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Indian Experience in Commercializing Institutionally Developed Biotechnologies

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The immediate benefits from the use of biotechnologies come from their applications by the society. In India, the initial efforts in promoting all facets of biotechnology were from the government side. During the past 10 y (1986 to 1995), seventeen institutionally developed technologies were transferred to the industry by direct government intervention. However, many of these technologies did not fare so well in the hands of the industry and some products were withdrawn from the market by the industry after initial introduction. The lessons learnt from these efforts were many. It was observed that institutions engaged in developing technologies lacked in adequate information, as well as the needs of the market. Claims made by the institutions would have the possibility of better chances of acceptance if third party independent validations were made in the beginning. Institutions had little knowledge about the value of securing their inventions by patenting. The incentives to the ground workers and investigators working for developing technologies were getting evolved as some of the technologies got transferred or the sale brought some cash proceeds. The R & D infrastructure and scientific capabilities of the industry were found to be inadequate and needed substantial improvement. Industry was not much interested to carry out subsequent developmental work on technologies procured by it but was interested in turn-key projects only. Industry was less interested in dealing with technologies which were available on non-exclusive basis. The role of technology managers catalyzing the development and the transfer of the technologies was inadequately appreciated both by the institution, as well as by the industry. The success in commercializing institutionally developed biotechnologies in future could be modulated by learning from the above experience.

Introduction

The immediate benefits from the use of technology from any sector come from their direct application by the society. The enthusiasm and excitement of changing the life styles of people in certain facets of conscious existence encompassing health, agriculture, processed food, industrial organic products, and environment, through the application of biotechnology the world over in late seventies had brought in strong ripples in the Indian subcontinent too. India has a strong background in biochemistry, microbiology, and immunology, besides hands-on expertise in agricultural and engineering sciences. India, therefore, decided through the initial efforts of the government to promote modern biotechnology in all the facets from the training of manpower to the building up +of R & D infrastructure, besides supporting R & D in institutions and universities in the country from 1982 onwards. In February 1986, a full-fledged Department of Biotechnology (DBT) in the Ministry of Science and Technology was established. A Product and Industry Development (PID) division was created in DBT in 1988, *inter alia*, to foster the development of biotechnologies through government funded projects and to transfer the institutionally developed technologies to the industry[1]. Institutionally developed Indian biotechnologies initially commercialized were mainly through the efforts of the PID division of DBT. With the passage of time as the developments are picking-up all over India, other agencies are growing up which are also contributing to such commercialization. As time passes and as the private sector industry gets more and more involved

*The views expressed in the paper are those of the author and do not necessarily express the views of the organisation to which he belongs.

Table 1 — Value additions for different biotech products

Particulars of cost elements	Examples of biotech products			
	Recombinant hepatitis B vaccine (Rs/adult dose, 20mcg)	Potassium penicillin G, Ist crystals (Rs/BU)	Ephedrine hydrochloride (Rs/kg)	Yoghurt (Rs/kg)
Purchased materials (B)	3	534	834	15
Current selling price at manufacturers' level (S)	330	1025	1410	18
Value additions, ratio of (S-B)/B	109	0.92	0.69	0.20

Note: Purchased materials include the cost of raw materials, chemicals, packing materials, electricity, furnace oil, and water. Current selling prices are either the existing selling prices in the market or government notified prices. Costs of purchase materials calculated by the author are based on his discussions with the industry personnel and personal experience. One mcg is 1/1000th of a mg; one BU is equal to about 600g

in the development and use of biotechnologies, the role of DBT will be reoriented from the one of piloting to the one of catalyzing the process. World over, there is a slow but steady process of shift and preference in the use of biological machinery for the development and production of genetically engineered organisms, plants, and molecules for use in pharmaceuticals, agriculture, food, and environment management. The core of the work plan in modern biotechnology emphasizes as follows:

(i) Purification of DNA, RNA, and protein enzymes;

(ii) Cloning and amplification of genes;

(iii) Standardization of cell culture techniques;

(iv) Standardization of separation and downstream processing methods for the isolation of gene products;

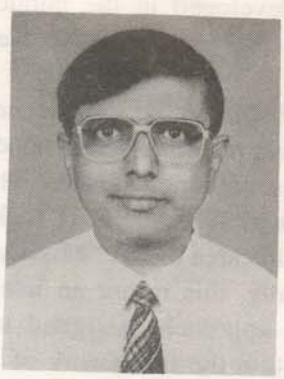
(v) Stabilization of gene products;

(vi) Management of research and applications; and

(vii) Technology packaging, patenting, and business development.

In such developments the quality of R & D assumes paramount importance as the applications are science based. Successful commercialization may be highly rewarding as the *value additions*† may contribute to 1 to 100 or even more, depending upon the invention and innovativeness of the product. In contrast, the established products have value additions of only 0.1 to 1.5 (Table 1). Innovative biotech products, thus have potentials of immense returns on investment and could turn the fortunes of companies in short duration.

†Value addition is the ratio between the difference in the manufacturer's selling price (S) and the cost of the items bought (B), and the cost of items bought, i.e. (S-B)/(B)



Dr Prasanta Kumar Ghosh obtained his M Tech in Chemical Engineering and Chemical Technology in 1963 and Ph D degree in Chemical Kinetics in 1968 from the University of Calcutta. He worked in various Central Government organisations in India including the Patent Office, the Directorate General of Technical Development, the Bureau of Industrial Costs and Prices and the Ministry of Chemicals & Fertilizers. He also worked at M/s Hindustan Antibiotics Ltd, Pune, during 1980-82 as the Planning Manager and at M/s Bengal Immunity Ltd, Calcutta, during 1983-84 as the Production Director. In industry, he had extensive exposure to fermentation, down stream processing, protein handling and separation, and vaccines production. Presently, he is working as an Adviser in the Department of Biotechnology, Ministry of Science & Technology. His responsibilities include promotion of biotechnology industry, facilitating evaluation and transfer of technologies from institutes to industry, patenting of biotech inventions and implementation of biosafety protocols for handling genetically engineered organisms and products in research. Dr Ghosh has more than 30 publications to his credit on various topics relating to drugs and pharmaceuticals and biotechnology. He has also authored a book titled "Biotech Industry Guide".

In an apparent potential high profit making arena of modern biotechnology, for high returns the inventors are required to work in high risk areas. For example, in the development of therapeutics in areas like thrombolytic agents, endocrine disorders, genetic diseases, cancer, nervous and brain disorders, and severe systemic infections the inventors are required to overcome larger innovative hurdles and more stringent registration requirements. Besides, the knowledge of the leader must be thorough in each of the components of product development such as the product discovery and the initial scientific leads, the biological and the pharmacological elements of research, the toxicity studies, the pharmaceutical formulation development, and other areas including patenting, documentation and registration. As one individual can not comprehend all the above areas, the innovative product development in biotech industry is increasingly becoming inter-connective and inter-expertise dependent. Investigators and experts of divergent specialization, therefore, must learn to work harmoniously, and industry should take a lead in playing the orchestra to enhance the elements of success. Such concepts have not yet been rooted adequately in India, although shifts in these directions are occasionally visible.

However, there is no scope of escape from such developments in the current environment of global competitiveness.

The Efforts of DBT in Technology Development

DBT was assigned the status of the Administrative Ministry (AM) for the Biotechnology Industries in 1988 (ref. 3) and the responsibilities to be discharged by the DBT under the purview of AM were, *inter alia*, the following:

"Act as a screening, advising and approving agent of the government with regard to import and transfer of new technologies for the manufacture of biological and biotechnological products and their intermediates.

Serve as the interministerial and interagency nodal point for all specific international bilateral and multilateral R&D of collaboration and agreement in the area of biotechnology and as the nodal point for all technology transfers in the area of biotechnology.

Serve as an administrative and implementing department of agencies, commissions, boards, etc. specifically formed by the government for fulfilling the national objectives in biotechnology and also to serve as the nodal point for the collection and dissemination of information relating to biotechnology".

From 1987 onwards, certain specific areas were taken up by the DBT for focused development. These included the health care area, the development of immunodiagnostics, vaccines, recombinant DNA molecules, targetted drug delivery systems, microbial strain improvement and process optimisation in antibiotics, and enzymes and bioactive molecules. In agriculture, the mass multiplication of elite planting materials by tissue culture techniques, development of hybrid high yielding seeds, region and crop- specific biofertilizers and biopesticides, and the development of transgenic disease-resistant and stress-tolerant plants were specifically taken up. In addition, perfection of embryo-transfer technology to develop high yielding milching animals and efficient draught cattle and buffaloes were also other focused programmes in agriculture. Development of recombinant organisms with high efficiencies of substrate conversion was emphasized under industrial biotechnology. Use of stress-tolerant microbial concentrates are being attempted for treating liquid effluents; concurrently planting of forest species of plants raised through plant-tissue culture are being attempted under environmental biotechnology[1,3].

The main thrust has been to build competence in research institutions, provide industry-institution research collaborations, promote socially relevant research, and stimulate international collaboration in research in publicly funded institutions. Initial thrust in applications had been to promote traditional biotechnology; during the past two years the strategies have been reoriented to promote modern biotechnology in preference to traditional ones. The contribution of the DBT in the areas of technology transfer discussed here is further elaborated. All these technologies were developed in the public funded R & D institutions and universities in the country.

Immunodiagnostics — Realizing the importance of early diagnosis, and having regard for the ground realities that no indigenous immunodiagnostic kit was commercially available in 1987, the DBT took up the task of developing this area as the "Mission Mode" project. Conceptually, this meant an integrated and goal oriented approach, designed to achieve specific results within the framework of a

fixed time schedule deploying the most appropriate persons through effective inter- agency participation and coordination. The diseases identified over the years for the development of diagnostic formats were tuberculosis, leprosy, filariasis, typhoid, viral hepatitis, diarrhoeal diseases, amoebiosis, malaria, leishmaniasis, toxoplasmosis, brucellosis, schistosomia, streptococci infection and sexually transmitted diseases. Concurrently, certain non- communicable diseases like cancer markers and detection of physiological status of body fluids (hormone detection/assay, etc.) and blood grouping sera were also added in the programme. Apart from pursuing R & D work on human diseases, several animal and poultry diseases like enterotoxemia, sheep pox, infectious bovine rhinotecheitis, bovine brucellosis, New Castle disease, egg drop syndrome, infectious bronchitis and certain other viral diseases of animals were also taken up for developing diagnostics.

Further, a countrywide survey was carried out on the status of development of diagnostic kits and the scientific work pursued in various laboratories and industries in India. Based on such study the gist of which was also published[4,5] in 1992, the DBT continued its efforts to identify expert groups and fund projects in public funded R & D institutions to develop prototype kits for transferring them to the industry. Wherever the knowledge was already mature enough for transfer to the industry, the laboratory work was packaged by the DBT in consultation with the working scientists of the institutes in the form of a techno- commercial profile. Efforts were then made to contact and identify industry and to initiate negotiations, using the profiles to enable the facilitation of teaming up between the institutes and the industry on an one-to-one basis. Memoranda of Understanding (MoU) was also drafted by the DBT, keeping in view the interest of both the parties through mutual discussions. In many cases, such efforts succeeded in the transfer of technology and in certain cases after the teaming up was initiated by the DBT, the institutes and the industry carried it further.

Prototype kits for the detection of filariasis, toxoplasmosis, leishmaniasis, typhoid, amoebic liver abscess, blood grouping sera, early detection of pregnancy, and human brucellosis were also developed by DBT. Kits for the detection of malaria and HIV infection are in the advanced stage of development. There has also been significant progress in the development of improved versions for the detection of leishmaniasis and filariasis (both antigen based). Dot immuno binding assay and ELISA formats have been developed for the detection of antibodies to the causative agents for egg drop syndromes in poultry birds.

During the initial phase of development of a diagnostic kit, its performance was evaluated by the inventors using a few sera samples. DBT facilitated the procurement of additional sera from resourceful institutes. In cases where opportunities existed, the prototype kits were sent for independent evaluation by pathologists and experts in the country, and the DBT provided the logistics. In some cases, DBT arranged to get the expert opinion on certain prototype kits from multinational companies from abroad.

A pilot plant for the development and production of immunodiagnostic kits was set up at the National Institute of Immunology, New Delhi, to facilitate the optimization of conditions of production, in comparatively commercial scale. The purpose was to develop industrially usable technology package. The facility is available for deployment by researchers in the country.

As the knowledge base for the detection of HIV infection was virtually non-existent in India in 1987, the DBT was entrusted by the Ministry of Health and Family Welfare (MOH & FW) with the task of assessing the utility of HIV kits marketed by foreign companies. The purpose was to choose from among the available stock to procure the best ones for use in the sero-surveillance programme of the government. Through the PID division the DBT carried out three rounds of evaluation; initially during 1988-90, nine kits were evaluated, during 1990-92, another 13 kits and during 1992-94, further 24 kits were evaluated. The evaluation was carried out in association with the ICMR, New Delhi, which extended its facilities existing at different parts of the country, i.e., at the National Institute of Virology, Pune; the National AIDS Research Institute, Pune; the National Institute of Cholera and Enteric Diseases, Calcutta; the Institute of Immuno- Hematology, Bombay; and the Christian Medical College, Vellore. In addition, the facilities of the All India Institute Medical Sciences, New Delhi, and the National Institute of Communi-

cable Diseases, New Delhi, were also made available through the intervention of MOH & FW.

Other Areas of Biotechnology — Like the development of immunodiagnostics, several application oriented projects were also funded and pursued by the DBT during the past 10 y. Outcome of these projects is summarized below:

A technique for the mass multiplication of two species of bamboos by tissue culture through the stages of callusing and somatic embryogenesis was developed at Delhi University, Delhi. Nearly 10,000 plantlets raised through tissue culture were planted throughout the country in different agroclimatic zones through the intervention of DBT. The DBT had written to the various state forest authorities requesting them to provide and allocate land for such plantations. The plants performed well in the field and in many instances their performance was found to be better than plants raised through seeds. The technique was transferred subsequently to the Tata Energy Research Institute, New Delhi, with a view to providing planting materials to reclaim wastelands and to regenerate forest cover. A liposomal amphotericin B formulation was developed at the University of Delhi South Campus, New Delhi; this was evaluated in comparison to the plain amphotericin B to assess the comparative efficacy of clearing aspergillosis (a systemic fungal infection occurring in mammals) in a balb/c mouse model. The liposomal formulation was found to be more efficacious. Consequently, this work was extended for human trial at the Seth G S Medical College and K E M Hospital, Bombay on systemic fungal infections. The phase I and phase II clinical trials have been completed with encouraging results and the work is moving to phase III trials. At Gulburga University, Gulburga, about a dozen of alkaline soil-resistant iron- utilization efficient sugarcane clones were developed by mutations followed by selection under alkaline stress conditions. The selected clones designates as GSBT 1 to 12 are being field evaluated; initial results of growth vigour, leaf morphology and sugar content in juice are encouraging, thereby showing improvement over the mother plants. *Bacillus lichiniformis* strains selected by the researchers of Bose Institute, Calcutta, were utilized for solubilizing silica from silica containing magnesite ore (more than 6% silica) at Salem premises of M/s Burn Standard Ltd, Calcutta, through a DBT funded joint project to Bose Institute and Burn Standard. The silica content dropped to below 1% and the enriched magnesite could be utilized for brick making in steel furnace. The cost of silica removal was not however economical. A method for selecting fungal pathogen- resistant tea clones has been developed to select resistant germplasms against *G. cingulata*, *P. theae* and *C. theae* at North Bengal University, Darjeeling. A small germ plasm bank with disease-resistant clones is also being established. A microbial strain for efficient production of cephamycin C, a cephalosporin group of antibiotic was developed at Osmania University, Hyderabad. The strains have been deposited at the Microbial Type Culture Collection Centre situated at the premises of the Institute of Microbial Technology, Chandigarh. The strains are available for commercial transfer. Two fish spawning inducing peptides were isolated from Muriel hypothalamus by the researchers of Vishwa Bharati University, Shantiniketan. These peptides showed increased spawning efficiencies in carps in field conditions; more field data are being generated. All these developments and many others, as would be evolved in the course of time, would eventually be transferred to the industry for field application for the benefit of the society.

The Growth of Industrial Biotechnology in India

The local Indian biotech industry has not yet been able to develop and introduce any genetically engineered product or process, which requires the transformation of a natural microbe or a cell or a living organism by applying recombinant DNA techniques. In R & D stage in the country[1], several genes have been cloned at the lab stage and constructs have been made using plasmids, viruses, and phagmids. In certain situations, synthetic genes have been made by cDNA and PCR techniques. Modified expression hosts have been created in *E.coli*, different species of yeast, and cell lines of insect and vertebral origin. A few transgenic plants in the arena of cash crops, cereals, and fruits have been made by incorporating bacterial genes, expressing toxic proteins to lepidopteran pests. Transgenic fishes have been made by incorporating growth hormone genes. Transgenic insects have been created by inserting certain reporter genes. All these works are, however, still at the lab

stage, far away from commercialization stage. On the other hand the industry has directly imported several recombinant pharmaceutical products and have marketed them after fulfilling the registration requirements of the Ministry of Health under the Drugs Act and after obtaining the clearance of the Genetic Engineering Approval Committee of the Ministry of Environment and Forests under the Environment Protection Act. These include recombinant human insulin, interferons, G-CSF, GM-CSF, erythropoietin, blood factor VIII, and hepatitis B surface antigen based vaccine.

The semi-high-tech biotechnology involving the use of hybridoma technology for creating mouse monoclonals and *E.coli* phage display system has made lot of progress and has reached commercialization stage in certain cases. Several diagnostic kits, such as those for the detection of early pregnancy, hepatitis B, and blood grouping have been introduced using locally developed monoclonals.

The conventional biotechnology involving fermentation, substrate conversion by microbial methods, production of toxoids and vaccines in bioreactors, raising of antisera in animals, multiplying approved cell lines, and culturing viruses therein, or directly culturing viruses in fertilized eggs and using the viruses, dead or alive (attenuated) for vaccination, production of polyclonal antibody based diagnostics, extraction of active principles from animal glands or plants, and other activities of similar nature are widely practiced in India. Development of hybrid seeds and high yielding cultivars by plant tissue culture, production of biofertilizers and biopesticides, selection of improved animals and poultry birds for improved traits and there multiplication by artificial insemination and embryo transfer technology, and use of improved feed and concentrates by enzymatic/microbial treatment methods are also being practiced in the country. The conventional biotech industry has developed very well in India.

A large consumption market has already been created in India for biotech products produced locally or made available through imports. These include primarily the products of old biotechnologies, although there is visible shift and preference in the marketing of modern biotech products too. Table 2 indicates the estimated turnover of biotech products in 1995 and in 2000 A D at manufacturers' or marketeers' premises[2].

The Indian Industrial-House Capabilities in High-tech Biotechnology

As modern biotechnology is of recent origin, there is not yet any company in India which is currently operating only in the high- tech biotechnology sector; however such companies would soon be emerging. There are however several dedicated biotechnology companies operating in medium level biotechnologies such as in fermentation (producing antibiotics, enzymes, alcohol, bakers, and brewers yeast), in the production of vaccines, diagnostics, tissue culture raised plants and hybrid seeds. Several other resourceful companies operating in other areas have also diversified in specific areas of biotechnology. Many of these companies have set up in-house R & D facilities for absorbing technologies and for conducting application oriented developmental research. The existing production set up is usually not based on in-house research efforts but rests on purchased technologies. Consequently, the in-house capabilities in basic research are generally low and basic research in high risk areas is not yet being

Table 2 — Estimated turnover of biotech products in India (in million Rs)

Product category	Estimated turnover at manufacturers' or marketeers' premises	
	1995	**2000**
Human and animal health	19590	35320
Agriculture	1540	3850
Industrial products	5700	15000
Other biotech products	300	1300
Total (in million Rs.)	27930	55470
(In million $ US)	904	1849

conducted. Similar conclusions were also drawn in another study on R & D capabilities in Indian industry[6]. The total resources diverted towards R & D are also low. The combined spending of the Indian pharmaceutical industry in R & D was however small, i.e., just over Rs 120 crore compared to total turnover of about Rs 9000 crore; besides, the emphasis of research was on the synthesis of new molecules and in the process optimization, besides pharmaceutical formulation development. In fact, less than 10% of the above sum was deployed specifically for high-tech biotechnology research.

Some pharmaceutical companies have recently diverted sizeable part of their resources for innovative research; these include the Ranbaxy Laboratories, New Delhi; Lupin Laboratories, Mumbai; CIPLA, Mumbai; Torrent Pharmaceuticals, Ahmedabad; Cadila Pharmaceuticals, Ahmedabad; Wokhardt, Mumbai; and Dabur Ltd, New Delhi. These companies on an average had individually allocated nearly 5-6% of their sales turnover in R & D during 1994-95, which by Indian standards are considered sizeable. There has been another significant shift in research in the Indian companies in the recent times; several of them have teamed up during the last 3 y with several national laboratories with commitment of sizeable sum for innovative R & D. Significant amongst such alliance are the individual collaborations between Ranbaxy, Unichem and CIPLA with Central Drug Research Institute, Lucknow; Ranbaxy Lupin and SOL Pharmaceuticals with Indian Institute of Chemical Technology, Hyderabad; Dabur with National Institute of Immunology, New Delhi; and Zandu with Regional Research Laboratory, Jammu. An understanding of the utility of innovative R & D in biotechnology in the industry through stand-alone mode as well as through joint research is gradually but surely emerging.

The current developmental capabilities in the industry include; microbial strain improvement by classical mutations, fermentation process optimization and downstream product recovery. Capability in production and immobilization of enzymes also exists. The local capabilities also include fabrication of sterile bioreactors and processing equipment for recovering products produced generally in concentrations of 1g/l or above. There is also fairly high capability of handling sterile operations. In hybridoma technology, which is the latest development, capabilities of cell fusion and cell culture have been built to some extent. Expertise has also been developed in the synthesis of peptides, production of antibodies, conjugates, substrates, and biological culture media. However, there is yet inadequate industry level development for handling products made in milligram or microgram quantities per litre of fermented broth. There is also inadequate expertise in the production of high precision separation equipments, and instruments for finer affinity measurements. Besides, the knowledge in protein chemistry, protein folding and protein engineering is inadequate. Similarly, there is inadequate experience in the development and handling of genetically engineered products and processes. Knowledge of production of membranes, latex particles and special plastics required for diagnostic research and product development is also inadequate. With time and experience, these areas would be strengthened in the industry. The diagnostic techniques transferred to the industry require in depth in-house knowledge of affinity measurements, precise knowledge on properties of latex particles, membranes, stability of substrates and conjugates, production of monoclonals and properties of special plastics. The knowledge base in the industry in these areas is only currently developing and is yet far from adequate.

The Indian Experience of Commercialization of Biotechnologies

The Indian experience of commercialization of biotechnology is to be viewed in the context of local capabilities. As mentioned earlier, the PID division of DBT had facilitated the transfer of technologies. Seventeen technologies developed locally at various institutes, during the last 10y were transferred, as indicated in Table 3. All technologies, however, did not get translated into commercially viable products for various reasons as discussed here. The filariasis detection kit was introduced by Cadila Laboratories in 1989 but was withdrawn subsequently as the sensitivity and specificity data claimed by the inventor (sensitivity and specificity 85-90% for positive results and 98% for negative results) could not be sustained in blood samples obtained from various places in India. The sensitivity and specificity data were generated by the Mahatma Gandhi Institute of Medical Sciences (MGIMS), Wardha, using night

Table 3 — Transfer of locally developed technologies to the industry

Name of the product/ technology	Institution where developed	Industry which purchased	Terms of transfer
Filariasis detection kit	Mahatma Gandhi Institute of Medical Sciences, Wardha	Cadila Laboratories, Ahemdabad	Rs 50,000 lumpsum plus royalty of 5% on sale for 7 y
Pregnancy slide test Latex agglutination	National Institute of Immunology, New Delhi	Ranbaxy Laboratories, New Delhi	Rs 25,000 lumpsum plus royalty of 1% on sales for 7 y
Pregnancy DOT-ELISA	National Institute of Immunology, New Delhi	Ranbaxy Laboratories, New Delhi	Rs 25,000 lumpsum plus royalty of 1% on sales for 7 y
Typhoid fever detection kit	National Institute of Immunology, New Delhi	Lupin Laboratories, Bombay	Rs 5 lakhs lumpsum plus 5% royalty on sales
Typhoid fever detection kit	All India Institute of Medical Sciences, New Delhi	Ranbaxy Laboratories, New Delhi	Rs 1 lakh lumpsum plus royalty of 5% on sale for 7 y
Amoebic liver abscess	National Institute of Immunology, New Delhi	Cadila Laboratories, Ahemdabad	Rs 8 lakh lumpsum plus royalty of 5% on sale for 10 y
Polypeptide P from bitter gourd	University of Rajasthan, Rajasthan	Lupin Laboratories, Bombay	Rs 5 lakhs lumpsum
Bamboo by tissue culture	University of Delhi, Delhi	The Tata Energy Research Institute, New Delhi	Transferred free of cost to TERI to eventually develop salable technology
Animal birth control injection (TALSUR)	National Institute of Immunology, New Delhi	Karnatka Antibiotics and Pharmaceuticals Ltd, Bangalore	5% royalty on sales for 10 y
Osmotolerant and high alcohol tolerant yeast strain	Institute of Microbial Technology, Chandigarh and Vittal Malaya Scientific Research Foundation, Bangalore	United Breweries, Bangalore	Rs 31 lakh lumpsum
Blood grouping monoclonals	National Institute of Immunology, New Delhi	Cadila Laboratories, Ahemdabad	Rs 3.5 lakh lumpsum plus 5% royalty on sales for 10 y
Microbial convention on benzaldehyde into L-phenylacetylcarbinol	Central Drug Research Institute, Lucknow	Atlus Laboratories, Ambala	Rs 3.5 lakh lumpsum plus 3% royalty for 5 y
F-MOC derivatives of 12 amino acids	Center for Biochemical Technology, New Delhi	Atul Products, Bulsar	Terms were to be worked out and initial payment was made
Hepatitis B detection kit	National Institute of Immunology, New Delhi	Lupin Laboratories, Bombay	Rs 5 lakh lumpsum for the monoclonals plus 5% royalty on sales for 10 y
Leprosy immunomodulator	National Institute of Immunology, New Delhi	Cadila Laboratories, Ahemdabad	Rs 15 lakh lumpsum plus royalty of 10% on sales
Leishmaniasis detection kit	Central Drug Research Institute, Lucknow	Span Diagnostics Ltd, Surat	Rs 50,000 lumpsum plus 5% royalty for 7 y
Monoclonals to M13 phage proteins III & VIII	University of Delhi South Campus, New Delhi	Pharmacia Inc., USA	US $ 20,000 lumpsum

blood samples containing microfilaria of *Wuchereria bancrofti* as the golden standard. The kit contained the excretory-secretory (ES) antigens of microfilariae of *W. bancrofti* obtained from the blood of patients positive to microfilariae. The kit was directed to detecting a level of IgG antibodies to ES antigens in human blood above a cut off value. The kit in the subsequent evaluation in the hands of Cadila also performed well on patients positive to *Burgiya malai*, another causative nematode for filariasis in the country, specially in the Southern India. Subsequently, during commercial use, it was reported that several clinical filariasis patients gave negative results. DBT intervened and got the observations confirmed through the assistance of the Malaria Research Institute, New Delhi, on blood samples obtained from Rourkela and Shahjehanpur. The sensitivity data dropped to about 20%, using blood of clinical filariasis patients. In anticipation of a this trouble in the market place, Cadila withdrew the kits from the market immediately after knowing these results. It was subsequently revealed in early nineties that clinical filariasis patients not having microfilarial nematodes in their blood for a long time (due to various reasons such as adult filarial nematodes not reproducing or microfilariae load eliminated by medicaments, etc.) may have no ES antigen load. In such situations, the IgG antibody level may drop sharply in clinical filariasis patients and this could be the main reason as the author surmises for such high drop in sensitivity. In other words the author feels that the reference blood samples used for evaluating the kits were not scientifically the proper ones as these were based on samples drawn from several clinically apparent filariasis patients, where the presence of microfilarial nematodes was not confirmed by microscopic examination of their blood. However, this hypothesis could not be tested as Cadila suspects about the utility of the kit, and the MGIMS also did not reconfirm the validity. The author believes that a sensitivity evaluation of the kit redone with confirmed microfilaria positive patients as the gold standard is expected to improve largely the situation. In that case, the kit could then serve the country to a greater extent as a simple and economic test for routine use for the primary surveillance of the filariasis population as well as for the diagnosis of early infection besides the monitoring of the efficacy of treatment of early infected patients with chemotherapeutic drugs (like diethyl carbamazine citrate, etc.).

The Pregnancy slide and DOT-ELISA formats were introduced by Ranbaxy Laboratories and the product remained in the market for a short duration. There were several similar products already in the market, and the products of Ortho Diagnostics (earlier M/s Ethanor India Ltd, Bombay and now M/s Johnson & Johnson India Ltd) were the market leaders. The consumers (pathological labs and gynecologists) did not find any additional advantage in the use of Ranbaxy's kits. Moreover, several more reliable and sturdy products were introduced subsequently by many companies and these compelled Ranbaxy to withdraw the above products due to tough competition. Typhoid detection kit of National Institute of Immunology (NII), New Delhi, has not yet been introduced by Lupin Laboratories as the company has not found substantial additional advantage in the kit over the conventional Widal testing format. The NII kit was based on sandwich enzyme immunoassay using monoclonal antibodies against somatic, capsular and flagellar antigens of *Salmonella typhi* as the capturing antibodies for detecting the presence of *S. typhi* antigens in human blood. The format had a culturing fluid for amplifying the *S. typhi* organism (in 6-12h) to generate sufficient bacteria for detection. The format was novel and could penetrate the market with competitive edge and advantage, although the cost would have been higher than the conventional Widal format. The reasons of Lupin for not introducing the kit in the market are not clear. The typhoid kit of All India Institute of Medical Sciences, New Delhi, was found to be unusable by Ranbaxy as well by the DBT on subsequent analysis, which was carried out by Ranbaxy and monitored by DBT. The amoebic liver abscess kit of NII had been introduced by Cadila in limited quantities and are in the market; however, the demand is not much. The physicians are generally not eager to find out the status of patients by this test but would like to diagnose by physical symptoms. The utility of polypeptide P isolated from bitter gourd was reassessed by Lupin who did not find it efficacious enough for marketing. As the product given orally, reduced the blood sugar in healthy volunteers, and as bitter gourd is traditionally believed to be useful for diabetic patients, the author

is of the view that the product should have been assessed by Lupin on a longterm basis over a period of at least 2-3 y, to find its efficacy in rejuvenating the target cells of the pancreas secreting insulin, before a final conclusion was drawn on its efficacy. TALSUR was not found to be of advantage by KAPL over the least expensive mechanical castration method and was therefore discontinued by KAPL. The efficient alcohol strain and technology jointly developed by IMTECH and VMSRF is being used by United Breweries in its distilleries. It took several months' persuasive work by a monitoring committee chaired by the author to demonstrate at one fermenter along with associated distillation unit of the United Breweries that there was a reduction in the consumption of furnace oil over a period of six months, and this eventually convinced the management of United Breweries about the utility of the new package, and to accept the strain and technology. The blood grouping monoclonals of NII purchased by Cadila were used by the company for making blood grouping reagents. However, due to availability of more sensitive and reliable products, Cadila withdrew the reagents subsequently after introduction. The author is of the opinion that in certain situations the Indian blood grouping monoclonals could perform very satisfactorily, and in order to make the product better it could be possible to achieve this by mixing purchased monoclonal antibodies of specific utility to make the Indian kit more useful. However, neither NII took interest in developing additional monoclonals for Cadila nor the Company pressed for it, probably because imported alternative products were readily available to Cadila in the finished form for marketing. Altus has set up its plant for the production of L-phenylacetyl carbinol, L-ephedrine and pseudo-ephedrine. The company has just introduced its products in the market. The F-MOC technology of Centre for Biotechnology (CBT), Delhi, was found to be commercially non-viable by Atul in its subsequent assessment. The Hepatitis B kit developed at NII has not yet been introduced by Lupin and it was realized that the kit needed further improvement to increase its sensitivity. Cadila has not yet introduced the Leprosy immunomodulator injection. Span has manufactured Leishmaniasis detection kit but is finding hindrances in marketing because of its limited market demand. The bulk of the consumption is expected to be in the National Leishmaniasis Eradication Programme of the government where currently the painful bone marrow puncture samples are used for diagnosis. The M13 phage monoclonals have been sold to Pharmacia recently; the company will introduce the reagent in the market somewhere in 1996.

Discussion

It is observed that several products have been withdrawn after introduction primarily because better imported products were subsequently available. In most of the cases the locally developed products were not even suitable for introduction because of their unsatisfactory performance in the hands of the industry. In certain cases, the industry did not show adequate interest to improve and revalidate the kits with more scientific inputs, e.g. filariasis detection kit and blood grouping sera. None of the products or production processes were patented except for M13 phage monoclonals and monoclonal antibodies therefrom, for which application for *process patenting* has been filed.

While negotiating for technology transfer, the DBT realized that the industry wanted to procure technologies on exclusive basis. Indeed, some of the Indian companies and all the foreign companies enquired if the technology was protected by patents. As the technologies were developed in the public funded institutions using grants from the government, the technologies could not be transferred on exclusive basis. In order to provide a practical solution initially it was decided that certain minimum period of exclusivity would be built in, or otherwise the industry would not be interested in the procurement. Therefore, a clause was introduced in the MoU to provide a period of exclusivity of 3 y (extendable up to 5 y depending upon situation) from the date of commencement of commercial production by the company. Further, in order to safeguard public interest, a clause was also introduced by stating that as and when required the product shall be made available in bulk to the government at special (subsidized) rates. Further, in order that the industry launches the product soon after signing the agreement, a clause was also introduced specifying the maximum time period within which the product shall be commercially launched after the technology was transferred by the institute and proven to the industry. The interest of

the industry was also adequately taken care of by incorporating clauses of obligations of the institute emphasizing complete description of the technology (including complete scientific data, information, know how for the manufacture of the product and components; specifications of materials; sourcing of materials; process control; quality control, etc.) and relating the payment of technological fees with the achievement of preset milestones by the industry during the technology transfer process. Although the MoUs were well-written and were accepted by both the parties, while implementing them in situations of difficulty relating to various aspects of the product improvement (beyond the normal clause of MoU) the institutions could actually do much less than was expected to enable the sustenance of the products in the market after they were introduced by the industry. When the industry was compelled to withdraw such products, the institutions in some cases were requested to provide assistance. However, very little in additional intellectual support was provided by the latter. It is believed that the main reasons for such happenings were that the industry did not have an adequate in-house R & D capability to improve the products. It was also not keen to provide additional money to the institutes for further developmental work, probably because the former was not convinced that the institutes would be able to deliver the goods up to their expectations. On the other hand, the institutions also did not find such product developmental work much rewarding to their ground level investigators from their career development point of view as they were academic minded. Institutes took up most of the product development work on DBT's persuasion. In the process, the products suffered and this brought in distrust among the institutes and the industry. The two cultures do not generally communicate with each other. Based on experience, it is suggested that for salvaging the situation the institutes and the industry must be incited to do so as continuous interactions will only enable to appreciate individual's shortcomings and to improve upon the relationships so as to be mutually rewarding.

It was further observed that there were whispers amongst the scientific community that the product oriented groups of investigators were involved in less nobler and intellectually easier areas of research, and that a few highly placed scientists were making mockery of the scientific temper by drifting themselves away from the difficult-to-contribute basic sciences areas. There was also no method of sharing the fees received by the institutions with the working scientist in most of the institutions and universities. However, as some technologies got transferred and as initial technological fees were received, the institutes had to devise methods for rewarding the working scientist. The institutes like NII, New Delhi, Delhi University, Delhi, Jawaharlal Nehru University (JNU), New Delhi, etc., developed and adapted such systems and methods of rewarding individual scientists from the technology sales received only recently, after some of their technologies were transferred to the industry and some others had the potential of transfer. The ball was thus set rolling primarily by the efforts of the DBT. The DBT also emphasized on patenting before publishing from the later part of 1994. Money required for patenting was made available by the DBT. This strategy is helping in bringing in a temper of patenting before publishing, and during the small period of one-and-half year, several patents have been filed[7], and many more will be filed soon. There was definite indications that an well informed academic sector was getting generated in universities and research institutions about the utility of patents. It is anticipated that by 2000 AD, about 100 patents could be taken through the DBT funded projects. Interestingly, these two prong gains of the product-oriented scientists of sharing technological fees and securing inventions by patenting brought in greater respectability to them

The work culture in an institute is driven primarily by the leadership and the foresightedness of the head of the institution. If the prime leadership is successful and can provide guidance to the group leaders to achieve organizational goal and further if the organizational goal is innovative research then there is no reason why institutional research will not deliver products and processes. Unfortunately, the prime moving leadership in the Indian institutions had not been for innovative research but it opted for basic investigations. Such cultures got imbibed into the group leaders and percolated down the line into the investigating ground level scientists. Consequently, the attempted move of the DBT to imbibe corporate cultures in institutions with directed move of conducting product-oriented research, enthused only a

few scientists. DBT's belief that basic understanding and product development could move together was largely not borne out in the existing scenario. This is one of the reasons for poor performance of the transferred technologies. The motivation and the work environment of the basic investigators are needed to be reoriented towards corporate culture if the existing R & D infrastructure is expected to deliver innovative products processes and technologies in future.

Technology driven research is comparatively easier to conceive but difficult to conclude and commercialize as the work plan proceeds through conceptualization, basic work, applied research, pilot demonstration and commercialization. The road from concept to commercialization is tedious and difficult. Market driven research on the other hand is based on the need of the market which may be perceived from existing products seen in the market place. If these are already protected, and if intentions are to use them as the starting point for further research, it may become an expensive proposition as the procurement cost of the existing protected technologies may be high. On the other hand, if market driven research is thriving on essentially copying known ideas, products and processes the path of R&D may perhaps be much simpler and easier to prepare. But introduction of such products in the market may often be difficult as better and competitive products would already be available in the market place. From the limited experience of the author, it was evident that the technologies which could not be sustained in the market were primarily based on copying of already known ideas, products and processes with much lesser novelty traits.

With the globalization of Indian economy and with India accepting to become a part of the World Trade Organization, the country has already accepted the product patenting in all branches of technology which includes biotechnology sector too. The control on prices of drugs and pharmaceuticals has also been substantially lifted in the Drug Policy of 1995 (ref. 8). There already exists a pool of skilled manpower. An impressive scientific R & D infrastructure has been built by the government to promote research in biotechnology. Under these circumstances there is noticeable shift in the attitude of some partners of the industry to go in for innovative R & D. It is anticipated that this trend will be stronger in future.

The technology managers (specially in the DBT, PID division) were faced with enormous difficulties in convincing the industry that the technology being offered could be utilized by the latter. This required a reasonable grasp of the technologies being offered for sale. Besides, the market potential of the technology was also to be assessed in advance to provide wider discrimination of the market information collected with hard work. Gists of some such information were published from time-to-time[4,5,9]. The institutes claiming to have developed a technology, often felt that the last word had been said by them and that there was little scope for further improvement. As in every case of technology transfer, there had been problems during executing transfers, such as variation in results from the claims in the hands of the industry and difficulties in setting up production processes based on lab protocols provided by the institutes. Both the industry and institute often felt impatient in appreciating the problems of each other and the technology managers had played the interphase well to keep the relationship from breaking. However, in better times when things improved, benefitting both the institutes and the industry, there was inadequate appreciation of the efforts of the technology managers by both these organizations. The efforts of the managers were taken for granted as part of their obligations. When technologies were successfully transferred and the investigators were rewarded, the roles of the technology managers were not remembered. During bad phases, when the technologies did not work the first to be blamed were the technology managers.

The intention of commercializing the institutionally developed technologies, using public funds was to bring in competitive advantage to the society through the continuous interaction between the institutes and the industry. The three concerned cultures, namely, the government, the institutes and the industry that normally do not communicate effectively with each other came closer through such an endeavour, which was felt by the partners in the successfully concluded projects, where the floor limit was the market acceptance of the innovation. Let us learn to recognise the bottom line !

Concluding Remarks

It is thus observed that the initial phase of transfer of locally developed technologies to the industry in the biotech sector was not so successful. However, long, patient and persuasive efforts have brought in a host of experiences which would be useful in future in tackling such an endeavour. The lessons thus learnt are summarized below:

(i) Institutions engaged in developing the biotech products and processes were generally inadequately resourced for the job. They lacked in market information and market requirements. It is expected that this situation shall improve in due course if there is continuous interaction between the scientists of the institutes with the production personnel and the marketing people in the industry. It would be wiser if institutions involved in product development and technology packaging reoriented themselves to work together with the industry for a joint development; it would enable both the partners to appreciate the problems of each other and therefore to find quicker solutions to complete the common project.

(ii) Claims of the institutions are required to be validated independently before technology transfer is effected. Funding organizations like DBT should provide the logistics for the purpose, as the institutes are ill- equipped to activate such studies.

(iii) Indian system has just started to provide incentives to the ground workers and investigators who are responsible for the technology development. The provisions did not exist in many institutes earlier. There is an emerging trend currently to share the benefits of technology transfer with the ground workers and this will enable to encourage the investigation and to enforce commitments from them too.

(iv) Industry had by-and-large, inadequate scientific capabilities to absorb and improve upon what it received. R & D capability of the industry is yet generally low and needs upgradation. Industry expects turn-key projects and is not quite interested to carry out the subsequent in-house developmental work. With the upgradation of the R & D infrastructure this situation shall change.

(v) Products/processes, wherever developed should be patented because otherwise the interest of the industry to procure and exploit the invention gets substantially reduced. In other words, product developmental work should be patentable and therefore be innovative; the culture of copying research is fast becoming redundant without a taker.

(vi) Industry always wanted to procure technologies on exclusive basis. There is a need to evolve policies to meet these goals in the public funded R & D institutes.

(vii) The role of the technology managers in catalyzing the development and transfer of technologies will be appreciated both by the institutions as well as by the industry if the society recognises and rewards the contributions of the managers.

In future, many technologies will be developed in Indian R & D institutions and many would be transferred to the industry. The probability of success in commercializing such technologies may brighten by learning from the above experience and by taking corrective steps in all the sectors of technology development, transfer, and deployment.

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