BioSpectrum the business of Bio & Health Sciences

On health super highway with biotech drugs

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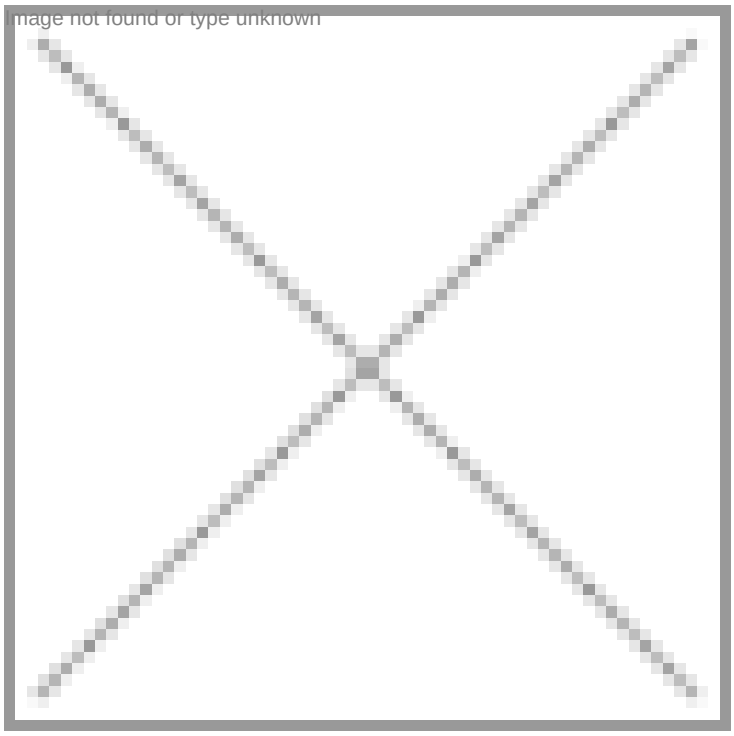


It's circa 2010. A baby is discharged from a hospital somewhere on the planet few days after birth. Along with baby care instructions, the hospital also hands over a digital video disk (DVD) or a CD-RoM. No, it is not some games to keep the baby entertained. The disk contains the entire genetic code of the baby. And it will help doctors to tailor their treatment regime for the baby for decades to come.

" Such a scene will become common place in 10 years," predicts Dr Craig Venter, the celebrated president of The Institute of Genomic Research (TIGR) and the co-author of the human genome.

The genetic code will provide clues to the increased risk factors of particular diseases the baby may be prone to in the future. It will also provide information about the effectiveness of drugs for various treatment the individual may require during the life time. Most of the drugs in use now work effectively only in 30 to 50 percent of the population. And in cancer treatments, thereapeutics work effectively only in 20 to 30 percent cases.However, doctors are forced to give them to all hopes on the assumption that these drugs.

So with the genetic information, pharma companies will be able to design drugs that would actually treat a disease and not kill the patient. " Initially the pharma industry has been vary of this because they were afraid it is going to decrease their markets instead of giving the drugs to every body. But in the meantime the leading companies have realized that they have no ethical choice and that in fact this will lead to increased diversity of drugs," said Dr Venter.

Welcome to the future world of personalized medicine. This is a segment which is heavily dependent on biotechnology. Gene

therapy is likely to be one of the hottest segment of the future. Here, scientists attempt to treat diseases at the genetic level itself. Some of the diseases are caused by defective genes which result in non-production of required proteins. Armed with the information about the human genome, scientists are aiming to locate the specific genes that cause the problems and reprogram it to correct the problem. So far some 250 types of gene therapy treatments are under various stages of advanced research. The first successful gene therapy has yet to get regulatory approval.

However, scientists have been able to rely on the self-healing capabilities of the human body extensively to cure various diseases in the last 20 years or so. There are several such drugs and treatments approved for safe use by the US governments Food and Drugs Adminstration(FDA), the world's most-respected drug regulatory authority. These include treatments for anemia, cystic fibrosis, growth deficiency, hemophilia, hepatitis, genital warts, organ transplant rejection treatments and leukemia and many other cancers.

Among the first biotech treatment available was the replacement protein therapy for Factor VIII, a protein that induced blood clotting in hemophiliacs, people who lack this capability. The other famous one is insulin, a protein hormone that regulates glucose levels in blood and its inadequate supply leads to diabetes.

" In 1982, we marketed the world's first biotech product, rDNA Human insulin. In1996, we became the first company to launch the world's first recombinant Human insulin analogue, Humalog [insulin lispro], " said Rajiv Gulati, chairman and managing director of Eli Lilly and Company's Indian wing.

Eli Lilly is one of the world's leading pharma companies with increasing focus on biotech-based products. Gulati said in 2002, Lilly brought to market the world's first and only bone building agent for post-menopausal osteoporosis- Forteo [teriparatide]. Last year, the company also received the Translational Medicine Award cosponsored by Univ. of California and San Diego Institute of Molecular Medicine in recognition of Lilly's new biotech product-Xigris [Drotrecogin Alfa]. The sales of insulin and insulin analogue last year touched $1.9 billion and Xirgis raked in revenues of over $ 100 million in in over 140 countries.

According to the US-based Biotech Industry Organization (BIO), more than 325 million people in the world have benefited from 130 biotech products approved by the US FDA. Interestingly, over 70 percent of these drugs and vaccines were approved in the last six years. Currently, some 350 biotech drugs are in the clinical trials stage for 200 diseases. Some of these include various types of cancers, Alzheimer's disease, heart disease, diabetes, multiple sclerosis, AIDS and arthritis.

A Confederation of Indian Industry (CII) survey said at least eight industrial units are producing recombinant DNA products. Take the case of Mumbai-based Wockhardt. It introduced a hepatitis-B vaccine, Biovac-B, in early 2000. " We are now the market leader in this segment," said Wockhardt chairman Habil Khorakiwala. In fact, it got another global recognition when its manufacturing facility was certified by the World Health Organization (WHO) as a GMP (global manufacturing practice) compliant facility, the first Indian plant to achieve this for its bulk and formulation facilities, Khorakiwala said.

Wockhardt has followed it up with the launch of Wepox, a human Erythropoietin, in early 2001 to treat a critical type of anaemia due to cancer or kidney failure. This product has a 25 percent market share now. Wockhardt chairman said these two biotech products accounted for 10 percent of the company's sales revenue in 2001. Khorakiwala said both these products will be launched in the international market soon.

According to a recent study by Tufts University, it costs approximately $ 800 million (Rs 4,000 crore) to bring a new chemical drug to the market in 15 years. The biological alternates will take less than half this time.

Experts say that the distinction between pharma and biotech companies is blurring fast. It is spurred by the fact that future drugs could be delivered through food items (vaccine fortified vegetables or cereals or edible vaccines) and not through pills, potions or injections.

Biotech based diagnostic kits have become very popular in recent years. There some some 600 diagnostic kits and products in the world market notching up sales of $ 20 billion (Rs 100,000 crore). The sale of these diagnostics in India is estimated to be Rs 100 to 200 crore annually. Most of these kits are imported. Companies like J Mitra and Co in India are marketing AIDS diagnostic kits manufactured from technologies developed by a government laboratory.

In fact, the Department of Biotechnology (DBT) has facilitated the transfer of technology for 11 diagnostic kits to the industry. Major research programs are on in India to develop cures for diseases such as tuberculosis, HIV, malaria, leishmania, cholera, dengue, typhoid, cancer and heart diseases. Vaccines are under development against cholera and rabies.

" I see a great scope in diagnostics and vaccines in India. We can become the world leaders only when we come out with new molecules. We can compete with major players in biopharma," said Prof G Padmanabhan, honorary professor at the

Indian Institute of Science, Bangalore. " We have to go for indigenous drugs. Already many firms in India are developing such drugs. I hope they will come out with good results soon."

Sure. Indian companies are working on development of new molecules. Nicholas Pirmal India Limited, Mumbai, is a key player in this segment. " The business driven R&D (BBRD) is a major activity at our research center, the Quest Institute of Life Science," said the company's director(strategic alliances and communications, Dr Swati Piramal.

Nicholas Piramal has filed a patent application for a new anti-cancer molecule, NP102. This molecule is a cyclin-dependent kinase 4 inhibitor. It is also working on five other compounds in areas such as cardiovascular (two), and one each in diabetes , anti-fungal and cancer . " We have completed the first phase of the 12-year project. Each project will cost around Rs 12 crore," she said.

Eli Lilly has just launched Forteo, a recombinant Teriparatide in the US market recently." We are looking at a late 2003 launch in India and this drug is expected to be Rs 8-10 crore product in the first year of launch, said the company's CMD Rajiv Gulati. The heartening fact is the recent study by Ernst & Young which expects the Indian pharmaceutical industry to growth exponentially to an innovation-led $ 25 billion industry by 2010. The market capitalization of this sector may reach $ 150 billion from mere $ 5 billion generic-based sector right now.The industry was worth $ 3.8 billion in 2000 and may grow to $ 9 billion by 2005.

From all available information, Indian biopharma companies are placed firmly on the path of a successful journey on the health superhighway with biotech drugs.

N Suresh
Tapping the CRO market

With the global pharmaceuticals companies looking outward to reduce their ballooning research costs, countries like are in a good position to tap the new business opportunities. Countries with excellent training and experience in process development, manufacturing and formulations such as China, India, Russia, South Korea, Thailand and Malaysia are the major destinations for contract research opportunities (CRO) market. The global market for such services in 2002 was estimated to be $ 1.2 billion (Rs 6,000 crore) and may grow to $ 3 billion (Rs 15,000 crore) in 2008.

" India has a distinct advantage over its competitors," said Gautam Das, COO, Syngene International Ltd, Bangalore. India's competitive edge is in cost efficiency, the intellectual talent pool in biosciences, synthetic chemistry and information technology.This Bangalore-based Biocon group company is India's first CRO firm in biotechnology. Syngene was set up in 1994 to meet the emerging demand for outsourced research from Europe and the US. Syngene has clocked $ 6 milliion (Rs 30 crore) in revenues in 2002-03 and its growth rate was in excess of 75 percent. Syngene's clients include AstraZeneca, Bristol Myers Squibb, DOW Chemicals and Glaxo Smithcline Beecham.

Global companies are looking at ways to speed up the drug discovery process by simultaneous screening of a large number of potential new molecules and identify promising ones quickly. In addition, Indian companies have good potential in developing new chemical entitites (NCEs) from natural remedies and plant-based materials, according to a Rabo India report. Top 10 pharma companies may increase their primary screening of compounds from 10-15 million now to 200 million per year in another two years. Besides Syngene, Chembiotek is a major player in this area.

Similarly, contract manufacturing is a major opportunity area. Recently, Hyderabad-based Bharat Biotech has got a major order to manufacture a vaccine for Wyeth. And Eli Lilly plans to make India as the global hub for its global requirements." We are already looking at alliances with Sun Pharma, Ranbaxy and Austin-Shasun. We want to act as a catalyst and provide the world class manufacturing facilities of some operators in India to our parent company for meeting their global requirements. Nizatidine and Dobutamine are two drugs that may soon start to be exported from these third party manufacturers to meet global markets," said Eli Lilly(India) chief Rajiv Gulati.

The vaccine maker

The Hyderabad -based Shantha Biotechnics is the first Indian company to develop the recombinant DNA vaccine in a segment dominated by global pharma major.A small-time entrepreneur with limited ambitions broke several myths and reworked the paradigm in the 1990s.

Shantha Biotechnics is the brain child of Varaprasad Reddy, an electronics engineer by training and experience, achieved in a field that India's leading pharmaceutical firms did not have the courage to tackle till then: genetically engineered drugs.

Shantha is a company engaged in the development, manufacturing and marketing of biologicals/biopharmaceuticals for human healthcare.

Varaprasad Reddy, managing director, Shantha Biotechnics, who is instrumental in developing indigenously- rDNA vaccine (Shanvac-B) at a cost less than Rs 20 crore, albeit over a five-year period, says, "R&D is our core competence. And the company's success can be mainly credited to its team of highly qualified and world-class scientists in the R&D team." Shantha has received several awards, the most prestigious being the first ever cross industry 'National Technology Award' and 'The Ernst & Young Entrepreneur of the year Award'.

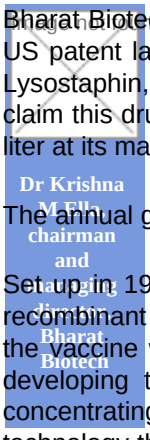
With half a dozen of the country's most prestigious technology awards to his credit, Reddy said, "We will launch a new drug every year for the next six years. At present our manufacturing capacity is 100 million doses of Shanvac B and 2 million doses of Shanferon annually. Our hepatitis B vaccine (Shanvac B) is WHO approved and we supply to the UNICEF. Our global markets are Russia, Kenya and South Asian countries. Shantha had an export sale of Rs.60 lakh in the year 2001-02.

About the action plan of Shantha, Reddy said, "We will focus on manufacturing and drug discovery. The company is extending its manufacturing facility to facilitate manufacture of its various products. Shantha's new drug discovery program involves work on monoclonal antibodies against non-small-cell lung carcinoma. The products in the pipeline are Shantyph (Typhoid vaccine), Shankinase (Streptokinase), Neisvac C (Meningococcal infection), DPT-Hep B combivac and Insulin among others."

"On the regulatory and fiscant bottlenecks that the government has to remove to make India a global market for biopharma research and related activities, Reddy said, "A single window approval of biopharmaceuticals (like the CBER in USA) will cut down on the time to market and costs. The current system of seeking approvals from various departments is time consuming. There is also no level playing field. On one hand the government encourages indigenous manufacturers and on the other hand the import of vaccines still continues. This is a scenario even when the Indian companies have proved that their product quality matches international standards and the companies are more than capable of meeting the domestic demand."

First Indian biotech drug gets US patent

Indian companies are making rapid strides in developing biotech based drugs. Hyderabad-based Bharat Biotech has got the US patent for the first Indian biotech drug-Lysostaphin which can treat infections caused by a fearsome bacteria, Staphylococcus in humans and animals.



Bharat Biotech chairman and managing director Dr Krishna M Ella said that the drug was undergoing animal trials. It got the US patent last year. Developed jointly by his company and the Delhi-based Institute for Genomics and Integrative Biology, Lysostaphin, a biological protein can kill the germs in 40 seconds after it degrades inside the body on intake. Test results claim this drug was more effective than its chemical counterpart. Bharat plans to mass-produce it at the rate of two gram per liter at its manufacturing facility in Hyderabad, Dr Ella said.

The annual global market for this drug is estimated at $ 12 billion (RS 58,000 crore).

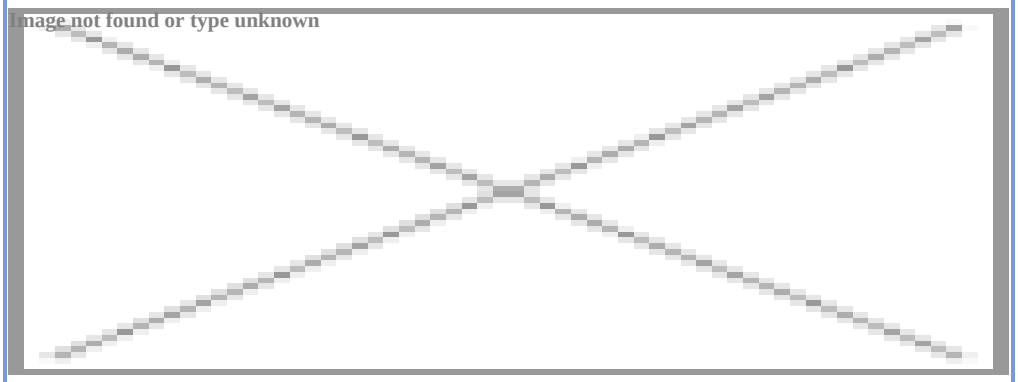
Set up in 1996 by Dr Ella, a US-trained molecular biologist, Bharat Biotech is a trailblazer in Indian biopharma sector. Its recombinant vaccine for hepatitis-B, Revac-B, hit the market in 1998. Today it is sold in many foreign countries. Dr Ella said the vaccine was made in India when the international management consultancy, McKinsey, ruled out any Indian company developing the expertise to make this high tech vaccine. " Having proved our point that we can do it, now we are concentrating on other vaccines, " he emphasized. Bharat Biotech was the first company in the world to perfect the technology that permits the purification of the hapatitis-B surface antigen without the use of toxic heavy metals. The company has the capacity to produce over 100 million doses a year.

Bharat Biotech has patented the HIMAX technology which was developed in house to enable recovery of the surface antigen protein to the tune of 85 approximately. The global average recorded in the scientific literature is only 12-20 percent.

At the heart of the company is the 375,000 sq. ft clean room manufacturing facilities, one of the largest in Asia. The company has invested over Rs 125 crore and had annual sales of Rs 27 crore last year. Bharat has alliances with some top Indian and foreign institutions such as the Indian Institute of Science, Bangalore, the Center for Biochemical Technology, Delhi, the International Center for Genetic Engineering and Biotechnology, New Delhi, the Center for Disease Control, Atlanta, and the

National Institute for Allergies and Infectious Diseases, Washington D.C.

Hepatitis-B market shares by revenues

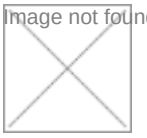


The company is developing other biological vaccines against rabies, Japanese encephalitis, a vaccine against malaria and a vascular endothelial growth factor. Bharat also has products like recombinant streptokinase, a protein produced from genetically manipulated Escherichia coli and urokinase, a plasminogen activator useful to treat acute myocardial infarction, pulmonary embolism, etc. A typhoid vaccine is ready for release in early April. " We have just got the license for the typhoid vaccine," said Dr Ella. The typhoid vaccine has been
prepared in collaboration with the National Institute of Child Health, US, under the guidance of Dr John Robins. It will be at least one-third cheaper than the typhoid vaccines now imported from Russia and China.

" We manufacture it with facilities having global manufacturing standards. Yet, we have to send these for regular tests at the government run institute, CRI, Kasauli, Himachal Pradesh. Whereas the imported vaccines do not follow such rigorous standards," he pointed out.

Dr Kalam on stem cells

Stem cells are one of the most fascinating areas of biology today. Stem cells have two important characteristics that distinguish them from other types of cells. First, they are unspecialized cells that renew themselves for long periods through cell division. The second is that under certain physiological or experimental conditions, they can be inducted to become cells with special functions such as the beating cells of the heart muscle or the insulin-producing cells of the pancreas.



Research on stem cells is advancing knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. This promising area of science is also leading scientists to investigate the possibility of cell-based therapies to treat certain diseases. As scientists learn more about stem cells, it may become possible to use the cells not just in cell-based therapies, but also for screening new drugs and toxins and understanding birth defects. It has been hypothesized by scientists that stem cells may, at some point in the future, become the basis for treating diseases such as Parkinson's disease, diabetes, heart disease and brain disorder.

A number of experiments over the last several years have raised the possibility that stem cells from one tissue may be able to give rise to cell types of a completely different tissue, a phenomenon known as plasticity. Examples of plasticity include blood cells becoming neurons, liver cells that can be made to produce insulin, and haematopoietic stem cells that can develop into heart muscle. Therefore, exploring the possibility of using adult stem cells for cell based therapies has become a very active area of investigation by researchers.

Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including Parkinson's and Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, and arthritis.

In people who suffer from type I diabetes, the cells of the pancreas that normally produce insulin are destroyed by the patient's own immune system. New studies indicate that it may be possible to direct the differentiation of human embryonic stem cells in cell culture to form insulin-producing cells that eventually could be used in transplantation therapy for diabetes. To summarize, the promise of stem cell therapies is an exciting one, but significant technical hurdles remain that will be overcome through years of intensive research.

(Excerpts from the inaugural address of President Dr APJ Abdul Kalam at the ASSOCHAM's Knowledge Millennium III meet on the Business of Biotechnology in New Delhi on 23, March 2003)

India on good wicket in stem cell research

There are six major centers where research on stem cells is done in India. These are the National Center for Biological Sciences, Bangalore, Reliance Life Sciences, Mumbai, the Center for Cellular and Molecular Biology, Hyderabad, the LV Prasad Eye Research Institute, Hyderabad, the Institute of Immunohaematology, Mumbai and the Center for Human Genetics, Bangalore.

Stem cell research is picking up in India. According to Dr Rajesh Behl at the Center for Human Genetics, current government guidelines allow generation of stem cells and its export is banned. Making a presentation on the status of stem cell research at the Biotech India 2003 event in New Delhi recently, he said government permits only the use of embryos generated in invitro fertilization (IVF) clinics. Embryonic cells cannot be generated exclusively for stem cell research and researcher could use only supernumerary could be used. Of course, Indian situation is far better than in the US, said top geneticist Dr Craig Venter. Many sects of Christians in the US believe that embryo is a life form the moment conception takes place in the womb. So they are against any tinkering with human life. Because of this top American scientists are moving to Europe to do their research work, he said.

Reliance Life Sciences, Mumbai, has one of the world's top facilities for stem cell research. Set up in January 2001 by the $ 13.2 billion (Rs 60,000 crore) Reliance Group, this center has been recognized as one the 11 such centers in the world by the National Institute of Health (NIH), US. This makes it eligible to receive research funds from the US government.

The Reliance center is working on development of cell lines from human embryos obtains from human blastocytes. The embryos are received as donations from IVF clinics.

Industry welcomes positive budget measures

Rajiv Gulati, CMD, Eli Lilly and Company, New Delhi
The step of equating biotech sector to the IT sector by allowing them benefits like income tax exemption is laudable. The industry expects the budget will spur R&D due to steps like tax holiday, relaxation of the import duty for the equipment needed for R&D and clinical trials, reduction of GP on the import of R&D equipment to five percent from 55 per cent, IT exemption of the income from R&D. The reduction in customs duty on import of biotech products from 30 to 25 percent is good, although a further reduction to 20 percent was more
desirable.

Varaprasad Reddy, CMD, Shantha Biotechnics, Hyderabad.
The budget has encouraged the biotechnology industry by giving equal status to other knowledge-based industries like IT and Pharma in respect of taxing of export profits. The customs duty exemption on import of capital goods by R&D manufacturing facilities, linked to the export turnover is an encouraging step. The budget has given a boost to equity market by abolishing long-term capital gains tax on equity shares. The introduction of value added tax (VAT) is an encouraging and restructuring exercise. The dividend tax has been again imposed on companies at a higher rate of 12.5 percent, which is not a correct step and is a case of double taxation. The duty on biopharma products has been reduced on certain imported drugs which are also manufactured by Indian companies.

Habil Khorakiwala, chairman, Wockhardt, Mumbai.
The budget has given the healthcare sector comprising pharmaceuticals, biotechnology and hospitals the industry status for the first time. Enhanced rates of depreciation will not only bring fresh investment but will also benefit modernization of

hospitals. The benefit under section 10(23) G will provide access to long-term investment requirement for hospitals and biotechnology. For the first time, Finance Minister Jaswant Singh has put pharmaceutical and biotechnology sectors on par with IT. This is a clear recognition of pharmaceutical and biotechnology sectors not only as a knowledge industry but one with great export potential. He has removed some of the anomalies on import of some R&D equipment and consumables for clinical trials. However, this has been selective on notified items. One would have wished that the finance minister would have extended these exemptions across the board on R&D inputs because in any research project, it is difficult to predetermine the specific inputs.

Another disappointment is that royalty and income generated out of R&D in both the domestic and the international markets has not been given adequate consideration. The three lakh rupees limit prescribed may be adequate for an individual but is too insignificant for an organization. My budget rating is nine out of 10

Rana Kapoor, CEO & managing director, Rabo India Finance Ltd, Mumbai.
The Union budget has, for the first time, applied a comprehensive approach to the health sectors particularly the pharmaceutical, healthcare and the biotech sector. In so far as the provisions for faster depreciation, exemption from counter veiling duties (CVD), and exemptions from the excise duties on the life saving equipment would provide the stimulus for longer investments in the high-end medical facilities. Biotechnology and pharmaceutical companies will see a drastic increase in the fund allocation by pharmaceutical companies towards R&D . I congratulate the minister for a very positive and growth oriented budget.

Biopharma gains a lot from Budget '03

Finance Minister Jaswant Singh has heard the cries of biotech industry for some mercy from high taxes and removal of procedural and regulatory bottlenecks. Here are some of the highlights of Jaswant Singh's announcements which have a positive impact on this industry, particularly the biopharma sector.

1. The customs duty on import of glucometers and glucometer test meters reduced from 10 to five percent.
2. Duty reduced from 25 to five percent on specified life saving drugs
3. Drugs required for clinical trials will be exempt from all duties subject to a license from the Drug Controller of India.
4. Concessional customs duty of five percent extended to all importers of Pharmaceuticals Reference Studies.
5. Specified pharma and biotech equipment for R&D will be exempt from customs duty subject to the fulfillment of some prescribed conditions.
6. Specified life saving drugs and equipment exempted from Excise duty. Excise usually is levied on goods manufactured in the country.
7. Establishment of a central Drug Standard Control Organization to monitor quality, harmonize standards for clinical trials with international benchmarks, speed up new drug approvals and to ensure high standards of safety and efficacy of drugs and pharmaceuticals.
8. Drugs and Cosmetic Rules, 1944 amended to streamline procedures for manufacture and import of new drugs. Some of the important amendments are

a. no institution will be allowed conduct clinical trials for a new drug whether for clinical investigations or for experiments without the permission of the Drug Controller of India.
b. Post marketing surveillance studies have been made mandatory in case of clinical trials for import and manufacture of a new drug

9. The National Seed Policy 2002 has been announced to promote the entry of the private sector to establish R&D facilities for biotech research, increasing seed production in India and marketing of products at the domestic and international level.

10. Biotech industry to be treated on par with IT and telecom in terms of income tax concessions of export profits etc.