

Biopharmaceutical Patents: Emerging Issues for Biogeneric Industry in India

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Introduction:

Biotechnology can be broadly defined as 'the application of all natural sciences and engineering in the direct or indirect use of living organisms or parts of organisms in their natural or modified forms in an innovative manner in the production of goods or services and or to improve existing industrial production processes'. Particularly in the field of medicine, biotechnology has enormous potential as it can help in identifying the root cause of a disease. A panel of 28 international scientists who were experts in biotechnology and on global health issues, identified and prioritised 10 technologies when asked 'What do you think are the major biotechnologies that can help improve health in developing countries in the next five to ten years?'. Their responses pointed out that molecular diagnostics, recombinant vaccines, vaccine delivery systems, bioremediation, sequencing pathogen genomes, female controlled protection against sexually transmitted diseases, bioinformatics, nutritionally enhanced genetically modified crops, recombinant therapeutic proteins, and combinatorial chemistry would have valuable applications in improving health of millions in developing countries (Tara et al 2003) and thus has direct application in meeting the millennium development goals by 2015.

However, only a handful of countries have made significant inroads into this field. Particularly the US leads the rest of the world in this field. In the US, a number of dedicated biotech companies as well as diversified companies have invested billions of dollars in research and have come out with products that have applications for diseases like different types of cancers and blood factors. As the research in this area evolves and leads to uses in hitherto new medical

therapies, intellectual protection concerning these biopharmaceuticals poses new challenges. The underlying purpose of providing patents is to promote innovation. However, patents can also prevent flow of information which could hamper further research on generics coming up in this sector. In the West, where biopharmaceutical research is growing in leaps and bounds, there are a good number of theoretical literatures on the adverse impact of patents in the field of biopharmaceuticals. The empirical literature that confirms some of the concerns raised in the theoretical literature is small but nevertheless causes concern.

There are several entry barriers in the field of biopharma. First and foremost are the financial resources that are required for the growth of this sector. Table 1 indicates the cost involved in developing a cell line. Secondly, in order to set up a biopharmaceutical firm producing recombinant DNA therapeutics, a company should have R&D capability in molecular biology, genetic engineering, biochemistry and process engineering, technical know-how in fermentation and protein purification process, and in drug formulations. Besides it should also have marketing and legal capabilities. While these entry barriers also restrict competition, guidelines for the production of standard generics has not evolved still in the countries, which are active players in the field. Hence, countries which are new entrants to this field are looking for guidance from countries that are leading. Lack of bio generics in the field has resulted in higher costs and hampered flow of technology. Though UK has come out with guidelines for couple of products, in the US, where several products are nearing patent expiry, (Table 2) has not still announced clear guidelines. Hence, the growth of biopharmaceuticals is not uniform across the world as compared to the chemical based pharmaceutical industry. Particularly in the case of India, the role of the patent amendment that took place in the 1972 resulted in the development of the strong generic industry in India which presently caters not only to the demands of the domestic market but of the countries which do not have production facilities at all as well. Whether such a growth through the development of a strong generic sector can be replicated in the biopharmaceutical sector in India in the present product patent regime is an important concern. This is because, the patent system has become more complicated and as far as the biopharmaceuticals is concerned, there could be multiple patents involving each process. Hence in such a context, development of a generics sector that could cause effective threat to monopoly is delayed. Further, unlike the chemical based industry, biologics in India is slowly emerging and

is around 20 years old. Hence, the role of entry barriers as well as the developments concerning the generics elsewhere would have a strong impact on the growth and development of the industry.

So in this context, this paper analyses whether the prevailing patents governing the biopharmaceutical innovations prevent the growth of the generic industry in India or in other words it tries to analyse the prevalence of anticommons tendency in the biopharma sector in India. In doing so, this paper in Section 2 following this introduction presents a brief literature review on the anticommons. Section 3 describes the status of patent system governing the micro-organisms in India. Following this Section 4 presents with a chosen sample of biopharma companies¹ in India the major issues before the biogeneric sector and the last section presents the conclusion.

2 Do Patents Give Rise to Anti Commons?

Following the precedents set in the case of patenting of naturally occurring adrenaline and vitamin B12, the US PTO did not have any problem in allowing patents on purified DNA sequences and recombinant constructs (Einsburg, 2006) if the patent application disclosed a genuine function.

In 2001 over 5000 DNA patents were granted by the USPTO, more than the total of that was granted between 1991 and 1995. 9456 patents that include the term nucleic acid in their claims have been granted since 1996. Japanese patent office had granted 5652 patents since 1996. In 2000, more than 5000 patent applications have been filed that include the word genetic engineering or mutations of which 605 relate to human or animal DNA sequences (OECD, 2002). The scientific community also did not oppose patenting DNA sequences until the Human Genome Project, when the National Institute of Health began filing patent applications on expressed sequence tags (ESTs).

¹ The sample consists of 19 companies totally selected from Gujarat (7), Karnataka (5) and AndhraPradesh (7).

Genetic patents by and large cover (1) genes or partial DNA sequences such as cDNAs, SNPs, ESTs promoters and enhancers, (2) proteins encoded by these genes and their functions in the organism (3) vectors used in the transfer of genes from one organism to another (4) genetically modified organisms, cells, plants and animals, (5) process used for making the genetically modified product, (6) uses of genetic sequences or proteins which include specific tests for specific genetic diseases or predisposition to such diseases, drugs developed on the knowledge of proteins and their biological activity, industrial applications of protein functions (OECD, 2002, P.28). Hence a single DNA which is used in all of the above mentioned would qualify for separate patents and thus stand in the process of wider dissemination of knowledge and use and create the situation of anti commons.

Access to key information and understanding of the patent landscape is very essential in order to enhance innovative capacities and carry out research or developing products in the field of biotechnology. But, concerns have been raised that by allowing patenting on genes, restriction have been placed on the researchers to access and work on biological information and most often shows the ability of the patent holder to exclude others from using the material. There are evidences of both extremes where (1) the patenting of genes were licensed to academia and others on a non-exclusive basis thereby promoting further research as in the case of Human Genome Sciences and the Wisconsin Alumni Research Foundation and (2) withholding of data, results and research materials that have delayed the pace of research or increased the duplication of research.

While patenting could be a tool to encourage innovations, it could have detrimental effect if it prevents further research and dissemination of knowledge thus leading to the sub optimal utilisation of a useful innovation leading to a situation of 'anti commons'. Companies try to block new products coming into the market by variety of strategies like introducing a second-generation product with an improvement over the previous product, bioprocess improvements and reformulations and vigorous patent litigations etc. IPR protection also becomes a barrier if broad patents cover the biopharma products. In such cases a firm wishing to commercialize an invention will have to have access to various patents protecting one product. If access to one patent is denied or delayed, it prevents further scope of research. Firms which want to work on

the patented technology will either have to spend huge resources to (a) get the license to work on or (b) invent around the existing patent to avoid any litigation. In some cases it could lead to the abandoning of the project altogether. Such a situation could lead to under utilization of research (resources) and thereby deprivation of benefits to the society, which would have otherwise occurred. Popularly referred to as the 'tragedy of anti-commons', when it happens in the case of pharmaceuticals it means access to new drugs is curbed in the initial stages itself because of under utilization of research. In future it is extremely unlikely that the situation of anti-commons is overcome without legal intervention. For instance in the recent case concerning US patents no 6410516 or called as 516, the patent covers a biological pathway (nuclear factor kB) and not any specific drug. Thus it is thought to cover more than 200 drugs in disease pathways such as inflammation, malignant transformation and in osteoporosis. The company concerned has already filed patent infringement cases² against companies using nuclear factor kB and also has sent licensing offers to around 50 other companies with products that work via the nuclear factor kB. The USPTO is currently re examining the patents validity (Frantz, 2006).

On the dissemination of research, Murray et al (2006) note that the anti commons theory predicts that if the grant of intellectual property hinders the ability of researchers to cumulatively build on a given piece of knowledge then the citation rate to the scientific publication disclosing that knowledge should fall after formal IP rights are granted over that knowledge. For instance, patent over research tools such as oncomouse, cell lines, or gene probes may be associated with larger anti commons effect for at least two reasons; 1. Research tools are of broad relevance to many researchers and hence patenting them may impinge on many ongoing lines of research. Second by and large research tools are subject to a high degree of transparency in use. Materials and tools are usually covered by material transfer agreements and other institutional arrangements. While contracts such as MTAs do facilitate the dissemination of tools, delays over the terms and use of the MTAs discourage the use and terms that come under their purview (Murray et al 2006). MTA³ governs transfer of tangible materials between two organizations

² The jury of the US District Court of Massachusetts has awarded the plaintiffs around US \$65 million in back royalties and a 2.3 per cent royalty on future sales of the drugs until the patents expiration in 2019 (Frantz, 2006).

³ MTA may involve biological materials such as reagents, cell lines, plasmids and vectors, chemical compounds etc.

and defines the right of the provider and the recipient of the materials. The issue here is if the material is covered by more than one patent, then the recipient has to get the license from each of the patentee to use the material for the research purpose. Further if the MTA is defined in such a way that the provider can claim rights on the derivatives of the material or any modifications made to the material, then the recipient could be hampered from using the results of the research. Thus in both the situations, it could lead to the anti-common situation.

Though there are limited empirical data that quantify the negative effects of patents on the supply and cost of molecular genetic testing in the US and elsewhere, there are evidences where many providers have discontinued or have been prevented from providing genetic testing for inherited breast and ovarian cancer, severe neurodegenerative disorders like Duchenne muscular dystrophy, a potentially lethal cardiac syndrome and a host of less commonly discussed conditions (Rojer Klein 2007). Also as many as 30 per cent of laboratories have discontinued or not developed genetic testing for hemochromatosis because of exclusive licensing of patents that assert rights over the most common mutations in the gene involved (quoted in Thomas et al 2002). Thus enforcement of gene patents have the effect of reducing innovation in assay development and limiting the number of test providers, thereby raising healthcare costs and reducing or eliminating patient opportunities to send specimens to alternate laboratories to confirm the accuracy of test results.

OECD (2002) discusses the case of malaria vaccine to highlight the impact of patent thickets (multiple patents). In considering the development of malaria vaccine which could be sold at a low cost to developing countries, the Programme for Appropriate Technology (PATH), commissioned a study of patents that need to be licensed for a vaccine that would rely upon MSP 1 protein of the malaria parasite. From an initial patent map of close to 40 patents, PATH narrowed down the relevant patent to be licensed to 5 core US patents relating to MSP 1, a dozen useful patents in constructing the vaccine and 5 specialised patents for the production of MSP-1 vaccines. Thus, this many patents have to be tackled to arrive at the malaria vaccine. The other problem in patent thickets cases is the royalty stacking by different parties or known as reach through claims which could cover even the end product attained through the use of the research tool.

In view of the increasing number of organisations claiming broad patents to whole or partial DNA sequences, the European Commission in 2002 indicated considering a halt in granting wide ranging patents in human DNA sequences. Similarly the Nuffield Council on Bioethics (NCB) views that the criteria of patentability such as novelty, inventiveness and usefulness are not very strictly enforced on the DNA sequencing applications. A stricter scrutiny would result in (a) very few product patents for gene based diagnostics, which NCB says do not in themselves meet the criteria of inventiveness; (b) limited patents on DNA sequences or research tools which are rarely justifiable and wherever already granted they should be freely licensed; (c) gene therapy-patent protection concentrated on developing safe and effective methods of gene delivery; and (d) narrowly defined patents on DNA sequences used to make new therapeutic proteins extending only to the protein described (ED, 2002).

While patent pool where patent holders come together and license the patents to each other or the third parties, could be one option to avoid the tragedy of anti commons, such an agreement can happen through an administrative agency set up for this purpose. However, the caution in such cases is that it should not lead to anti-trust violation (the OECD study points out that there has been no patent pooling in bioscience,- the one success patent pool story is with reference to the MPEG2 (digital video compression standard) which covers 116 patent families and 490 licensees worldwide. Walsh's study quoted in OECD (2002) concludes that the patent landscape has become more complex and the researchers have had to work around the solutions. Patenting of research tools has added to the complexity and adds to the transaction costs and delays. However, the potential for future 'anti-commons' problems have not been averted but to date breakdowns have rarely happened. The study observes that it was still possible to contract a licence to work on a patented invention that is relevant for R&D. Firms do avoid research projects where the research tools are covered by many patents.

Prevalence of the anti commons could vary among countries. Dianne et al (2003) note that the essential precondition to the prevalence of anti-commons is the existence of multiple patents covering different components of a single product, its method of manufacture or inputs in to the process through which it is discovered. Australia unlike the US and Europe where the bio patents have increased dramatically at a faster rate, in Australia, the number of patents though has been

increasing it is less compared to the US and Europe. Further the authors also note that unlike the US where a number of research tool patents are said to be aggressively enforced have either not been filed in Australia or where the applications have been filed, the patents have not been prosecuted. Hence the detrimental effects could be lower at the present point of time till such applications are pursued.

3. Patenting of Micro-Organisms in India:

A clearer definition of patenting than that was mentioned in the 1970 patent Act was introduced in the Indian Patents Act only with the amendments that came in 2002. The significant additions to the existing list of what are not considered inventions (and that have direct impact on patents involving living organisms alone are mentioned here) in the Indian patent are: (a) discovery of any living thing or non-living substance occurring in nature; (b) an invention whose use or exploitation would be contrary to public order or morality or which causes serious prejudice to human, animal or plant life or health or to the environment; plants and animals in whole or any part thereof other than micro-organisms but including seeds, varieties and species and essentially biological processes for production and propagation of plants and animals; (c) a presentation of information and (d) an invention which in effect is traditional knowledge or which is aggregation or duplication of known component or components. Thus the Indian patent Act while clearly excluding the biological processes of production and propagation of plants and animals leaves some scope for patentability if the same includes micro organisms.

Here, it may be worth noting an important case that reflects the stand on micro organisms by the patent office and the courts. The Indian Dimmainico case of 2002 is a landmark case in the Indian biotech patent debate which is comparable with the Chakrabarty case of the US. Dimmanico, a subsidiary of a US firm filed a patent application in the Calcutta patent office for a process of preparing Bursitis vaccine useful for protecting poultry against infectious bursitis. The issue was whether a process patent can be allowed in a case where a living organism formed a part of the substance being manufactured. The patent office rejected the claim saying it did not fall within the purview of the patentable criteria (The 1970 patent Act defined invention as anything new and useful such as art, process, method or manner of manufacture, machine, apparatus or any article; substance produced by manufacture and includes any new and useful

improvement or any one of them). The Court held that since the patent claimed was useful in protecting poultry against a disease and the end product resulted in a new article, patent has to be granted. Ultimately, a process patent was granted to this claim.

A five member panel under the chairmanship of Dr. Mashelkar was set up in April 2005 to recommend appropriate definition of 'patentability' since it was realised that a clearer position regarding the intellectual protection of the micro organism related invention need to be achieved. The terms of reference of the panel were to see if it would be TRIPS compatible to limit the grant of patents for pharmaceutical substance to new chemical entity or to new medical entity involving one or more inventive steps. The panel was also asked to study if it would be TRIPS compatible to exclude micro-organisms from patenting.

This committee after going through the procedures and process adopted by different countries regarding patenting micro organisms recommended that, 'Biotech industry is one of the fastest growing industries in the world, including in India.It would, thus, be in our interest to document, protect and modify new micro-organisms isolated from various parts of our country and find their new and improved industrial uses. This step would help Indian biotech industry. However, strict guidelines need to be formulated for examination of the patent applications involving micro-organisms from the point of view of substantial human intervention and utility. Excluding micro-organisms *per se* from patent protection would be violative of TRIPS Agreement' (Report of the Technical expert Group on Patent Law Issues, December 2006). However, this report has not been accepted by the Government of India. As of now, micro organisms are patentable in India. Hence, it is not clear in the Indian context how many of the patents that have been listed in Table 3 would be broad patents or patents on research tools that would have detrimental effect. Here again though like Australia, the number of patents filed is increasing, it is not increasing in the same way as it does in the US or Europe.

As far as regulatory procedures in India are concerned, a three-tier system of regulatory process governs the research, manufacturing and marketing of biopharma products. All biotech research institutions will have to set up an Institutional Bio safety Committee and will have to be

approved by the Review Committee on Genetic Manipulation and Genetic engineering Approval Committee.

4 Indian Biopharmaceutical Industry⁴

In this section first we present a brief view of the Indian biopharma industry, followed by an analysis of the chosen companies. The biopharma industry in India can be said to be evolving as compared to the pharmaceutical industry. Estimates of market size vary, but measured by the domestic sales of biomedical products was estimated at US\$120 million in 2003, compared with US\$3.5 billion in domestic pharmaceutical sales. More than 50 per cent of the 170 biotech companies in India are agricultural based. The rest are split among health care and environmental companies. This would constitute less than 3 per cent of the closer to 5000 companies that are operating in the pharmaceutical sector.

The biopharmaceutical sector in India consists mainly of dedicated start-ups and existing pharmaceutical companies that have diversified into biopharmaceuticals. Though the number of public undertakings operating in the biopharmaceutical sector is limited, the public research institutions play a significant role in the growth of private biopharma in the country especially in the recombinant products. The public private partnerships have been in the form of providing facilities or assistance for standardization, testing, technology development, contract research, contract manufacturing or licensing a product. Some of these entrepreneurs have worked with a public research institute before starting their own biotech start-up firms.

Table 5 provides the list of products that have been commercially approved for sale by the Government of India. These products fall in the category of two important segments of biopharmaceuticals namely vaccines and recombinant DNA products. Presently, the Indian biopharmaceutical products available in the market comprise of the vaccines, diagnostic kits and recombinant DNA products and all the manufacturers are engaged in the production of bio generics only. India allowed two follow on biologicals in August 2003. Further 2002 August witnessed the phase 3 trial clearance for Shantha biotech's Filgratim for leukaemia as well as

⁴ This section draws from 'An Analytical Report on the Biotechnology Sector in Gujarat' (undated).

two marketing approvals for Bharat biotech's recombinant streptokinase to prevent blood clots and Wockhardts Wosulin, India's first biogenetic human insulin (Jayaraman 2003).

As far as the development of the bio generics are concerned, Krishna Ella, of Bharat Biotech observes that the markets for generic versions of first generation product may be limited given the threat of second generation products produced by the original inventors. 'As long as a company can continue making medically significant improvements on a therapeutic protein, it may be able to retain an exclusive market indefinitely. For example, Amgen's improved treatment for anaemia Aranesp has reached the market before its current patent for Eprex (epoetin alfa) expires in 2004 (Jayaraman 2003)

Krishna Ella also observes that Indian companies' advantage in cheap vaccine for hepatitis or rabies may also be eroded, by potential development of cocktail vaccines that promise delivery of multiple vaccines in a single shot. He also fears that Indian bio generics firms may face difficulties in obtaining vectors and expression systems to copy drugs whose patents will expire'.

In order to gain market share, Jayaraman (2003) observes that the biopharmaceutical companies do not focus on providing mere copies of existing drugs, they are also trying to improve manufacturing processes which may themselves bring new patents. For example, Bharat Biotech claims to have developed the world's first calcium chloride free hepatitis B vaccine with the discovery of a novel purification matrix and Shantha Biotech's expertise is in the use of expression systems with the yeast *Pichia Pastoris*, which have a higher yield and therefore lower production costs than other yeasts.

The Indian vaccine market revenues were estimated at US\$ 260 million in 2004. It accounts for 47.17 per cent of the total biopharma industry. The entry of Shantha Biotech, Bharat Biotech, Panacea and Wockhardt has changed the profile of the vaccine market in India. Before these companies entered the hepatitis B vaccine market, Glaxo Smithkline was the only company in the field and had absolute monopoly in the market charging a relatively higher price. However, after the entry of the Indian companies which launched their products with a different process, the competition reduced the price by thirty fold benefiting the consumers. Presently, Serum

Institute of India is one of the leading suppliers of vaccine to the WHO with a 138 country distribution network. Panacea Biotech supplies its oral polio vaccine to UNICEF's program. Bharat Biotech has the largest biological production facility in the Asia-Pacific Region and has a loan licensing agreement with the world vaccine major Wyeth to manufacture Hib Titter vaccine⁵ in Andhra Pradesh and also acts as a contract manufacturer for Agenix Inc, USA. Indian Immunological Limited, a subsidiary of National Dairy Development Board has the second largest veterinary vaccine producing facility in the world. With increasing emphasis on national immunization programmes to achieve the millennium development goals, the vaccine market is getting a big boost.

The total diagnostics market in 2003-04 in India stood at US \$ 56 million and accounted for 10.5 per cent of biopharmaceutical sector sales. There is a huge demand for immunology kits for pregnancy detection, HIV, TB and malaria. Presently, diagnostic kits for pregnancy, HIV and TB are available. Currently more than half of the diagnostic kits in the country are imported. One of the reasons for imports is the import duty structure of Government of India that favours import of the diagnostic kit itself than importing the constituents such as enzymes. The ancillary industry to produce these constituents is also yet to develop in India. The Department of Biotechnology (DBT) has also facilitated the transfer of many technologies developed at CSIR laboratories for diagnostic kits to the industry.

Presently only a few Indian manufacturers produce diagnostic kits in the areas of pregnancy, ovulation, estimation of TB, T3, T4&TSH, HIV, HBV and HCV infection, rheumatoid diseases and disorders, cancers of cervix, colon, prostate, lung, mouth etc, and kidney and liver function. India is becoming a competitive outsourcing destination for diagnostic testing. For hospitals in the UK, US and West Asia, it is cheaper to outsource diagnostic services to India. The services offered by Indian companies have been in the area of molecular diagnostics for autoimmune disorders, diseases related to abnormalities in chromosomes and hormones. Some of them can

⁵ Hib titter vaccine used in *Haemophilus influenzae* is a serious disease caused by bacteria. It usually strikes children younger than 5 years old. Hib was the leading cause of bacterial meningitis among children under 5 years old in the United States. Meningitis is an infection of the brain and spinal cord coverings, which can lead to lasting brain damage and deafness. Hib disease can also cause pneumonia; severe swelling in the throat, making it hard to breathe; infections of the blood, joints, bone, and covering of the heart; and results in death.

perform more than 1500 tests under one roof and can easily cater to the domestic requirements and that of the West. According to a study on Indian health care industry, the diagnostics and pathology services estimated at US \$ 864 million and are increasing at the CAGR of 20 per cent.

There are a number of institutions doing research in biotech such as the Indian Institute of Science, Indian Institute of Immunology, National Institute of Virology, Jawaharlal Nehru Centre for Advanced Scientific Research, International Centre for Genetic Engineering and Biotechnology, Institute of Genomics and Integrative Biology, All India Institute of Medical Sciences, Centre for Biochemical technology, IMTECH, the Central Drug Research Institute, the various laboratories of Council for Scientific and Industrial Research, to name a few .

Patenting in biotechnology increased between 1992-2003 (Uyen Quach et al, 2006). Patents filed by the research institutions (CSIR) were particularly high. Patenting in health biotechnology was higher than patenting in other fields of biotechnology. This study also observes that the patents filed were more relevant to the Indian health needs such as cholera, leishmaniasis, tuberculosis, cancer, viru. /fungi compositions.

With this background, an analysis of the chosen companies is made to understand the nature and spread of the product line, whether intellectual property rights pose an hinderance for the growth of the generic sector and the other issues before the biopharmaceutical sector.

4.1 Analysis of Sample Companies

Out of the total 19 companies chosen for the study, with the exception of one non profit organisation, 68 per cent of the companies are privately held and 26 per cent are public limited companies. Majority of the CEO's of the sample companies had had their teaching or initial work exposure abroad and mostly with the leading biotech companies of the West. 84 per cent of the companies are engaged in the manufacture and (or) research on recombinant therapeutics and other biologicals. Of these 42 per cent are also engaged in the production of pharmaceuticals as well. Of the remaining 42 per cent of the companies, one manufactures antigens that are used in the diagnostic kits. But for this company which does not have any

competition in the domestic market, the rest face competition within the domestic market as well as in the foreign market. 10 per cent of the companies are engaged in providing contract research services and one is a diagnostic kit manufacturer.

For the private limited companies the funds have come from own resources, and from venture capital in India and abroad. However, all the companies uniformly commented that funds are the serious constraint for the biotech industry. It takes a minimum five to six years for a start up engaged in the production of generics to move from pilot to lab scale to reach the commercialization stage. In this period, the firm would incur only capital expenditure to conduct experiments and no returns will take place. Therefore the venture capitalist has to wait for the project to start yielding. If the company fails in any of the initial stages it has to start all over again. The venture capital in India according to our respondents is not matured like the funds that are operating in the US. In the US, the biotech boom was supported appropriately by the venture capital funds where a failure is considered only as an experience, whereas in India failure means closure of the business. The venture capital funds in India moreover are willing to support established and diversified companies rather than start-ups. The diversified companies are better off as compared to the start-ups since, financially the pharmaceutical division supports the biotech division as the initial setbacks are absorbed by the other division and money continues to flow. Further to set up a lab with the minimum facilities would cost a minimum of Rs. 20 crores according to one respondent. 99 per cent of the machinery and other equipment requirements of the bio-pharma industry are met by imports from the US and Germany as this segment of the industry is yet to emerge in India. All these factors pose as entry barriers and require lot of investment.

Out of the 84 per cent companies engaged in the manufacture and research on biopharmaceuticals, 26 per cent are yet to market their product. Of the 57 per cent of the companies, 26 per cent are in the production of vaccines also. Table 6 gives the different products produced by these companies. Almost all the companies said that they chose the particular line of production for their company because: (a) there are no patents around the product, (b) technology is known (c) expertise to produce the said drug was available locally, (d) ready and growing market, (e) getting clearance from the domestic regulators was easy and

(f) the said product offered the advantages of being a pioneer in the field. In the production process, companies adopt both in licensing and out licensing procedures. In the licensing in procedures, products are licensed from other companies either to produce or to market. Similarly, in the out licensing, a company can license out its innovation to another for further development and get milestone payments.

All the companies are engaged in the production of products where patents have already expired and in the recombinant therapeutic category mainly concentrate on cancer related drugs and diabetes. Most of the respondents said that particularly for the start ups it is not feasible to concentrate on new product development. First the companies would like to stabilize themselves with the production of bio generics which itself is a long process. Even though they produce the biogenerics, their products are not exact copy of the original product for the reasons that were presented earlier. 26 per cent of them are engaged in the production/marketing of Erythropoietin (used in severe anemia or for cancer patients) the market for which was estimated to be US \$6.5 millions in 2005 (Maria et al 2004). 5 per cent of the companies import the same from China and sells it in the domestic market. Streptokinase is produced and sold by 16 per cent of the companies out of which 10 per cent are in Gujarat. Again 16 per cent of the companies are engaged in the production of GCSF of which 5 per cent imports and sell it in the domestic market. Recombinant human insulin is being produced by five per cent of the respondents which is also almost ready to market its oral insulin developed in house. Broad patents have also been filed in this area since this is a novel drug and there has been very little research done on the oral insulin.

Wide range of vaccines is being produced by the companies. Of the 16 per cent of the companies engaged in the production of hepatitis B vaccine, one has developed the recombinant hepatitis b vaccine which is cesium chloride free. The technology for which has been developed in house. As mentioned elsewhere in this report, competition in this sector has brought down the prices significantly.

Mention should be made here where the products in pipe line that include malaria vaccine, Japanese encephalitis and Rota virus vaccine which are the tropical country diseases. Clinical

trials are going on for these vaccines. With funding from Bill and Melinda Gates Foundation, Malaria Vaccine Initiative, Program for Appropriate Technology for Health (PATH), to undertake research in these areas, the innovator company is working to make the vaccines available at affordable prices. It should be noted, that but for the funds from these sources meant for tropical and neglected diseases, the interest evinced in this area from privately held companies would have been much less. According to one of the respondents, in the production of vaccines, like polio, TT etc the government institutions have played a significant role as the strains have been obtained from these institutions. But for the new kind of vaccines, the strains are under material transfer agreement (MTA) and one have to be cautious when working on these strains so as to avoid any patent related issues. 94 per cent of the companies export their product to the unregulated market. All the companies uniformly felt that the US is not a place to export as the domestic innovator industry's pressure not to allow generics is very high and the regulations are stricter. But it is possible to export to the UK at least those products for which the guidelines are available. However, as far as the export of vaccines is concerned, the current range of vaccines is for the diseases prevailing in the tropical countries and not meant for developed countries.

At least 50 per cent of the respondents have products in pipeline that deal with cancer. Besides the products mentioned here, companies have a wide range of products aimed at cancer and osteoarthritis. Similarly, the products in pipeline indicate the wide range of research going on in the biosimilars by the Indian companies. Presently, out of the 20 products approved by the Government of India (Table 5), about 8 products such as human insulin, erythropoietin, hepatitis B vaccine, GCSF, interferon alpha, streptokinase, blood factor are being pursued by the respondent companies. In this segment, there is competition within India as well as in the export market. As more companies are going to get into the production of these, the prices of the products could still reduce. In future we will have more companies concentrating on New Drug Delivery System (NDDS) of the existing drugs.

The product profiles of the different companies indicate that the biotech products are not exclusively aimed at the domestic markets but the markets elsewhere. These drugs are need based and not preventive except that of the vaccines. Hence the products are priced high. Though

the competition could have brought the prices down yet, in a country where the segment of population covered by health cover is low these prices are beyond the reach of many. Hence we find almost all the manufacturers are vying the unregulated markets.

In the process of getting into the production of bio-generics and concentration of the export market, 68 per cent of the manufactures mentioned that have established their research facility according to the international regulatory requirements such as US FDA or MHRA or TGA. Though this involves a huge cost, such recognition besides making the export process easy, also provide them the lucrative opportunity of being a contract research and manufacturer (CRM) for the companies in the West. Already couple of manufacturers undertake contract manufacturing for US companies. The respondents view that the CRM route would be helpful for gaining the confidence of the companies of the West which could later bloom into joint collaboration. Out of the 19 companies considered, 31 per cent of the companies have 100 or more than 100 people working in R&D. 37 per cent of the companies have 50 or less than 50 people working in R&D and 21 per cent have more than 50 and less than 100 people in R&D.

The diagnostic kit market in India is estimated to be around Rs. 800 crores. Our respondent manufacturer produces diagnostic kits where the technology is in the public domain and hence there is no patent issue. This unit produces diagnostic kits for pregnancy, hepatitis, HIV 1-2, malaria, cancer, other infectious diseases like (syphilis, dengue, TB, Troponin I card, chikungunya card), Elisa tests, immunology and rheumatology tests, haematology tests and kits for other clinical chemistry tests. Besides, this unit also produces micro pipettes, instruments, proteins and reagents, immunoglobulin and other recombinant proteins. This unit also produces antigen which is sufficient to meet the demands of its own. And only a small quantity is exported. Here it may be mentioned, that a gram of the antigen costs \$120 according to one of our respondents who is manufacturing antigens.

There is a growing market and competition for the diagnostic kits for HIV, pregnancy, malaria and hepatitis. It is noted that there is an urgent need for the government of India to change its duty structure for diagnostic kits as the present duty structure makes the Chinese products cheaper compared to the locally produced products. Hence, it makes lot of economic sense for

the Indian producers to import it from China and market it in India, in spite of the fact that the quality of the Chinese kits which are relatively poor as compared to the ones made by the domestic manufacturers.

10 per cent of the sample or 2 of the respondents are engaged in providing contract research services. One of the companies due to lack of international regulatory clearance does not get contract job orders from international companies. However, it has the accreditation from the National Accreditation Board for Testing and Calibration. This accreditation certifies that the said company has the necessary competence for testing and has the required process and procedures. Presently it caters to a few domestic companies. The other CRO carries out assays and clinical trials basically for the international companies. The fundamental principle of the CRO is that they work under strict confidentiality agreement. This unit has more than 200 personnel working in its R&D division which is US FDA recognized. In contract research, sometimes the client directs the CRO to carry out certain tests and procedures according to the instructions issued by the client. On such occasions the chemicals needed for the tests are also supplied by the client. Sometimes, the client just indicates what is expected out of the analysis. In such occasions, the procedures need to be innovated by the CRO. Sometimes the CRO gets to work on a patented molecule which they come to know during the process of work. As a CRO they sign the confidentiality agreement and do not disclose the kind of services carried out for a client. These services are time bound and the cash flow for the company depends on the flow of resources received from the services they don't pursue. Further as a CRO, the company needs to maintain proper documentation of the process and procedures that are adopted in the process of carrying out the research services. Hence, utmost emphasis is given to documentation and equipment handling and the employees are first trained in these two aspects.

4.2 Intellectual Property:

Most of the respondents have filed patents for the different processes that they have adopted (Table 8). Only one company has filed a product patent for its novel drug oral insulin. However, it appears that the companies have used such innovations within the company rather than commercialise. Similarly only one company explicitly said that they would consider licensing

their innovations to generate more income. Though it is premature to say in the absence of adequate information on the exploitation of the patents filed by the companies, as of now it appears that the companies use IP as an instrument to retain their monopoly over their invention and exclude others from using it.

As far as the IP over the chosen line of production, companies seem to be very cautious in their approach. Each of these established companies have an IP team which looks at the patent landscape and processes that would not infringe any of the patents. Further, the present financial status of the companies is such that except for two or three producers among our respondents who can afford to venture into new production lines, others are contend with working on bio-similars which itself takes a long time. The present approach of the industry is, to work on a product where the patent has expired, wherever possible, invent around the process and get adequate expertise on the regulatory requirement of the innovator country and then enter the regulated market. A few of the respondents who have diversified to biopharma viewed that it is better not to challenge the patents since it drains the resources. But none of the companies said that they are constrained by the prevalence of patents.

All the firms in this regard observed with concern the attrition rate prevailing in this industry. It is almost common to find people change jobs every three years. After acquiring training in a particular company, it is normal to find the person changing job for something else. Respondents observed that at lower level when it happens it affects the documentation procedures and also the company's investment on the human resource did not benefit the company. However, when the job turnover takes place at the higher level with people who were dealing with innovation/discovery, it becomes problematic for the company since with them the intellectual property is also lost. Though companies insist on the employee furnishing a bond for a huge sum and also take an undertaking that the employee would not work on the innovation/discovery line for three years or so, almost all the respondents agreed it is very difficult to monitor this and protect this IP. To quote one of the respondents 'it is very difficult in the Indian context to set up enforcement mechanism and further difficult to discover infringement'.

4.3 Regulatory framework:

All the producers in this field have to set up the Institutional Bio safety Committee (IBC) once the project is identified, which is the first step. The committee usually consists of the chairman of the company, a nominee of Department of Biotechnology (DBT), doctors, scientists (DBT nominee), and those suggested by the Review Committee on Genetic Manipulation (RCGM). This committee should approve the project. The next step is to apply to RCGM in the fixed format after the IBC sanction for starting the project.

In the next stage of preclinical or the animal testing stage permission has to be sought from RCGM. After this is through, in the product development stage, RCGM has to approve every step such as fermentation, purification, stability and standardisation and so on. Once RCGM approves all the procedures, then the clinical trials starts. Clinical trials need to be approved by the Genetically Engineering Approval Committee. After this approval, the Drug Controller General of India is approached for the approval of clinical trials protocols. The clinical trials should be multi-centric in nature. After this the final approval to market the product comes from the DCGI. If it is a new product to be introduced in India then the company should conduct all the three stages of the clinical trials for approval. But in case of the generic substitutes only the phase 3 trials are required.

Majority of the respondents felt that the regulatory frame work prevailing in India is very exhaustive and involves lot of paper work. If they are targeting the export market, then they have to upgrade their plants to the rigorous requirement of the US FDA or any other country which involves huge expenditure. .

4.4 Skilled Labour

All the respondents uniformly commented about the lack of skilled manpower. Though there are more than 60 educational institutions offering biotech education in the country, none of them offer the lab work environment. There is severe shortage of trained manpower at every stage of

production like R&D, up scaling, pilot plant, manufacture, purification, concentration and formulation. All the respondents felt that the scientific education imparted at the post graduate level need to be given a fresh look and the courses should be designed in such a way that the industry can absorb them.

Since at the entry level the fresh graduates from the educational institutes are very raw, they need to be provided on the job training. So companies have the policy of inviting experts to their unit to give lectures or organize workshops. While most of the companies train their recruits in house, a couple of firms said that they are sent abroad for certain specific aspect of training. 26 per cent of the respondents said that they offer internships for PhDs for a year in their premises, and students can also do PhD at these companies.

In order to continuously train the human resources, access to latest scientific journals are required. Some of the standard journals from abroad are expensive and not all the universities in India subscribe them. Even if they do, they are used only as a reference material. In this context, except for 31 per cent of the companies who said that their company subscribe to all the required online journals, the rest strongly felt the need for it. 10 per cent also viewed that the government should set up a common shared resources library in the proposed biotech park in Karnataka and Gujarat.

4.5 Public Private Partnership

In India, the public research institutions have played a significant role in the development of the bio pharmaceutical industry. Notable among these are partnerships with Indian Institute of Science, which has transferred the Hepatitis B technology. Centre for Biochemical technology has transferred technology regarding lysostaphin and staphylokinase. Indian Institute of Virology has transferred the technology regarding hepatitis A.

National Institute of Health, US is presently involved in transferring technology regarding Rota virus vaccines. This invention was developed by Dr, Kapikian at NIAID of NIH and commercialised by Wyeth Pharmaceuticals. Licenses have been issued to 8 organisations out of

which three are in India namely, Bharat Biotech, Shantha Biotech, and Serum Institute. Licensees will receive training at NIH. The terms of license would be based on each licensee's mission. Salicrup (2007) writes that the NIH Office of the Technology Transfer (OTT) in collaboration with several institutes around the world has launched an International Technology Transfer Training Program. This program provides exposure and practical experience in international technology transfer, negotiations, licensing and commercialization of technologies and examples of effective public-private partnerships for innovation. He also adds that the NIHOTT and the technology transfer offices of several US universities have recently developed and implemented a data base of neglected disease technologies available for licensing from these institutions which would be an important resource and capacity building tool for universities and research centres in developing countries. This should help the Indian companies to focus on neglected diseases, where already a few respondents are working. Such efforts would help the government to meet the 'health for all' objective.

Besides the collaboration with the academic institutions, companies also join hands for pilot scale processes. A few of the respondents have also received funds from the Department of Biotechnology for their projects.

A respondent voiced his concern about the lack of cGLP certification in some of the public research institutes. According to him, adequate emphasis is not paid to the documentation procedure in such institutes. In the absence of proper documentation that details every stage in the development of a molecule from the stage of invention, it becomes difficult to commercialise the same in the regulated markets where utmost importance is given to the documentation procedure. A few other respondents also said that they partner with the public research institutions to do very basic research or analytical development or to study the protein structure. While there are evidences of this sort, however not many respondents have tried to obtain and commercialise the patents filed by the CSIR. It is said that the patent commercialisation rate stands at 2-3 per cent at the national level.

Thus, the above discussion shows that the emerging biogeneric industry faces number of issues ranging from intellectual property to labour. However, since due to various constraints the

chosen companies have decided to tread cautiously in the development of bio-similars. Hence, the concerns of the West as we saw in the discussion on the prevalence of Anti-commons are not observed. However, IP is a concern. Nevertheless, since new product development by the biopharma is far away, presently, the patent issues are not as binding as the labour or finance.

Section 5: Conclusion

Biotechnology in the field of health care promises answers for many diseases which have remained mystery to the researchers. Theory and evidence show that intellectual protection does encourage innovation particularly in the health care. However, the conflict between the private interests and the public good causes concern. In this paper, we presented a discussion from the heartlands of biotechnology where the intellectual property protection could lead to situations of anti commons there by useful innovations remain under utilised. But such situations have been averted by effective non exclusive licensing procedures. While this has promoted research and dissemination of knowledge in the field of biotechnology, it has not resulted in the promotion of generic products to the proprietary innovator products. While one of the reasons is the complexity of the proteins and molecules used, prevent the usual procedures of bioequivalence to be applied to these products, the pressure of the innovator industry on the governments have also slowed the process. Hence, guidelines are available only for a few products. In the context of India, India so far has allowed a limited number of products and treads cautiously going through the evidences available elsewhere.

It was in this context that we have looked at the emerging Indian biopharmaceutical industry. Though in terms of number biopharmaceutical would constitute less than 3 per cent of the total pharmaceutical industry in India, this industry in India has already got a strong foothold in the field of vaccines where the public research institutions have played a prominent role in transferring the know how. In the case of diagnostic kits there are no patents and a few manufacturers are also manufacturing the antigens required for these kits. This leaves the field of recombinant therapeutics, where the challenge lies. Here all the companies are engaged in the production of drugs aimed at cancer, diabetics and other life style diseases. While it caters to the needs of the domestic sector as well, all the companies have a lot of emphasis on the export

markets. With this emphasis, majority of the units have invested in setting up their manufacturing and R&D facilities according to some of the international regulatory standards. All the companies are engaged in the production of bio generics only. Our study shows that these companies want to tread cautiously in this sector and do not want to get entangled in any patent infringement process. The IP department of each of the company advises the company in this regard. In the process, the Indian companies have created a lot of process innovations which have been patented. Very few companies are engaged in new product development where product patent application has been filed. At this juncture of the growth of the industry, it is evident that the companies are all concentrated on producing the generics alone which would help India's population, as well as those of other countries which are dependent on the Indian drugs. The Indian companies are also constrained by the fact that they are not backed by adequate venture capital funds. All the machinery required in this field need to be imported. The other constraint faced by the company is in the area of getting trained manpower in different areas of operation and retaining them.

While the domestic regulatory process need to approve the product to be pursued, the patent debate suggests that companies engaged in the production of biopharmaceuticals will have to be supported by a good IP team to go through the patent landscape covering the product and the research tools and find an alternate way of process. This could be a time consuming but in order to avoid any patent litigations this would be the way out. But looking at the other constraints faced by the industry in terms of finance, infrastructure and manpower resources, it appears that presently the intellectual property protection is not hindering the growth of the bio generics, but the evolution of the industry could take some more time.

Though presently the production concentration appear to be in oncology and diabetics yet the promise shown in the area of neglected diseases brings lot of hope for emerging economies. As experienced in the pharmaceutical sector earlier, India's development in the field of biopharmaceutical sector would not only meet the domestic health needs but also of other countries and help in achieving the health related millennium development goals.

Table 1: Estimated Cost of Development of Recombinant Cell Lines

Type of expression cell	Estimated cost	Specific costs entering the estimation
Bacteria E.Coli	0.1 to 0.2 US\$mn	Molecular biology at the shake flask level Analysis and evaluation of target proteins by Elisa Finding the authenticity of polynucleotide sequence by PCR method
Yeast	0.2 to 0.6 US \$mn	Development of clone in lab scale Standardization of the process in small fermenters Isolation of protein from the yeast
Animal Mammalian cell lines	0.4 to 1 US \$mn	Development and screening of clones Analytical methods for testing the absence of opportunistic organisms

Source: Table 6, Maria et al (2004)

Table 2: Patent Details of a Few Bio Pharmaceuticals

Brand	Active Substances	Marketer	Year of Approval	Biogenics under development	2003 Sales in \$ millions
Epogen	Epoetin alfa	Amgen	1989	Yes	2400
Procrit	Epoetin alfa	Ortho Biotech	1990	Yes	3984
Neupoge	Filgrastim	Amgen	1991	Yes	1300
Humulin	50% human insulinsophane suspension 50% human insulin (recombinant DNA origin)	Eli Lilly	1992	Yes	1060
Intron A	Interferon alfa 2b, recombinant	Schering Plough	1986	Yes	1851
Avonex	Interferon beta 1a	Biogen	1996	Yes	1168
Engerix B	Hepatitis B vaccine, recombinant	GlaxoSmithKline	1989	Yes	540*
Rebif	Interferon beta 1a	Ares-Serono	2002	No	630.8
Neo Recormon	Epoetin beta	Roche	1991	No	998
Cerzyme/ Cerdase	Glucocerebrosidase	Genzyme	2003/1991	No	734
Humatrope	Somatropin	Eli Lilly	1987	Yes	371
ReoPro	Abcicimab	Eli Lilly/Centocor	1994	No	364
Betaseron	Interferon beta 1b	Schering AG	1993	Yes	929
Kogenate	Antihemophilic factor, recombinant	Bayer	2000	No	497
Enbrel	Etanercept	Amgen	1998	No	1300

Note: *sales figures for 1999, Source: Yakatan Seth and Clifford Mintz (2005)

Table 3: Details of Biotech Patents Filed in Indian Patent Office 1995-2003

Area	Number of Patents filed
Protein Enzyme	700
Bacteria Bacillus	236
Fungi (including fungicides)	219
Virus	162
Therapy	138
Gene	136
Vaccine	123
Sequence	120
Nuclein Acid RNA	115
Fermentation	109
Antigen	88
Vector (plasmids&phages	66
Mutation	54
Transgenic	47
Microorganism	45

Source: Intellectual Property Rights (IPR), Vol.10, No.6-7, June- July 2004.

Table 4**Select Prices of Biotech products Discussed in Price Control Debates**

Product	Indication	Average monthly cost@
Zevalin (Ibritomomab)	Lymphoma	\$24,000
Erbixax (Cetuximab)	Colorectal cancer	\$ 17,000
Corozyme (imiglucerase)	Gaucher disease	\$15,000
Avastin (bevacizumab)	Colorectal cancer	\$4,400-\$8,333
Zavesca (miglustat)	Gaucher disease	\$4,200
Herceptin (tratuzumab)	Breast cancer	\$3250

@ Dosing duration of all medicines is highly variable but most regimens require at least one month

Source: Stephen Herrera (2006), Price Controls: Preparing for the Unthinkable, NBT, VOI24, No.3, March 2006.

Table 5: Commercially Approved Recombinant Therapeutics Approved for Marketing in India

Sr.No.	Molecules	Therapeutic applications
1	Human insulin	Diabetes
2	Erythropoietin	Treatment of anaemia
3	Hepatitis B vaccine (recombinant surface antigen based)	Immunization against Hepatitis B
4	Human growth hormone	Deficiency of growth hormone in children
5	Interleukin 2	Renal cell carcinoma
6	Interleukin 11	Thrombocytopenia
7	Granulocyte Colony Stimulating Factor	Chemotherapy induced neutropenia
8	Granulocyte Macrophage Colony Stimulating Factor	Chemotherapy induced neutropenia
9	Interferon 2Alpha	Chronic myeloid leukemia
10	Interferon 2Beta	Chronic myeloid leukemia, Hepatitis B and Hepatitis C
11	Interferons Gamma	Chronic granulomatous disease and Severe malignant osteopetrosis
12	Streptokinase	Acute myocardial infarction
13	Tissue Plasminogen Activator	Acute myocardial infarction
14	Blood factor VIII	Haemophilia type A
15	Follicle stimulating hormone	Reproductive disorders
16	Teriparatide (Forteo)	Osteoporosis
17	Drerecogin (Xigris) alpha	Severe sepsis
18	Platelet Derived Growth Factor (PDGF)	Bone marrow induction and osteoblasts proliferation
19	Epidermal Growth factor (EGF)	Mitogenesis and organ morphogenesis
20	Eptacogalpa (r-F VIIa) r-coagulation factor	Haemorrhages, congenital or acquired hemophilia

Source: Department of Biotechnology, Government of India

Table 6. Product Profile of the Chosen Companies

Company	biotherapeutics	Products in pipeline	recognised by	Patents filed	collaboration	app.no. of R&D people
1	several low volume molecules for gastrointestinal respiratory,cardiovascular, anti-diarrheal, tetanus toxoid (tt), diphtheria detatus (dt), Diphtheriaia detanus whole cell pertusis (dtpw), anti tetanus serum equine (ats) and hepatitis B vaccine. Infectives and allergy medicines infectives and allergy medicines	hemophilus influenza type B (hib 2005) dtpw-hbv combination (2005), dtpw-hib combination (2006), dtpw hbv-hib combination.	WHO, US FDA		domestic and international	30
2	generic filgrastim or gcsf, generic rituximab (Monoclonal antibody)	out of the 9 products in pipeline, mostly in oncology: 2 are in toxicological study stage, 5 in process development stage of which 2 are in late stage and 3 early stage and 2 are in cell line development	US FDA, MHRA, UK MCC (SA), TGA (Australisa Anvisa (Brazil, TPP, Canada	process patents filed	domestic and abroad	800
3	tacrolimus and EPO meningococcal meningitis**, universal meningococcal meningities, Heamo philus influenza B-Hib, DTP+HIB+Hep B combination. Hepatitis A+B combination	NDDS oral delivery of insulin, oral delivery of hepatitis B vaccine, pegylation of protein drugs for sustained release, multiple myeloma, Baretts esophageal cancer, colon cancer, breast cancer				50
4	number of diabetic products and recombinant human insulin, GCSF, monoclonal antibodies, erythropoietin products in oncology, nephrology, cardiology, diabetology streptokinase	oral insulin, MAB for hematological malignancies, inflammmation, and autoimmune disorders cardiovascular, inflammation, oncology, are in preclinical stage	ISO 9001, USFDA, GMP	800 applications of which 130 have been granted	domestic and abroad	100

Company	biotherapeutics	Products in pipeline	recognised by	Patents filed	collaboration	app.no. of R&D people
5	Cesium chloride free recombinant Hepatitis B vaccine, typhoid vaccine, probiotic yeast, poliomyelites vaccine, anti rabies vaccine thiomersal free hepatitis b vaccine, tetanus vaccine, scorpion venom anti serum, zinc with ORS, recombinant epidermal growth factor gel for diabetic foot ulcer, growth factor gel for burns and skin graft, streptokinase, heparin sodium, progesterone injection etc.	japanese encephalitis, malaria vaccine candidates PVrII, rotavirus vaccine candidates, ORV116E Anti infectives, Lysostaphin, combination probiotics, chikunguniya vaccine, pandemic influenza vaccine.	KFDA, USFDA, UKMCA WHO	6 patents filed	domestic and abroad a number of	80
6	peg rhu GCSF, rHu Gcsf, rHu EPO, rHu interferon alpha 2b	NDDS for proteins, a cloning facility, developing MABs, cytokines, hormones and blood factors, G8, cancer vaccine	EMEA, WHO, US FDA	NA	NA	80
7		novel expression systems, development of product specific bioassays and designing of novel animal component free production media, generation of over expressing stable cell lines development of proprietary expression platforms, research on TB, diagnostic kits		patents filed	domestic and abroad	50
8	streptokinase, sodium Hyaluronate, anticancer biotherapeutics, diagnostics using recombinant antigens and natural thrombolites anti rabies	diagnostics for HIV, thrombolites for myocardial infarction, prop-biotic, immunoprophylaxis, diagnosis of hepatitis C, therapeutics for cancer, viral hepatitis, diabetes mellitus and anemia.	USFDA, TGA, MCA, MCC	anumber of patents on the chemistry side		150

Company	biotherapeutics	Products in pipeline	recognised by	Patents filed	collaboration	app.no. of R&D people
9		cloning, fermentation and purification of therapeutic proteins and vaccines, therapeutics aimed at pain, diabetes, dyslipidemia, arthrities, inflammation and plague are in pahse II, phase I and pre clinical development stage. Interferon alpha, GCF, EPO	US FDA	more than 108 patentsl several of them been granted		300
10	penicillin G Amidase Enzyme, lovastatin, pravastatin, simvastatin and tacrolimus	three drugs for immunosuppressant	US FDA	NA	NA	
11	biologics and protein pharmaceuticals for osteoarthritis, anti coagulants, gyneaecology and anti cancer segement	NA	WHO GMP, US FDA	NA	NA	60
12	antigens for Hepatitis C and HIV, recombinant human erythropoietin, nephrology segment	human serum albumin, interferon beta, hepatitis c vaccine	DSIR	2 US Patents	abroad	30
13		process development, peptides, biodegradable implant injection is at pre clinical stage	UK MHRA, USFDA	number of patents filed		
14	Recombinant human erythropoietin,Granulocyte colony stimulating factor-Filgrastim, streptokinase	Research on Monoclonal antibodies and recombinant technology NDDS	US FDA, MHRA, TGA, NAM GCC, Anvisa, Invima	NA	NA	60

Company	biotherapeutics	Products in pipeline	recognised by	Patents filed	collaboration	app.no. of R&D people
15	has developed sensitive assays for screening of new molecules for in house drug discovery, development of recombinant clones for production of therapeutic proteins, achieved hyper expression of two commercially important cytokines in e.coli.	focuses on rDNA in e.coli systems including gene manipulation RTPCR, DNA sequencing, cell cultures and other immunological tests like antibody purification, immunoblotting, ELISA etc plans for novel treatment of parasitic diseases, use of gene expression for drug discovery, expression of therapeutic proteins in mammalian cells	US FDA, Uk, Germany Australia and South africa	219 patents out of which 123 granted		560
16		human insulin based on recombinant DNA technique using saccharomyces cerivesiae, technology characterization and validation in progress	DSIR	domestic, US and EPO	domestic and abroad	40
17	contract research organisation, pharmacological profiling ,biological evaluation of new molecular entities, bioinformatics, clinical research		US FDA, Japan and Brazil			200
18	CRO, invitro assays to screen putative candidates, batch release assays for biotherapeutics, bio similars and biotransformation for APIs		NationalAccreditionBoard for testing and calibration (NABL) accredited,ICS,9001-2000	3 patents		18

Company	biotherapeutics	Products in pipeline	recognised by	Patents filed	collaboration	app.no. of R&D people
19	diagnostic test devises for hepatitis, pregnancy, hepatitis HIV 1&2,, malaria, cancer, other infectious diseases tests, elisa tests, iimunology and rheumatorlogy tests, haemotology tests and other clini clinical chemistry tests, instruments, proteins and reagents, immunoglobulins and recombinant proteins	HIV-!& 2 Western Blot, HIV-1&2 PCR tests, Leprosy test kits pregnancy elisa kits, latex tet kits and tuberculosis test kits.	GMP certified		domestic	12
Source : interview with companies and website of the chosen companies						

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