications in forensics, paternity testing, anthropology, conservation biology and ecological research.

DNA ligase

An enzyme that rejoins cut pieces of DNA.

DNA sequence

The order of nucleotide bases in the DNA molecule.

E. coli (Escherichia coli)

A bacterium commonly found in the intestinal tracts of most vertebrates. It is used extensively in recombinant DNA research because it has been genetically well characterized.

Enzyme

A protein that accelerates the rate of chemical reactions. Enzymes are catalysts that promote reactions repeatedly, without being damaged by the reactions.

Eukaryote

An organism whose genetic material is located within a nucleus. Yeast, fungi, protozoans, plants and animals are eukaryotes.

Expression

The physical manifestation of the information contained in a gene.

Fermentation

A process of growing microorganisms to produce various chemical or pharmaceutical compounds. Microbes are usually incubated under specific conditions in large tanks called fermenters. Fermentation is a specific type of bioprocessing.

Gene

A unit of hereditary information. A gene is a section of a DNA molecule that specifies the production of a particular protein.

Gene amplification

The increase, within a cell, of the number of copies of a given gene.

Gene mapping

Determining the relative locations of genes on a chromosome.

Gene therapy

A new therapeutic approach which consists in adapting the functioning of the organism's cells by modifying the genetic material in each cell.

Genetic engineering

The technique of removing, modifying or adding genes to a DNA molecule in order to change the information it contains. By changing this information, genetic engineering changes the type or amount of proteins an organism is capable of producing.

Genome

The total hereditary material of a cell.

Genomics

Genomics can be defined as the branch of science devoted to the investigation and understanding of genomes.

Genotype

The specific genetic makeup of an organism, as contrasted with the actual characteristics of an organism (see phenotype).

Hybridoma

A type of hybrid cell produced by fusing a normal cell with a tumor cell. When lymphocytes (antibody-producing cells) are fused to the tumor cells, the resulting hybridomas produce antibodies and maintain rapid, sustained growth, producing large amounts of an antibody. Hybridomas are the source of monoclonal antibodies.

Immunoassay

A technique for identifying substances, based on the use of antibodies.

Immunotoxin

The coupling of an antibody and a molecule that is toxic to the cell.

In vitro

Performed in a test tube or other laboratory apparatus.

In vivo

In the living organism.

Interferon

A protein produced naturally by the cells of our bodies. It increases the resistance of surrounding cells to attacks by viruses. One type of interferon, alpha interferon, is effective against certain types of cancer. Others may prove effective in treating autoimmune diseases.

Interleukin

A protein produced naturally by our bodies to stimulate our immune systems. There are at least 18 known kinds of interleukins.

Leukocyte

A white blood cell, an important component of the body's immune system.

Marker gene

Genes that identify which plants have been successfully transformed.

Molecular genetics

The study of the molecular structure and function of genes.

Monoclonal antibody

Highly specific, purified antibody that is derived from only one clone of cells and recognizes only one antigen.

Nucleic acid

A biological molecule composed of a long chain of nucleotides. DNA is made of thousands of four different nucleotides repeated randomly.

Nucleotide

A compound made up of these three components: a sugar, phosphate and a nitrogen-containing base. Found as individual molecules (e.g., ATP, the "energy molecule"), or as many nucleotides linked together in a chain (nucleic acid such as DNA).

Oncogene

A gene thought to be capable of producing cancer.

Oncology

The study of tumors.

PCR Polymerase Chain Reaction:

A laboratory technique to rapidly amplify pre- determined regions of double- stranded DNA

Phenotype

The observable characteristics of an organism as opposed to the set of genes it possesses (its genotype).The phenotype that an organism manifests is a result of both genetic and environmental factors. Therefore, organisms with the same genotype may display different phenotypes due to environmental factors. Conversely, organisms with the same phenotypes may have different genotypes.

Plasmid

A small, circular piece of DNA found outside the chromosome in bacteria. Plasmids are the principal tools for inserting new genetic information into microorganisms or plants.

Prokaryotes

Organisms whose genetic material is not enclosed by a nucleus. The most common examples are bacteria.

Protein

A complex biological molecule composed of a chain of units called amino acids. Proteins have many different functions: structure(collagen); movement (actin and myosin); catalysis (enzymes); transport (hemoglobin); regulation of cellular processes (insulin); and response to the stimuli (receptor proteins on surface of all cells).The information for making proteins is stored in the sequence of nucleotides in the DNA molecule.

Protein engineering

A technique used in the production of proteins with new or artificial amino acid sequences.

Recombinant DNA

DNA that is formed through combining DNA from two different sources. Humans direct the formation of recombinant DNA through selective breeding and genetic engineering.

Recombinant DNA (rDNA) technology

The laboratory manipulation of DNA in which DNA, or fragments of DNA from different sources, are cut and recombined using enzymes. This recombinant DNA is then inserted into a living organism. rDNA technology is usually used synonymously with genetic engineering.

Recombination

The formation of new combinations of genes. Recombination occurs naturally in plants and animals during the production of sex cells (sperm, eggs, pollen) and their subsequent joining in fertilization. In microbes, genetic material is recombined naturally during conjugation.

Regeneration

The process of growing an entire plant from a single cell or group of cells.

Restriction enzymes

Bacterial enzymes that cleave DNA at very specific locations.

Retrovirus

A certain class of virus that utilises the enzyme reverse transcriptase to reverse copy its genome into a DNA intermediate, which integrates into the hostcell chromosome. Retrovirus can be used as vectors for the insertion of genetic material like in the case of gene therapy.

RNA (Ribonucleic acid)

Like DNA, a type of nucleic acid. There are three major types: messenger RNA, transfer RNA, and ribosomal RNA. All are involved in the synthesis of proteins from the information contained in the DNA molecule.

Tissue culture

A procedure for growing or cloning enough cells through in vitro techniques to make a tissue.

Vector

The agent used to carry new DNA into a cell. Viruses or plasmids are often used as vectors.

Virus

An infectious agent composed of a single type of nucleic acid, DNA or RNA, enclosed in a coat of protein. Viruses can multiply only within living cells.

Abbreviations

AIBA	All India Biotechnology Association
AIDS	Acquired ImmunoDeficiency Syndrome
AIIMS	All Indian Institute of Medical Science
BARC	Bhabha Atomic Research Centre
BCIL	Biotech Consortium of India Limited
BSc	Bachelor of Science
BT	Bio-Technology
CBT	Centre for Biochemical Technology
CCMB	Centre for Cellular and Molecular Biology
CDFD	Centre for DNA Fingerprinting and Diagnostics
CDRI	Central Drug Research Institute
CDSCO	Central Drugs Standards Control Organisation
CEO	Chief Executive Officer
CII	Confederation of Indian Industries
CII	Confederation of Indian Industries.
CSIR	Council for Scientific and Industrial Research
DAE	Department of Atomic Energy
DBT	Department of Biotechnology
DCGI	Drug Controller General of India
DNA	Desoxyribo Nucleic Acid (cf. glossary)
DPCO	Drug Price Control Order
DSIR	Department of Scientific and Industrial Research
EPO	Erythropoietin
FDA	Food and Drugs Administration
GCP	Good Clinical Practices
GCP	Good Clinical Practices
GMP	Good Medical Practices
Hep.	Hepatitis
HGP	Human Genome Project
HTS	High Throughput Screening
IBAB	Institute of Bioinformatics and Applied Biotechnology
IBMP	Institut de Biologie Moléculaire des Plantes
ICAR	Indian Council for Agricultural Research
ICGEB	International Centre for Genetic Engineering and Biotechnology
ICH	International Conference of Harmonisation
ICICI	Industrial Credit and Investment Corporation of India
ICMR	Indian Council for Medical Research
ICRISAT	International Crops Research Institute on the Semi-Arid Tropics
IDBI	Industrial Development Bank of India
IFCI	Industrial Finance Corporation of India
IICB	Indian Institute of Chemical Biology
IICT	Indian Institute of Chemical Technology
IICT	Indian Institute of Chemical Technology
IIPC	Indian Integrated Pharmaceutical Company
IISc	Indian Institute of Science
IIT	Indian Institute of Technology
IIT	Indian Institute of Technology
IMT	Institute of Microbial Technology

IMT	Institute of Microbial Technology
IPR	Intellectual Property Rights
IT	Information Technology
JNU	Jawaharlal Nehru University
JV	Joint Venture
MIT	Ministry of Information Technology
MKU	Madurai Kamaraj University
MNC	Multi-National Company
MSc	Master of Science
Mtech	Master of Technology
MTU	Michigan Technological University
NASSCOM	National Association of Service
NBTB	National BioTechnology Board
NCBS	National Centre for Biological Sciences
NII	National Institute of Immunology
NII	National Institute of Immunology
NIMHANS	National Institute of Mental Health and Neuro Sciences (NIMHANS)
NRCPB	National Research Centre for Plant Biotechnology
PCR	Polymerase Chain Reaction
PhD	Philosophy Doctorate
R&D	Research and Development
rDNA	recombinant DNA (cf. glossary)
RNA	Ribonucleic Acid (cf. glossary)
SIDBI	Small Industries Development Bank of India
SKB	SmithKline Beecham
TCS	Tata Consulting Services
TERI	Tata Energy Research Institute
TIFAC	Technology Information Forecasting and Assessment Council
TMC	Tata Memorial Centre
TRIPs	Trade-Related Aspects of Intellectual Property Rights
U.Penn	University of Pennsylvania
UGC	University Grant Commission
UTI	Unit Trust of India
WTO	World Trade Organization

Tables Index

Charts Index