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REVIEW PAPER

Health Care Biotech Industry

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ABSTRACT

Modern biotechnology became possible because of the ability to clone genes and produce gene products across barriers of species and sex. Potential entrepreneurs are getting interested in venturing into health care biotech industry, stimulated by the success story in information technology. Products of protein therapeutics, such as insulin, growth hormones, interferons, blood proteins, streptokinase and vaccines have received special attention. Pharmaceutical companies got into the field of diagnostics, a major thrust area being products of antigen/antibody and nucleic acid-based diagnostic kits. The ability to clone and sequence genes from a variety of organisms has culminated in the subject of genomics. High throughput screening of thousands of organic molecules against a battery of drug targets using robotic machinery is the current approach to come up with lead molecules. New drug delivery systems for slow, sustained and direct delivery to target tissues are under way.

There is hope that hereditary and metabolic disorders may have a cure through replacements of defective genes by normal cloned genes and by blocking the expression of unwanted genes, respectively. This mega approach would call for the availability of DNA chips, a product of collaboration between molecular biologists and electronic engineers. The tendency now-a-days is for a marriage between biotech and pharmaceutical industries. Animal cloning, spearheaded by the birth of *Dolly*, has revolutionised cell biology and is of promise to generate animal bio-vectors to produce desired protein pharmaceuticals in milk. Stem cell research has assumed a lot of importance. In our country, reasonable competence has been built-up in the field of biotechnology. Around two dozen institutes carry out front-line research in medical biotechnology. Successful commercialisation of a few diagnostic kits and recombinant vaccines has provided an impetus and enthusiasm to exploit biotechnology in a big way. Industry needs to leap-frog, with adequate investments.

Keywords: Biotech, information technology, bioinformatics, molecular medicine, gene therapy, pharmacogenomics, genetic engineering, protein therapeutics, genomics, throughput screening

1. INTRODUCTION

In recent times, one tends to meet a stream of potential entrepreneurs, who are examining possibilities of venturing into health care biotechnology industry. These interested parties fall into three categories. Interestingly, the first category represents those who have made it in information technology and are looking at biotech industry for future investment. The second category is a relatively few successful industrial houses willing to do something in biotechnology. The third one is an odd group of non-resident Indians, who want to invest in India. These are in addition to about a dozen industrial groups in the country, who are either making or assembling a few biotech-based health care products in the country.

The conversations reveal a general lack of appreciation of the nature and scope of the industry in the health sector. At the same time, one can discern the feeling that it is not something that

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India should miss and the success story in information technology forms the backdrop. There is a general tendency to lump information technology and biotechnology together. This is because of a similar projection globally as well as in India. The Central and the state Govts have always added biotechnology as an appendage to information technology. In view of its relevance to health care, agriculture and food production, environment and industry, biotechnology appeals both to the common man and the political system. Based on this, biotechnology programmes have been initiated at the graduation and the post-graduation levels in a large number of universities and there is a substantial demand for these courses. However, the scope of biotechnology industry in the country and the future of the students specialising in this area (other than going to greener pastures in the West) are not clear at the moment.

Looking at the scenario in North America, health care biotech industry started in late 1970s with a handful of companies. At present, there are 1280 companies with a market capitalisation of exceeding $200 bn. The last year sale amounted to $13.4 bn and the revenue touched $18.6 bn. The R&D expenditure was $9.9 bn and the industry employed 153,000 people. In 1998, the US had filed 9000 patents. Food and Drugs Administration (FDA) has, so far, approved 90 drug products and vaccines, besides scores of medical diagnostic kits and use of deoxyribonucleic acid (DNA) fingerprinting in forensic science. About 350 products are in clinical trials. It is projected that the best years are yet to come, particularly, in the pharmaceutical trade.

2. CHANGING FACET OF BIOTECH INDUSTRY

It is obvious that biotechnology is a promising industry. It is a very rapidly evolving field and changes its colour and complexion constantly. It is not a field where Indian entrepreneurs can invest and go into a slumber, expecting automatic returns. This is coupled with the fact that while the complexion changes, the returns are slow to come. Thus, this knowledge-based industry would need smart entrepreneurs on toes and with patience (the two may not go together!). Unlike information technology (in the Indian context), biotechnology is grounded in experimental science and the products cannot be virtual, except perhaps in the new evolving areas of bioinformatics. The real products, be it a diagnostic, a drug, a vaccine or a gene, would need intense research validation, time and money to reach the market.

3. PROTEIN THERAPEUTICS

Modern biotechnology became possible because of the ability to clone genes and produce gene products across barriers of species and sex. It all started with the slogan, 'clone a gene and make a million'. This essentially meant products of protein therapeutics, such as insulin, growth hormones, interferons, blood proteins, streptokinase (to dissolve blood clot), modern vaccines, etc. This was the goal of the companies, such as Genentech, Chiron, Amgen, etc. While many of these products are in the market, they are expensive. The efforts cannot be described as runaway successes. There were technical problems. While cloning and expressing useful genes in bacteria, yeasts, etc. was relatively easy (the molecular biology part), the large-scale production, purification and packaging under good manufacturing practice (GMP) conditions (downstream processing) was difficult and expensive. Besides, litigation between major companies for proprietary hold on the genes and the processes involved led to a significant slowing down of the process of commercialisation.

4. DIAGNOSTICS

In the meanwhile, pharmaceutical companies and small entrepreneurs got into the field of diagnostics. One of the success stories of biotechnology is the production of antigen/antibody and nucleic acid-based diagnostic kits. These range from the detection of pregnancy to diagnosis of a variety of infectious diseases, cancers and genetic disorders. It is relatively easy to produce diagnostic kits compared to what is involved in commercially producing a therapeutic.

5. HIGH THROUGHPUT SCREENING

Major pharmaceutical companies need a constant source of lead molecules. Biotechnology has become

the ideal ground for prospecting. Drug discovery is fast changing over from hit-and-miss approach to rational designs. The ability to clone and sequence genes from a wide variety of organisms, including the human and pathological tissues, which has culminated in the subject of genomics, has provided the pharmaceutical industry with a variety of new drug targets. An understanding of the fundamental processes of gene expression and signal transduction pathways leading to gene expression has given a gamut of drug targets. At another level, conventional organic chemistry has given place to combinatorial chemistry, where thousands of small molecules can be generated in a record short time by brute force approach and automation. Thus, high throughput screening of thousands of organic molecules, including extracts from traditional medicinal plants, against a battery of drug targets using robotic machinery is the current approach to come up with lead molecules. Novel drug delivery systems that can lead to slow and sustained release and direct delivery to the target tissues are underway to enhance efficacy and prevent side effects.

6. MOLECULAR MEDICINE

While the industry and the community are used to a pill or injection of small organic molecules as a drug, the fast completion of the human genome project has ushered in the field of molecular medicine. Serious research is underway to use genes, as such, to treat genetic disorders. Thus, there is hope for the first time in the history of mankind that hereditary disorders may have a cure through replacing defective genes by normal cloned genes. Simultaneously, research is underway to block the expression of unwanted genes in a variety of cancers and cardiovascular diseases through anti-sense and ribozyme therapies. DNA vaccines are making a wave as the third vaccine revolution. The concept is to directly inject the gene (naked DNA) for a foreign antigen (eg, gene for an appropriate protein from a disease-producing organism) into the muscle or skin and let the body make the concerned foreign protein, which, in turn, can elicit antibodies and cell-mediated immunity to protect the individual against a real infection.

7. GENOMICS/BIOINFORMATICS

The changing facet of biomedical research also reflects the changing interests of the industry. Efforts to clone, express and produce single useful therapeutic proteins are giving way to studying the expression of thousands of genes between a diseased and normal tissue or between a virulent pathogenic organism and its avirulent counterpart. This subject of genomics would eventually result in a large number of candidate genes that can become diagnostic and drug targets or vaccine candidates or be used in gene therapy. This mega approach would call for the availability of DNA chips. These are wafers of say 2 cm × 2 cm, carrying DNA probes (parts of gene sequences) to fish out the difference in the expression of thousands of genes between any two living states. DNA chip is the product of collaboration between molecular biologists and electronic engineers. The input to put appropriate gene probes on the DNA chip has to come from data mining of the mind-boggling sequence information that is pouring from human and other genome sequencing efforts all over the world. Bioinformatics has to play a key role in sifting the grain from chaff. This is because the DNA sequence coding for genes constitutes less than 10 per cent of the total human DNA. Thus useful information is embedded in a sea of useless information or nonsense DNA for which one still does not have the code to decipher the function. Then, even among the 10 per cent of the genes coding for 35,000 to 40,000 proteins, the function of only around 15-20 per cent may be known. The rest come under the category of open reading frames or proteins of unknown function. Therefore, comparison of such sequences from a variety of organisms available in the databanks can throw light to some extent on the possible functions, if the functions are known in any of the organisms compared with. Ultimately, painstaking biochemical studies would be needed to decipher the function of each protein.

A particularly appealing area of genomics to drug companies is pharmacogenomics. Therapeutic drugs are metabolised in the body of an individual and this has a genetic basis. Some are poor metabolisers where the concerned genes do not

function properly. Secondly, one drug can induce or suppress a drug-metabolising gene for a second drug. This becomes important in multiple drug therapy. It is visualised that an understanding of pharmacogenomics would lead to designing a drug regimen for an individual and not just for a disease.

8. TISSUE ENGINEERING

The excitement in genomics research is equalled by the development in techniques for animal cloning. The birth of *Dolly* from the nuclei of an udder cell has revolutionalised cell biology in that a terminally differentiated DNA can be reprogrammed to de-differentiate and give rise to an embryo in an appropriate egg cell cytoplasmic environment. It is now considered that this approach is good to generate animal bio-reactors to produce desired protein pharmaceuticals in milk, starting with a genetically engineered embryo. While this has led to serious ethical debates on human cloning, specific organ cloning is considered as appropriate and eventually feasible. The stem cells in the bone marrow and blood circulation are known to be pluripotent and can differentiate into different lineages, giving rise to different end organs. Therefore, serious efforts are on to understand stem cell biology and the visions of cloning one's own organ, such as kidney or liver, are tantalising drawing heavy research investments in biotech companies.

9. STABILITY OF BIOTECH COMPANIES

It is obvious that the agenda for a biotech company is always in a flux and has to undergo changes, although it is possible to concentrate on a niche area, such as diagnostics. Even here, there is a rapid evolution towards simplicity, sensitivity and cost advantage. Diagnostics can get out of date soon and, therefore, companies do look for expanding their portfolios. This needs investment in top priority research to keep abreast with the changing facets described earlier and come up with newer leads.

The slogan 'clone a gene and make a million', did attract investments in the early 1990s. But as the investors realised the slow pace of commercialisation possibilities, their interests started to wane. The emergence of internet has sealed the fate of many biotech ventures. But, as venture capital industry drifted to dot coms, pharmaceutical companies have stepped in. Therefore, only a few of the original biotech companies, such as Amgen, Biogen and Genzyme have survived as self-sustaining stand-alone companies. The original trail blazer, Genentech, has become a division of Roche. Despite initial criticisms of the loss of uniqueness of a biotech venture and admittedly loss of some autonomy, this marriage between biotech and pharmaceutical companies has proved to be mutually beneficial. While the biotech company can concentrate on innovative research and generation of lead molecules, the pharmaceutical company can take care of clinical trials, financing and marketing. Thus, in the last couple of years, the pharmaceutical companies have moved in to acquire biotech companies and licenses, besides getting into mega-mergers among themselves. Many of the biotech companies or divisions concentrate on basic research, licensing promising leads to major partners. Many other biotech companies are tool box companies and undertake service and contract research for major pharmaceutical companies or academic institutions. A large number of small biotech companies in the US provide backup for research by manufacturing a variety of sophisticated molecular biologicals and immunological reagents, besides offering services, such as expression cloning, oligonucleotide DNA synthesis and sequencing, peptide synthesis and protein sequencing. There is a big demand for these services in the US. A similar demand may also be placed on bioinformatics companies. Data mining can be a successful operation, if it is tied up with a pharmaceutical company. On the other hand, it is also likely that big pharmaceutical companies will have their own bioinformatics divisions.

Public perception is an important element in the eventual success of biotech companies. Ethical debates on gene therapy, human embryo research and genetically modified food do slow down investments in such areas. However, areas such as diagnostics, therapeutics, rational drug design and bioinformatics pose very few ethical questions and

are making rapid progress. Even in contentious areas, there is tremendous public and industry pressure to go ahead, and therefore, governments come round to evolving mechanisms to provide safeguards and make risk-benefit assessments to grant approvals for a particular line of research and its exploitation. In general, one finds that there is less activist resistance to apply genetic engineering methods in health care than in agriculture.

10. INDIAN SCENARIO

Several research groups in about two dozen institutes carry out front-line research in medical biotechnology, although there is always a gap between international frontiers and national accomplishments. The biotech industry scenario is not heart-warming, when compared to the scenario in North America.

Research in modern biotechnology received a fillip not only from mid-1980s and there is always a gap to bridge. Initial efforts on application were centred around the generation of diagnostics. The efforts of different laboratories resulted in the generation of about a dozen diagnostics for different diseases. But none of them really made to the market, even though MoUs were signed with companies. The reasons are many. Scientists were not aware of the problems in the field. Diagnostics that work well in the laboratory may not necessarily perform in the field. The companies had very little research expertise to solve the field problems and depended almost completely on the academic institutions even to solve minor problems. Moreover, companies find it more attractive economically to sell imported kits than indigenous kits. Besides, there are also non-scientific reasons for an indigenous kit failing to compete with imported diagnostic kits. For example, an indigenous HIV diagnostic kit in the market, approved by the Drug Controller of India and WHO, is facing an acute survival problem. The policies of the agencies concerned preclude encouragement of an indigenous product, although it meets all the scientific standards. Indigenisation is more a slogan than a practice in this area. Diagnostics has a large market and should be available to the people of this country at an affordable price. An industry that has this concern and has the money power to develop a first-class product and the muscle power to push through the product can still make a dent. Expertise is available in the country.

Things are looking up in the new millennium. In addition to the HIV diagnostic kit already mentioned, three other HIV kits including these for a simple agglutination test and western blot analysis have been released. Diagnostic kits for hepatitis C and cysticercosis are in the market. The manufacture of recombinant hepatitis B vaccine using indigenous technology has made a substantial dent in the sense that the market price has fallen by almost 10-fold. A DNA vaccine against rabies has shown excellent promise at the trial stage. Many players are now entering the modern vaccine manufacturing sector. There is also commercial interest in the indigenous production of recombinant insulin, interferons, streptokinase, epidermal growth factor, etc. This effort has to grow and many more protein therapeutics, such as serum albumin, factors VIII and IX, erythropoietin, GM-CSF, etc. offer tremendous scope. The patents for many of these products are old or on expiry list. The Govt policy, especially that of the Health Ministry should be conducive for promoting indigenous technology.

Other areas, such as rational drug design, cell and gene therapy, molecular medicine, DNA vaccine, etc. are in the realm of intense research and clinical trials in the US. Research has been initiated in these areas in the country. Industry needs to leap-frog with adequate investments into these areas. DNA vaccines are particularly relevant for this country. One approach could be to undertake contract research from big international pharmaceutical companies to deliver the intermediates rather than the final products. Contract research for data mining is an option which information technology companies may like to diversify into. However, the bottom line is that a real biotech industry has to have its moorings in hard-core basic research, in experimental science. This is more demanding than research on the hardware part of the industry, which itself is a major lacuna in the country. This needs investment and patience to reap the fruits. Health care research is meaningful only if the poor can benefit from the fruits of such an effort.

11. CONCLUSION

Modern biotechnology has received support during the past 15 years. Thanks to major support from the Department of Biotechnology and other agencies, such as CSIR, DST, ICMR and ICAR, a reasonable level of infrastructure and competence in the area has been built. The response of the industry was lukewarm, but it is now picking up consequent on the initiative of the Central and the state Govts and slow down in the information technology sector. Commercial successes with the recombinant vaccines and successful production of indigenous molecular diagnostic kits should spur the country for other commercial ventures in new drug development, manufacture of protein pharmaceuticals, stem cell research and bioinformatics. India has a great opportunity to address health care issues of the poor through biotechnology. At the same time, the entry of private sector and the organisation of biotech parks by the different state Govts should lead to an extensive network of small and medium entrepreneurs to embark on a successful health care industry base that can become globally competitive.

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