Biotechnology: Its global impact and relevance to India

Harish Padh

Biotechnology industry is maturing as an economic sector in the West. Approved products in the market, over 500 therapeutic products in the pipeline and renewed public confidence make it one of the most promising areas of economic growth in the near future. With liberalized economy, India offers a huge market for these products as well as cheap manufacturing base for export. However, for a variety of reasons, India has failed in developing these technologies for commercialization and the demand at the moment is met by imports. The proper technology licensing and transfer is suggested for immediate growth in this sector. Requirement of good infrastructure including a technopark is warranted in catalysing this growth.

BIOTECHNOLOGY encompasses aspects of biology, medicine, chemistry, and engineering. It has been defined by the US Government as '... any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses', in other words it is Applied Biology. Although the word biotechnology is new (around 1980), the science is not. Some examples of biotechnology used in ancient times, without knowledge of the underlying microbial processes, include beer fermentation by Babylonians (6000 BC), cheese making in Iraq (6000 BC), bread making by Egyptians (4000 BC). India can also take pride in contributing to the development of ancient biotechnology in the form of septic tanks in Mohenjodaro and Harappa regions (3000 BC). Four new technologies are responsible for bringing about the recent revolution in this field: viz. (i) Genetic engineering enabling us to identify and transfer genes from one organism to another, (ii) Cell fusion technology and resultant monoclonal antibodies, (iii) Bioprocess technologies to produce large quantities of important biological drugs, and (iv) Structure-based molecular design expediting new drug development. Various combinations and derivatives of these technologies are now available. The new biotechnology is a rapidly expanding collection of tools and technologies that allow, among other things, unprecedented control over and manipulation of the genetic material of organisms. In a short time, its impact is already visible, while its long-term potential is still unrealized at the moment. The book *Jurassic Park* by Michael Crichton and the movie by Steven Spielberg helped educate the general populace about the potential of genetic engineering.

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What can be done with these technologies?

Human body is a chemical factory running thousands of chemical reactions at a time. These reactions are catalysed by proteins which are made from respective genes. Therefore, a state of our body, healthy or otherwise, is determined by coordinated proper functioning of these proteins and genes. Recent advances have made it possible to isolate these genes and transfer them to another individual. In addition, biotechnology provides us ability to make rare but important proteins in abundant quantity. These advances have made it possible to use these genes and their protein products for therapeutic and diagnostic purposes. Unlike chemicals, these biologicals can be used for more effective treatment of various ailments, specially those for which there are no cures available at the moment. These possibilities also offer tremendous opportunities to improve agriculture products, animal stock, and to correct genetic disorders.

New biotechnology and its impact

The potential of biotechnology is responsible for bringing about the current revolution in biology. We now have in our grasp the means to produce large quantities of rare, medically valuable molecules, to modify plants and animals to carry specific hereditary traits, and novel means to detect disease, produce useful chemicals, and clean up and restore the environment. Thus, biotechnology has profound impact in the fields of health, food/agriculture and environmental protection. It has the potential to provide a wide array of benefits to humanity, including treatment for previously incurable diseases, healthier dairy and agricultural products, more resilient and productive crop plants and increased production of renewable sources of energy.

The US industrial sector now includes more than 1200 biotechnology start-up firms. More than 200 established companies, including many major chemical and pharmaceutical firms, have diversified into biotechnology. The distinction between biotechnological and pharmaceutical sector is fading because of the heavy involvement of pharmaceutical firms in biotechnology business. In little over a decade, this nascent industry has grown to be a multibillion dollar sector. By the end of the century this sector will match or surpass the computer industry in size, importance and growth.

Health care

Health care to-date has utilized biotechnology the most. The primary reasons are lack of good alternatives for treating the sick, dramatic results, big profits and good publicity. We still have many ailments for which we have no treatment or cure, for example, numerous genetic diseases, Alzheimer's disease, many types of cancer, hypertension, and AIDS. Biotechnology has allowed use of previously unavailable biologicals as medicines and made it possible to produce therapeutic biologicals in large quantities. Biologicals are our own molecules and are unlike chemical drugs. Biotechnology-derived proteins and polypeptides form the new class of potential drugs. For example insulin, used in the treatment of diabetes, was once primarily extracted from slaughtered animals. Since 1982, human insulin (Humulin®) has been produced by microorganisms in huge fermentation tanks. The global sales of Humulin® and other biotechnology drugs like Epogen® (Epoetin alfa from Amgen) and Recombivax HB® (Hepatitis B vaccine from Merck) have reached around US$ 1 billion each. These products are convenient to make and more compatible with biological systems. In the recent past, the discovery of conventional drugs (heterocyclic chemical drugs including antibiotics) has slowed down. The number of biotechnology-derived new protein drug candidates has surpassed new chemical drugs since 1987 (see Figure 1).

At present there are about 35 biotechnology-derived therapeutics and vaccines approved by the US FDA for medical use and over 500 additional drugs and vaccines by 150 companies are in various phases of clinical trials. Biotechnology has also spurred growth in diagnostics and over 600 biotechnology-based diagnostics are now available in clinical practice.

Gene therapy offers the potential to correct diseases at the genetic level. After creating scores of genetically modified plants and animals, human gene therapy looms on the horizon. The year 1995 marked significant developments in gene therapy. In USA there are about 130 approved gene therapy protocols. Half of these protocols are active with a total of about 600 patients under trials.

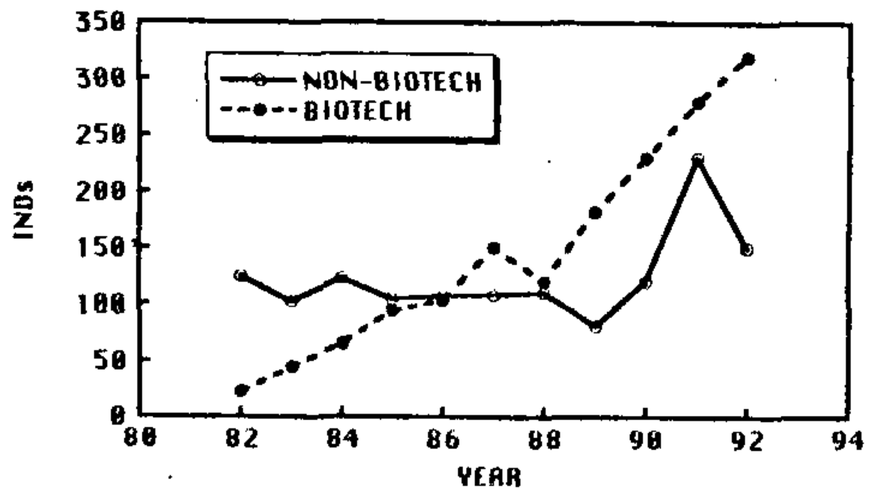

Figure 1. Investigational new drugs: Biotechnology vs non-biotechnology.

Agriculture

Although this area has benefited most from the ancient biotechnology, food/agriculture has been slow to utilize the modern advances in biotechnology. The reasons for this are numerous: a plentiful supply of food in the Western countries, the availability of other alternatives, apprehension over new technology, the complexity of plant and animal genomes, etc. The potential applications of biotechnology in foods and agriculture include better management of agro-ecosystems through decreased use of chemicals, increased use of pest and herbicide-resistant plants, new methods of maintaining soil productivity, better water management and new healthier foods with increased societal value. Functional foods (neutraceuticals) represent an active area of research to increase the nutritional value of foods, prevent diseases, and reduce healthcare costs. At present there are 14 or so sources of phytochemicals known to fight or retard malignancies. Biotechnology in the food/agriculture area is breaking new ground. Current public debate about BST (bovine somatotropin, a hormone administered to cows to increase milk production) typifies an example of a biotechnology product testing public acceptance. Similarly, the FlavrSarv™ tomato (produced by transgenic plants engineered by antisense technology to preserve flavour, texture and quality) is an example of a new breed of value-added foods. Food biotechnology offers valuable and perhaps the only viable alternative to food problems of developing countries. Food biotechnology also offers workable solutions to nutritionally influenced diseases like heart diseases, hypertension, arthritis, cancer, and diabetes.

Environment

Biotechnology products, like other 'high-tech' products, are inherently resource conserving, especially in comparison with older industrial methods of production.

Biotechnology offers additional environmental advantages when applied to current and emerging manufacturing processes. When applied to environmental issues, biotechnology is enhancing the pre-existing ability of nature to degrade compounds – disposing of wastes in a very *natural* way.

In March 1989, the oil supertanker Exxon Valdez lost 33 thousand tons of oil off the coast of Alaska at Prince Williams' Sound. For the first time, bioremediation technologies were employed in an actual oil spill to clean up crude oil contamination at the site of spillage. Several of the field tests were highly successful, with the added advantage that subsurface contamination (contamination below the surface of the soil or beach) was also remediated up to a depth of several feet.

Economic impact of biotechnology

Biotechnology companies develop technologies and products that expand the boundaries of medicine, agriculture, industrial processes and environmental science. They also build sustainable companies that bring new ways of competing and succeeding into traditional industries. The following are the highlights of biotechnology business in the USA. The European market is roughly of the same size as that of USA and no information is available for the market size in other continents.

General business highlights

- In Europe and USA, the sale for biotechnology-derived therapeutics is estimated to be 15 billion US dollars (Rs 52,500 crore). The sale of diagnostics is estimated to be another 15 billion US dollars. It is a multibillion dollar sector. Market size in the developing countries is not known. In USA, biotechnology has captured 10–15% of the total healthcare market.
- The sales, revenues, and equity in this sector are increasing with an annual rate of about 10–20% (Table 1). With many products in the pipeline and increasing public education and acceptance of biotechnology, the momentum will continue.
- Table 2 shows ten years history of biotechnology.
- It is a R&D-intensive sector (Table 1). At the moment, much of the revenues are poured back into R&D, compared to about 6% invested in R&D by US pharmaceutical sector and about 1% of sales invested in R&D by the Indian pharma sector.
- Total public equity raised is about $1 billion a year (Figure 2). Some decline since 1992 has been reversed since 1995.
- Financing (raising capital) varies from year to year averaging about $2 billion per year contributed almost equally by public offering, venture capital and private placement. Total money raised in 1995 through venture, private placements, initial public offerings and followups and strategic alliance was about 3.5 billion US Dollars.
- Agriculture biotechnology is expanding with a total market value of $600 million with Calgene, which introduced FlavServ tomato, leading the market with $200 million.
- Many genetically modified plants and plant products have obtained 'deregulated' status in USA and Europe, meaning no special approval necessary from FDA or USDA.
- The Biotech Equity Index (by Coopers and Lybrand, CLBI) has done better or as good as Standard & Poor 500 (broad-based equity index) over the period of time.
- Figure 1 shows that most of the new drugs coming to the market are biologicals manufactured by biotechnology.
- Biotechnology is entrepreneurial in nature. Over 90% of the biotech companies are small or medium size.

Table 1. Highlights of biotechnology industries in USA (billion US$)

	1995	1994	Per cent change
Sales	$9.3	$7.9	18%
Revenues	$12.7	$11.3	12%
R&D expenditure	$7.7	$7.1	8%
Market capitalization	$52.0	$41.0	27%
Number of companies	1,308	1,311	0%
Employees	108,000	103,000	5%

Table 2. Ten-year history of the biotechnology therapeutics in USA

	1985	1990	1995
Sales ($ in billion)	$1.1	$2.9	$9.3
Revenues ($ in billion)	$2.2	$4.7	$12.7
R&D expenditure ($ in billion)	$1.7	$2.6	$7.7
Number of companies	850	1,107	1,308
Employees	40,000	66,000	108,000

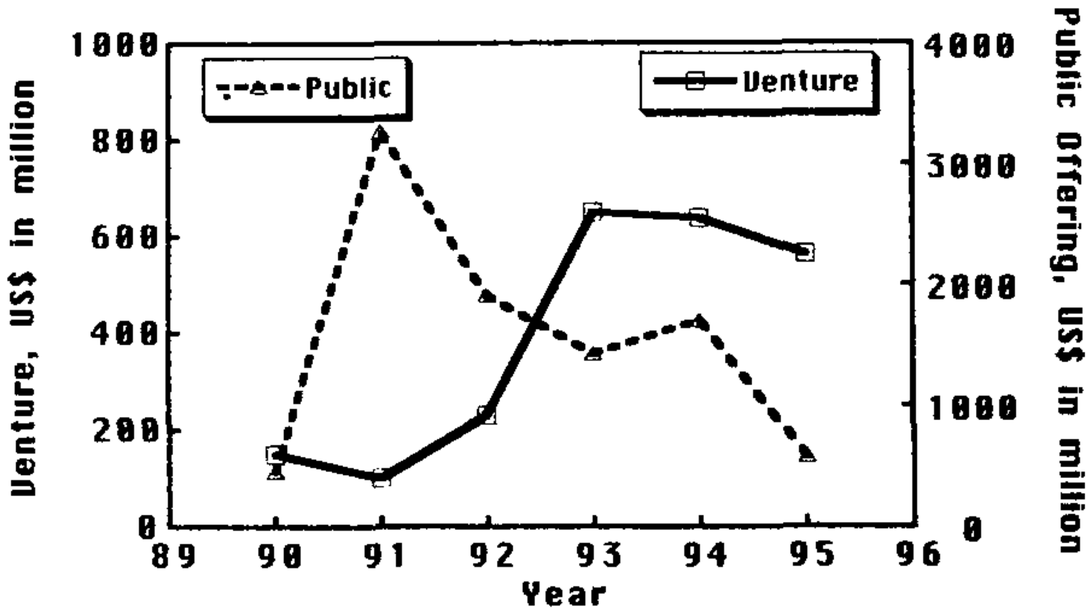

Figure 2. Biotechnology financing.

The larger companies are now entering the area by merger and acquisition.

- In later half of 1995, the stock market has come around for this sector and biotechnology is viewed as a promising area.
- Recently, European countries in general and Germany in particular have become receptive to biotechnology.
- Global market for industrial enzymes was about 1825 million US $ in 1995 (Table 3) and increases about 20% a year.
- Top ten biotechnology companies are: Amgen, Genentech, Chiron, ALZA, Biogen, Genzyme, Genetics Institute, Centocor, IDEXX, Immunex.

Healthcare sector – Business highlights

- The Healthcare sector has so far benefited the most out of biotechnology. The Agriculture and Environment sectors are picking up. Among healthcare companies, therapeutic is followed by diagnostic.
- There are about 35 biotechnologically-derived therapeutics in the market in USA and Europe. About 500 more products by 158 companies are in human clinical trials. Many of these products will be in the market in coming years (Table 4).
- Human Genome Project, a mammoth undertaking to get a complete blueprint of human genetic material, is viewed with tremendous potential for future products. Many established pharma companies paid handsome price for biotech firms with expertise, technologies or products from this project.
- There are over 600 new biotechnology-based diagnostics approved for use. Most of them are based on monoclonal antibodies (Table 5).
- Table 6 lists major biological therapeutics in use. Their sales are multibillion dollars each.
- Table 7 lists some of the recently approved biological therapeutics.

Table 3. Global market for industrial enzymes

User industry	1995, US$ in millions
Detergent	710
Starch	220
Textile	245
Others	650
Total	1825

Table 4. Biotechnology pipeline

Status in clinical trial	Phase I	Phase II	Phase III	Approved
No. of therapeutic products	144	205	127	33

Agriculture and environment sectors – Business highlights

- Some of the applications of biotechnology in agriculture are in biopesticides, animal growth hormones, genetically modified plants and animals, animal and food diagnostics, animal vaccines, etc.
- *Pharming* is a new concept where therapeutic drugs are produced in the farm animals. For example, therapeutic proteins secreted in goat milk. There are about half a dozen companies specializing in this technology to make products like lactoferrin, tPA, hemoglobin, melanin and interleukines in cows, goats and pigs.
- Biopesticides are coming to the market and their sales are increasing.
- Bioremediation, which is environmentally friendly approach to clean the environment, is projected to reach global sales worth of 1 billion US $ by the year 2000.

Future prospects for biotechnology industry

The biotech industry is just coming out of its infancy. Its potential is being tested, realized and used. The public awareness and acceptance will accelerate the process. This sector is expected to expand at least 3-fold by the end of the century and will match or surpass the computer industry in size, importance and growth (Table 8). It holds a good promise in a number of areas, specially those for which presently we have no treatment. There is tremendous potential for developing countries like India to apply biotechnology for agriculture and environmental resources.

Table 5. Approved biotech diagnostics

Type	Infectious disease	Tumour marker	Analyte and drug	Blood screening	Total
Monoclonal antibody	127	2	433	9	571
DNA probe	42	0	11	0	55
Recombinant DNA	11	1	1	0	13
Total	180	3	445	9	637

Table 6. Biotechnology-derived drug products

Products	1996 sales (billion US$)	Selected manufacturers
Human insulin	2.3	Eli Lily, Novo Nordisk, Hoechst, Yamanouchi
Growth factors	2.0	Eli Lily, Novo Nordisk, Genentech, Pharmacia
Blood factors	5.0	Amgen, J&J, Sankyo, Chugai, Sandoz, Immunex
Interferons/interleukines	3.0	Schering-plough, Roche, Sumitomo, Wellcome, Daiichi
Monoclonal antibodies	0.4	J&J, Cytogen
Vaccines	1.0	SmithKline, Merck, Shionogi
Others	1.0	Genentech, Baxter, Bayer, Genzyme

Table 7. Examples of new biotechnology derived drugs recently approved

Company	Drug	Indication
ALZA	DynaCirc CR	Antihypertensive drug
DNX	Biodigm	LDL reduction
Quadra Logic	Photofrin	Photodynamic therapy
Amgen	Neupogen	Severe neutropenia (new indication)
Centocor	ReoPro	Anti-platelet for angioplasty
Immunex	Thioplex	Cancer
NeXstar	DaunoXome	AIDS-related Kaposi's sarcoma
U.S. Bioscience	Ethyol	Prevent kidney damage by cisplatin

Table 8. Comparison of biotech and computer industries

US biotechnology industry	US computer industry
Young	Maturing
Technology intense, R&D critical	Technology intense, R&D critical
Heavily regulated	Unregulated
Capital intensive	Moderate capital requirements
Global market	Global market
Long product development timeline	Short product development timeline
Annual sales of $9.3 billion	Annual sales of $80 billion
Number of companies 1,308	Number of companies 2,134
Number of employees 108,000	Number of employees 350,000

Biotechnology in India

- India has a number of good academic institutions with expertise in basic sciences relevant to biotechnology. India also has a fair number of suppliers and stockists who market required reagents and supplies. Assuming that the academic–industry interaction will improve, India is poised to explore biotechnology for business.
- Their is a surge in testing facilities, technology transfer, R&D institutions, small equipment fabricators, repackers and sellers of imported materials, etc.
- Proliferating private medical care and its importance in creating demand for biotech products.
- Catching up with the Western way of healthcare.
- India has rapidly swelling population of upper and middle class which has created unmet demand for newer diagnostics and therapeutics.
- Proliferation of diagnostics – mostly imported.
- General failure of diagnostics (imported as well as locally developed).
- Pharmaceutical industry in India is very strong and vibrant with expertise for chemical drugs. It has little experience in biotech diagnostics and no experience in biotech therapeutics.
- India is competing well in bulk drug production market. This is largely due to the more efficient nature of the processes and manufacturing costs. The same can hold true for the biological drugs.
- India's economic liberalization and signing of GATT and DUNKEL Draft clears the way and need for significant R&D activities by pharmaceutical industry.
- Impending patent changes will make it necessary to either develop our own technology or obtain proper license from others.
- Globalization of economy and liberalization of our economy make this an appropriate time to seek outside licensing and technology transfer.
- R&D activity in pharmaceutical industry will surge but with no significant experience in biotech, the pharmaceutical industry will need help.
- Local problems (malaria, tuberculosis, etc.) have remained untouched by biotechnology either in India or overseas. These problems will need innovative approaches.
- Agriculture, seed technology and environment could benefit tremendously by use of biotechnology.
- Table 9 indicates various factors influencing growth in a particular segment of economy. For example, in USA the growth is driven by innovation while in Germany the growth is driven by capital investment and proper technology management. In places like Thailand (and India?) the factors like cheap labour or availability of raw materials, etc. can spur growth. In a place like India and China, sudden growth is evidenced simply because of the rapid opening of huge consumer market. These and other factors lead us to believe that India is poised to enter biotechnology market.

Table 9. Driving forces influencing industrial growth

Driving force	Precondition	Strategy	Example
Factor	Factor advantage	Low tech sectors	Thailand, India???
Investment	Mature user industry	Investment in getting foreign technology, joint government and private ventures	Germany
Innovation	Developed science base, mature industry base, venture capital	New companies led development	USA
Market base	Sudden opening of large consumer market	Careful import and promotion of proven technologies	India, China, Eastern Europe? Former Soviet countries

- Infusion of foreign technologies and collaboration has already taken place in other sectors of economy. It is now time for Biotech/Pharma sector to seek proven technologies from outside.
- Import of technology will be a necessity. Government should provide proper channel and infrastructure to the pharma industry. This will lead to value added better stable, tested and validated products in the market.
- Other governments, including Germany has government-supported agencies for technology identification and import.
- Pharma industry is located between Mumbai and Ahmedabad (90% of the drug production in India is in Gujarat and Maharashtra). There is no government institution or university in this region with expertise in this area to help pharma industry.
- State industrial development corporations (SIDCs) should get serious about this sector and promote this sector by providing infrastructure and expertise.

Indian pharma industry

Indian pharmaceutical industry, with an expertise in chemical drugs, has done excellent job in the recent past. Total pharmaceutical industry sales is estimated to be Rs 50 billion. India is competing well in bulk drug as well as formulation markets. This is largely due to the more efficient nature of the processes and reduced manufacturing costs. The same can hold true for the biological drugs once the industry enters into manufacturing of biologicals. Moreover, India's economic liberalization and signing of GATT and DUNKEL Draft clears the way and need for significant R&D activities by pharmaceutical industry. Therefore, for a variety of reasons, the Indian pharmaceutical industry will sooner or later enter in manufacturing of biotechnology-based diagnostics and therapeutics.

Western India (Gujarat, Maharashtra and Rajasthan) with more than 50% of the registered pharmaceutical units accounts for 90% of pharmaceutical production. The region also accounts for more than 70% of import and export of the pharmaceuticals.

Diagnostics

Worldwide there are about 600 new biotechnology-based diagnostics in the market with a value of about 20 billion US$. Many more are about to enter the market, the most prominent among these will be PCR-based diagnostics. In India the diagnostics sales are expected to be between Rs 1 billion and Rs 2 billion. India relies on imports for many of the immunodiagnostics kits. Many of the locally developed diagnostics have failed, while the imported diagnostics are either unsuitable or expensive.

Therapeutics

Expression of foreign genes in convenient prokaryotic cells and the large-scale production of gene products is now routine. These protein products could have applications as therapeutics, diagnostics, restriction enzymes or industrial enzymes. At present, there are about 35 biotechnology-derived therapeutics approved for human use in USA. The total market value of these products is about 50 billion US$. About 150 companies have 490 more products in various stages of clinical trials and development. With increasing acceptability of biotech products, there will be about 200 biotechnology-derived therapeutics available in the market by the turn of the century. In 1987, the number of new drugs produced by biotechnology has overtaken investigational new drug (IND) produced by conventional means (chemical and antibiotic drugs). This is an indication of the trend that in future new therapeutics will be made by cellular factories through recombinant technologies.

In India, there is no locally manufactured recombinant

therapeutic product available in the market. Few imported biological therapeutic products are marketed in India, e.g. human insulin and streptokinase.

Need for licensing and transfer of technologies

We have witnessed that indigenously developed diagnostics have shown less than satisfactory performance in the market. The imported diagnostics are not suitable because they are expensive, not directed against local pathogenic strains, and with little or no quality and stability controls. In addition, the Indian pharmaceutical industry has little or no experience in modern diagnostics or biological therapeutics. Their approach of process improvization that worked well for chemical drugs will not work in biotechnology-based diagnostics or therapeutics. In addition, the number of newer diagnostics in the international market every year is burgeoning. Therefore, the national interest is better served by a systematic approach in identifying and transferring and licensing of appropriate technologies.

In the international market, biotechnology drugs are very expensive. For example, Genentech's tPA is priced at about $2,000 per injection and streptokinase is marketed at about $200 per injection. A genetically engineered Factor VIII used in the treatment of hemophiliacs cost $25,000 a year. The next generation of these products will have to be less expensive and more effective. India can provide inexpensive manufacturing base for Indian as well as export market. Imported therapeutics traded in India are exorbitantly priced (Rs 300 per dose of human insulin compared to Rs 65 per dose of traditional insulin) and about Rs 4000 per dose of streptokinase. What will be our strategy when in five years there will be over 200 therapeutics and vaccines available? Shall we still rely on imports?

Need for technology development

There are a few diagnostics developed in the country but overall performance has been dismal. There seems to be a gap of culture, communication or something between the academic and corporate worlds as a result of which the indegenous technologies have not been developed. The products do not reach the market or fail in the market. For a long-term interest of the nation there is a need for local development of technologies, especially against tuberculosis and malaria.

Agriculture

India which can use biotechnology for agriculture and environment cleaning has not really begun to exploit biotechnology in these areas. We have not produced genetically altered plants or engineered microorganism for bioremediation. The only activity India has developed is in plant tissue culture and plant micropropagation. In this sector, entrepreneurs have by and large imported technologies from abroad (mostly northern European countries) with buy-back arrangement for exporting the plant products. Locally developed technologies have found very limited use in the market. Local demand for these products is also highly underdeveloped.

Summary

We have to stop relying on imports and think about local manufacturing of the products mentioned above. This can be best achieved by proper technology licensing and transfer. We should also focus on technology development for the diseases of the developing countries.

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