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Patents and Biopharmaceuticals in India: Emerging Issues

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Abstract

Modern biotechnology has useful applications in the field of medicines with new therapeutics for chronic and in certain diseases that were considered non-treatable so far. The fact that biopharmaceuticals are made of living organisms in their natural or modified form, controversies surround patenting new innovations. This paper highlights the status of the Indian biopharmaceutical industry and also makes a comparison with the global scenario. It also discusses the current situation regarding patenting biopharmaceuticals in India. The discussion on patenting biopharmaceuticals points out that patenting research tools can actually prevent further research, access to diagnosis and access to medicines. India while providing for patenting of microorganisms, is also simultaneously working on defining patentability in a TRIPS compatiable manner. Prevailing regulatory procedures also prove that entry of generics in this sector will be delayed due to lack of clear procedures. Indian biopharmaceutical industry has good potential in biogenerics sector, but the limited R&D would be a constraint to enter the arena of new product development and taking the product through different stages of clinical trials. Already established biopharmaceutical companies have proved themselves in the field of vaccines and recombinant therapies particularly in global diseases such as diabetes and cancer. More entrants to the biogenerics would help in the reduction of the price of such therapies. Nevertheless, the governments decision on the patentability criterion and data exclusivity would decide the course of further investment in the generics and new product development.

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N. Lalitha, Diana Joseph[•]

1 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'. Modern biotechnology as distinct from the classical fermentation technology began in the 1970s, with the two basic techniques of recombinant DNA technology and hybridoma technology. In recombinant DNA technology, also referred to as gene splicing or genetic engineering, genetic material from an external source is inserted in to a cell in such a way that it causes the production of a desired protein by the cell. In hybridoma technology different types of immune cell are fused together to form a hybrid cell line producing monoclonal antibodies. The techniques of genetic engineering are being applied to replace missing or defective genes in humans or to produce transgenic animals and plants and thus have tremendous application in medical and agricultural sector. Genomics has an important role in the field of pharmaceuticals with its important application in gene therapy particularly in understanding the root cause of certain diseases and in screening for new drugs. But as the research in this area is indicating use in hitherto new medical therapies, intellectual protection governing biopharmaceutical pose new challenges, which could hamper further research or generics coming up in this sector. Microorganisms contain living organisms and hence both ethical and moral issues govern protection of living organisms. Hence, there is no uniformity in the position taken by various governments concerning patenting microorganisms. This paper attempts to understand the status of the Indian biopharmaceutical sector and its growth prospects in the context of the (a) developments that are taking place in the biopharmaceuticals elsewhere and (b) recent amendments made to the Indian patent Act. This paper is organized as follows. Patenting microorganisms elsewhere and in India is

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detailed in Section 2. Section 3 provides the status of biopharmaceutical industry in India. Section 4 presents opportunities and challenges surrounding the development of biogenerics. Section 5 presents the summary.

2 Patenting Micro Organisms

There have been certain landmark judgments on granting patents concerning important biotech innovations, which are briefly mentioned here to highlight the viewpoints that changed over time. The first patent involving microorganism was the Louis Pasteur's patent on `yeast ' that was granted in the US in 1873 as an article of manufacture. After this, till the late '80s there had been a self-imposed moratorium on patenting live organisms in the US. However, in other countries some developments took place. For instance, in 1969, the Supreme Court of the Federal Republic of Germany held a judgment in the red dove case. Patentability of the invention in this case was denied by the Supreme Court which held that the method of breeding doves having red feathers lacked reproducibility (breeding process or creating process) which begins with a variety of the doves and ends with the desired red doves after going through the process of mating and selection. The decision made in the red dove was actually equivalent to denying patentability of animals even though the Supreme Court indicated that inventions related to living organisms including animals are theoretically patentable *if they were produced by any other method. (Emphasis added by us).*

Again, in 1975, the same Court delivered a judgment in the Baker's Yeast case where it was stated that, the microbiological method and the products thereof should not be excluded from patentability for the sole reason that the microorganism is a living organism, thus recognizing the patentability of microorganisms. This judgment indicated further that in order to render the present microorganism patentable, not only evidence for propagation from the culture is needed, but also the process of producing the present microorganism from a starting microorganism must be furnished (reproducibility by breeding process or creating process). Though patent was granted in this case, the Supreme Court ultimately revoked it for failing to meet the above conditions. It was this judgment, which made clear that microorganisms are patentable subject matter.

In 1980, Anand Charkabarty filed a patent claim in the US on a new strain of bacteria that was produced artificially and was capable of feeding on and dispersing the oil slicks. The patent controller Diamond dismissed this patent application on the grounds that it involved the living organism. The Supreme Court of the US however decided that the invention involved a new strain of bacteria that was produced *artificially* by *human intervention* and hence is a *patentable invention* (emphasis added by us). The case generated a lot of interest because the final product that would be sold would be the bacterial strain itself and hence `it was important to obtain a per se claim to the microorganism'. Thus this claim satisfied the patentability criteria of novelty, non-obviousness and utility. It may be noted that the British patent office had already granted a patent for this in the year 1976. The British patent office more or less follows similar criteria for granting patents except for the utility criterion of the US. The UK patent office requires an invention to be useful in any kind of industry or industrial application and should not be used as a method of treatment (Malathy et al 2005). Thus, both UK and US agree that in order to be eligible for patenting, a microorganism should have been produced using an artificial method involving human intervention.

Following the Chakrabarty case, the US started taking a more liberal view of patenting of animals and plants. The first US patent on a multicellular organism was granted in 1987 and in 1988, a US patent was issued on the oncomouse invented by Harvard scientists. The oncomouse was a genetically modified mouse carrying an oncogene thus making the transgenic mouse highly susceptible to cancer. The grant of the patent was questioned on the public order and morality issue and `degrading animals to the level of property'. In the UK, this patent claim was initially refused on the grounds that it was an animal variety and the refusal was further appealed. Finally, patent was granted on the grounds that it was a `transgenic variety'. However, it was decided that patent claims on animal varieties would be examined and granted on a case-by-case basis. No other patent on animal was issued till 1993, during which it was made clear that patenting of any life form would be allowed only if it involved a human and technical intervention in its production. Thus, transgenic plants were brought under patentability. Though the US takes the view that anything under the Sun is patentable' patenting of human beings is not allowed (thus it rules out patenting of cloned human beings), as this will be against the US Constitution that prohibits slavery and thus rules against any property rights on individual human beings.

2.1 Patenting of Microorganisms in India

The TRIPS Agreement via the articles 27.1 and 27.3b has broadened the area of coverage of patents by stating that `*patents shall be available for any inventions, whether products or processes, in all fields of technology, provided they are new, involve an inventive step and are capable of industrial application'.* Since, this phrase would bring in all fields of technology under its fold, Article 27.3b states that `*members may exclude from patentability plants and animals other than microorganisms and essentially biological and microbiological processes. However, members shall provide for the protection of plant varieties either by patents or by an effective sui-generis system or by any combination thereof*[1]*'. The provisions of this sub-paragraph shall be reviewed four years after the date of entry into force of the WTO Agreement'*[2] Microorganism itself has been defined broadly so as to include not only the bacteria and fungi but also viruses, animal and plant cells, it is up to the member countries to adopt suitable definition.

In India, the amendments made to the Indian Patents Act in 2002[3] brought significant additions to the existing list of what are not considered as inventions in the Indian patent system. A few of these 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; (c) plants and animals in whole or any part thereof other than microorganisms but including seeds, varieties and species and essentially biological processes for production and propagation of plants and animals; (d) 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

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1 While US protects its plant varieties by patent protection, India has developed a sui-generis system to protect the plant varieties called, `Protection of Plant Varieties and Farmers Right Act, 2001'. This has already been enacted and became operational with the establishment of Protection of Plant Varieties and Farmers Rights Authority under the chairmanship of Dr Nagarajan, Director, Indian Agriculture Research Institute (Down to Earth, 2005).

2 Keayla (2006) observes though the mandated review process started in 1999, the WTO has not been able to come to an agreed solution covering article 27 3 (b).

3 This section draws from IPR Bulletin, Vol8, No6, 2002.

patentability if the same includes microorganisms. Microorganisms include both non-biological and microbiological processes. Hence, while genetically modified organisms would fit the criteria of patentability, biological material such as cell lines and genes cannot be patented unless there is human invention involved and they qualify for the category of microorganisms. Therefore, it should be left to the national policy to carefully decide what are patentable micro organisms. Following the debate in the parliament in April 2005 on the amendments made, a five-member panel under the chairmanship of Dr. Mashelkar has been set up in April 2005 to recommend appropriate definition of `patentability'. The terms of reference of the panel are 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 will also study if it would be TRIPs compatible to exclude microorganisms from patenting. However, though this committee met thrice an agreeable solution has not been arrived so far. It is important that a solution is arrived at for this, otherwise the patent offices will be spending lot of time in litigation[4]. Similarly a high level committee has also been appointed to look at `whether data protection can be offered under the existing legal provisions or an appropriate new dispensation is required for this purpose'[5] is yet to submit its recommendations. Both these committees recommendations will have significant implication on the regulatory procedures concerning manufacture and investment in biogenerics, as well as new investment in this area.

According to Keayla (2005), microorganisms occurring in nature are not patentable since these are discoveries and not inventions. Nevertheless, he opines that genetically modified organisms perform certain activities and only such specific activity can be patented as process patents[6]. It may be worth mentioning here the Dimmanico case, which is a landmark case in the Indian biotech patent debate that is comparable with the Diamond- 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 could be allowed in a case where a living organism formed a part of the substance being manufactured. The Calcutta patent office rejected the claim in

[4] Pharmabiz, October 19, 2005
[5] Pharmabiz, May 15, 2006
[6] Express Pharma Pulse, June 9, 2005.

2002 saying it did not fall within the purview of the patentable criteria[7]. The Court nevertheless 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.

With this background, in the following section, we present the status of the Indian biopharmaceutical sector.

3 Indian Biopharmaceutical Industry[8]

Before we discuss the Indian biopharmaceutical scenario, a brief highlight of the global biopharma industry would be helpful in understanding the status of the Indian biopharmaceutical sector. A survey conducted by pharmaceutical manufacturers association in the US (PhRMA) suggests that about 144 companies targeting 200 diseases are developing about 371 biotechnology medicines. In the US, R&D (both domestic and abroad) by PhRMA alone increased from mere $ 2 billion in 1980 to $ 38.8 billion in 2004. A substantial jump in the investment is observed between 1990-2000 perhaps indicating the transformation of several traditional pharmaceutical companies to biopharma companies which has provided a spurt to the growth of this sector (Table 1).

Table 2 presents the top 10 global biopharmaceutical companies and the revenue earned by them. The global biopharmaceutical segment grew by 24 per cent to reach a level of US$ 33.3 billion by the end of 2003 and is expected to register US$ 59 billion by the end of 2010. In 2002-03, more than 40 per cent of new drug applications were noticed as biotech based. During this period, the global biotechnology companies had introduced 7 blockbuster biological drugs.

Within the biopharmaceutical market, the global vaccine market was estimated to be around US$ 6 billion in the year 2002. With a compound annual growth rate (CAGR) of 10 per cent, it is estimated to reach US $10 billion by 2006. Large pharmaceutical companies such as Aventis, Glaxo Smithkline (GSK), Merck and Wyeth account for approximately 85 per cent of the global vaccine sales. The

[7] 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

[8] This section draws from `An Analytical Report on the Biotechnology Sector in Gujarat' (undated).

global market for clinical diagnostics was estimated to be growing at 4-5 per cent per annum in 2002. In 2003, nearly 21 new molecular diagnostic products were cleared to seek the Food and Drug Administration's (of the US) approval in 2004.

In the global biotherapeutics segment, the sales of biotherapeutics are expected to increase from US$ 1439 millions to US $46093 millions in 2005 (Maria et al 2004) as presented in Table 3. This table reports that sales of biotherapeutics doubled between 1990 and 1995, and a steady growth is observed in the later years. Particularly EPOs, Alpha Interferon, GSF (granulocyte stimulating factor) and GMSCF have contributed to this significant sales[9]. The value of new products that were expected to be introduced in 2005 was estimated at $32959 million.

The biopharmaceutical sector in India consists of mainly dedicated start-ups and existing pharmaceutical companies that have diversified into biopharmaceuticals. In the public sector, we have only one unit producing vaccines namely Bharat Immunologicals and Biologicals Corporation Ltd. BIBCL was set up to manufacture oral polio vaccine (OPV) in 1989 and works towards eradication of malaria from the country. This unit started manufacture in 1996 under cGMP (current good manufacturing practices) conditions to supply to the national immunization programme. During 2004-05, it manufactured and supplied 120 million doses of OPV. The Indian Vaccine Corporation Ltd was established in March 1989 as a joint venture unit to promote research and manufacture vaccines. But due to change in product mix and non-availability of viro cell technology from Pasteur Merieux Serum and Vaccines, France, this project has

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9 Erythropoietin, or EPO, is used to treat severe anemia in these people whose kidneys are not working properly. EPO may also be used to prevent or treat anemia caused by other conditions, such as AIDS, cancer, or surgery, kidney diseases and dialysis.

Alpha interferon has been approved for therapeutic use against hairy-cell LEUKEMIA and Hepatitis C. It has also been found effective against chronic hepatitis B, a major cause of liver cancer and cirrhosis, as well as for treatment of genital warts and some rare cancers of blood and bone marrow. Nasal sprays containing alpha interferon provide some protection against colds caused by rhinoviruses.

Granulocyte colony-stimulating factor (GCSF) or granulocytemacrophage colony stimulating factor (GMCSF) help the bone marrow to make new white blood cells. When certain cancer medicines fight the cancer cells, they also affect those white blood cells that fight infection. Hence, to help prevent infections when the cancer medicines are used, colony-stimulating factors may be given. Colony stimulating factors also may be used to help the bone marrow recover after bone marrow transplantation and stem cells transplantation.

been put on hold since 1992. Presently, the National Brain Research Centre has been setup in this premise. Though the number of public undertakings operating in the biopharmaceutical sector is limited, yet the public research institutions play a significant role in the growth of private biopharma in the country especially in the recombinant products as shown Table 4. In the case of dedicated start-ups like Bharat Serum and Vaccines, Biocon etc, the collaboration between public research institutes and the private companies is evident. The collaboration could be for contract research, manufacturing or licensing a product. Some of these entrepreneurs have worked with a public research institute before starting their own biotech start-up firms. Nevertheless, as Maria et al observe both the Indian public research institutes and the industry do not have the `scale up competency' necessary to transfer the technology developed on a lab scale to take it to the industrial scale, which has to be nurtured in future.

As mentioned earlier, the important segments of biopharmaceuticals are vaccines, recombinant DNA products and diagnostic kits. 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 and Wockhardt has changed the profile of the vaccine market in India. For instance, after Shantha Biotech introduced its hepatitis B vaccine (shanvac-B) priced at Rs.145 per dose, Glaxo SmithKline was forced to reduce its price. Serum Institute of India, is one of the leading suppliers of vaccine to the WHO. 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 vaccine[10] in Andhra Pradesh. Indian Immunologicals 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 the vaccine market is getting a big boost.

[10] 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.

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 kits. Currently half of the diagnostic kits in the country are imported but the major constraint with these being that they are not designed for Indian climatic conditions or variant Indian strains of microbes. 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, kidney function 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 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 is increasing at the CAGR of 20 per cent.

Table 5 presents the top 10 Indian biopharmaceutical companies and their revenues. Some of these companies' products are briefly mentioned here[11]. Serum Institute of India manufactures vaccines & immuno-biologicals that include tetanus toxoid, diphtheria, measles, mumps, rubella and hepatitis-b vaccines, pharmaceutical formulations, anticancer products, viral vaccines, bacterial vaccines, tetanus vaccine, tetanus toxoid vaccine and plasma products. Panacea Biotech is a leading manufacturer and marketer of vaccines and biotechnology-based products. Its manufacturing plant for Oral Polio Vaccines (OPV) in New Delhi has been awarded the WHO-GMP certification and meets most of the state requirements of OPV under the Pulse Polio Program in India. This company is also developing a host of new vaccines employing genetic engineering and recombinant technology. The Hepatitis B vaccine, Enivac HB, is being manufactured in collaboration with Center for Genetic Engineering and

[11] The information was collected from the relevant companies' websites.

Biotechnology, Havana, Cuba. Amongst other forthcoming vaccines is an Anthrax vaccine. The Indian subsidiary of Eli Lilly has indigenously produced the r-DNA human insulin and named it Huminsulin, which was previously being imported in a fully finished form. The major thrust areas of Eli Lilly's Indian subsidiary include diabetes care, critical care, oncology and cardiovasculars. Novo Nordisk concentrates on three therapeutic areas - diabetes care, growth disorders and women's health and is the leader in diabetes care in India. Venkateshwara Hatcheries is a leading poultry vaccine manufacturer. Wockhardt is among the few Indian pharmaceutical majors to have focused on biotechnology as an engine of growth. The company's pioneering efforts in biotechnology have led to three successful brands -Biovac-B (Hepatitis-B) vaccine, Wepox (erythropoietin) and Wosulin (r-DNA human insulin), which is India's first indigenously developed r-DNA human insulin. With three successful biotechnology products in the market, Wockhardt has received marketing registrations for biopharmaceuticals in three countries. Bharat Biotech, one of India's leading biopharmaceutical players, is engaged in genetic engineering and vaccine production. The company has pioneered the manufacture of the world's first Cesium Chloride free Hepatitis-B vaccine and market recombinant Streptokinase. Biocon has evolved into an integrated biotech enterprise with focus on healthcare and enzymes, ingredients and process aids, industrial enzymes like amylases, proteases, celluloses, human insulin, recombinant protein vaccines. Biocon's focus areas are diabetes and oncology and is working with the US based Surromed Inc. to identify biomarkers for diabetes in the Indian population. Nicholas Piramal India Ltd (NPIL), one of India's pharmaceutical majors, has commenced research activities in biotechnology with a focus on four key areas - new drug discovery, genomics, clinical research and naturals research.

This discussion indicates that Indian biopharma majors are focusing on global diseases, which have marketability both domestically (Table 6) and else where. Particularly there is tremendous market for drugs like insulin, streptoknise and GCF.

3.1 Innovative Capacities in Indian Biopharmaceuticals

As the discussion in the earlier paragraph shows, Indian manufacturers have good potential in diagnostics vaccines and recombinant therapeutics where the

patents have already expired and other biogeneric manufacturers are also in operation. A major constraint would be the small size of investment in R&D. Compared to billions of US $ spent on R&D by the US companies, the Indian companies spend far less on R&D (Table 7), where some of the leaders like Ranbaxy, Reddys, Wockhardt and Biocon, have spent US $53.2, 46, 10.3, 3.3 on R&D respectively, which will be highly inadequate to direct R&D in new product development. This nevertheless doesn't undermine the innovative capacity of the Indian biopharmaceutical industry. A number of biotechnology applications have been filed eventually as process patents, on which some information is available from the Indian Patent Office. As indicated in Table 8 a total of 2378 applications have been filed from the year 1995 to June 2003. A highlight of these applications is that 716 are convention applications and 774 are Patent Cooperation Treaty (PCT) applications[12]. As the Table shows that as many as 700 patents have been filed in the area of protein and enzymes (popularly called as proteomics), followed by bacteria and bacillus. In the field of microorganisms 45 patents have been filed. The other interesting feature is that CSIR has filed (Table 9) as many as 202 applications[13] (only limited information is available on the number of patents filed by companies). This opens up the possibility of whole area of public private partnership in this area of research where the patent lead provided by the CSIR can be licensed/commercialized by the private sector. This concept is not entirely new in the field of biopharmaceuticals since there is already a few well working examples of public sector providing the support for the private sector is evident. There is need for more allocation of financial resources for research in biotechnology as well as for protecting the intellectual property generated. For instance, Rs. 15 crore was allocated in 2003-04 in the Central Budget for Intellectual Property Rights Management (IPRMGT) which was

[12] PCT applications are those which enable the innovators to file their applications in the countries of their choice after studying the marketability for their products in those countries. An important advantage of PCT is that it provides up to 18 months on top of the 12 month priority period (from the date of filing the application) to explore the possibility of marketing the product and seeking patent protection in those countries. Thus, payment of the fees and translation costs associated with national applications are delayed. Another advantage is that PCT applicants receive valuable information about the patentability of their invention in the form of PCT international search Report and Written opinion of the International Searching Authority on the basis on which the applicant can decide to proceed further with filing of applications in different countries.

[13] It should be mentioned that this table consists of information only on those companies, which have filed more than 20 applications. Hence, a few important applications filed by the domestic companies may not find their mention here.

reduced to Rs. 5 crore in 2004-05. The allocation for IPRMGT is meant to `enhance the volume and value of intellectual property (IP) generated by CSIR and to share the best innovation and technology management practices organizationally and with the Indian science and technology (S&T) community at large. The volume of IP rights secured by CSIR (as presented in Table 9) has greatly increased, however the task of realizing adequate and appreciable value from the IPR is yet to be achieved (P.178, Notes on Demands for Grants, 2003-04, Min of S&T, Demand No.81).

Realizing that India needs to strengthen its excellence in this field several international collaborations in the form of bilateral agreements have been formulated which will help in sharing, creating and exchanging ideas in different fields of biotechnology. MOUs have also been signed with both developing and developed countries like US, EU, Australia Denmark, Germany, France, Thailand, Singapore, Switzerland, Ukraine, Tunisia in the fields of agricultural, medical and environmental biotechnology.

The DBT has also designed the biotech park and incubator schemes. This has been designed to help small and medium enterprises that do not have huge financial resources to invest but have the capacity to develop, design and perfect new projects in the incubators and the pilot testing facilities.

4 Opportunities and Challenges in Biopharmaceuticals

There are several areas of openings available for biopharma companies such as: 1. Focusing on new product development; 2. Entering the foray of biogenerics involving recombinants, vaccines; 3. Production of diagnostic kits; 4. Marketing of biogenerics, diagnostic kits; and, 5. Clinical trials and contract research. While resources will be the major constraint in new product development, yet there are opportunities that emerge through outsourcing research and manufacturing. In the following paragraphs a few of these aspects are discussed briefly.

According to the PhRMAs' 2005 annual report, R&D investment in biopharmaceutical by the industry alone stood at $49.3 billion (estimated), whereas the National Institute of Health's investment in industry was $28 billion,

which indicates the growing private investment in this area. Importantly, the R&D investment abroad has increased from 0.4bn in 1990 to $8.2 billion in 2004 (Table 1). Though we do not know the amount that would be invested in India, yet it shows that an increasing amount is invested in R&D outside that would benefit the contract researchers and manufactures including those in India. According to an estimate, 50 per cent of the biopharma manufacturers are expected to outsource their manufacturing in 2008 to India and China, a rise from the present 35 per cent (Business World, Dec12, 2005). This is because of the long gestation period and the high cost of setting up of the project abroad, but the gap between the demand and supply offers the scope for outsourcing. According to the same source, in India, in 2004, the biopharma contract manufacturing was worth $1.7 billion, which is expected to go up to $2 billion in 2006. As evident from Table 10, there is scope for increased outsourcing in all areas. However, a hitch in this option would be whether the facilities in India would be able to meet the demands as a contract manufacturer, which may sometime involve bringing in new investment. If the Indian company has the FDA approved facility for biopharma manufacturing, it can be a partner in conducting clinical trials also.

Elsewhere in the paper, we had discussed the scope for diagnostics and recombinant therapeuticals. In this case, though a number of products are nearing patent expiry/ or have expired, the generic version of such products may not enter the market very soon. A generic drug can be broadly defined as to contain an active substance whose patent has expired and the said drug can be proven to be similar or equivalent to the original product. The question is can these conditions be applied to biogenerics?

Between 2002 and 2007, when the US patents on 35 drugs with global sales of more than $73 billion are expected to expire (Table 11), in the normal course, we would expect the generic competition to increase. But, the problem in biopharmaceuticals is that whereas chemical identity between molecules can be established by assay technologies, it becomes impossible when the identity has to be proven between two macromolecules produced through recombinant technologies. It is recognized that product comparability between innovator and biogeneric product cannot be established based on chemical and biophysical characters alone.

Polostro and Little (2001) list several factors that affect the biogenerics sector, which are briefly mentioned below. (1) The most intricate obstacle of biogenerics

is the non- availability of bulk active biopharmaceuticals through non-patent infringement route and (2) lack of regulations governing biogenerics (particularly in developed countries) is the reason for the lack of development of biogenerics in emerging economies including India.

These authors observe, "traditionally biologicals have been considered by regulatory authorities as a distinct category from synthesized drugs…. For example in Europe, it is not clear whether a biogeneric should be registered through the abbreviated procedure applicable for well defined traditional generics requiring that the generic is essentially similar to a reference product. If not the generic should undergo a full registration process logged with the European Medicines Agency". But, Kulkarni and Dureha (2005) report the changes in the European regulatory system, which had started accepting applications for abbreviated market approval of new bio generics. These guidelines will enable Indian companies to apply for approval to market generic versions of biotech products in Europe. Polostro and Little note that in the US, regulatory guidelines for biologicals and chemicals differ. "Biologicals are approved by the Centre for Biological Evaluation and Research (CBER), under the Public Health Act while conventional drugs are regulated by the US Food, Drugs and Cosmetics Act and are evaluated by the Centre for Drug Evolutional Research…. Biologicals approved under the CBER are specifically excluded from the generic abbreviated approval process[14] that is applied for synthetics. The rational for this is the viewpoint that current bio analytical methods are not adequate to assess bio pharmaceutical equivalent. However, biological approved under the CDER is theoretically subject to generic competition, an element of critical importance. Even if biogenerics were made available for the abbreviated procedure, there is a hurdle to demonstrate essential similarity to a reference product…Unlike synthetic chemicals where equivalence can be demonstrated through full analytical characterization, biopharmaceuticals most often consist of complex substances that are difficult if not impossible to fully characterize from a physico-chemical perspective given the limitation in current analytical techniques".

(3) The third important factor identified by Polostro and Little (2001) is that, in biopharmaceuticals the process itself makes the product. Therefore minor modifications in the bioprocess such as agitation or aeration systems, reactor size or culture media, changes in the cell line or microbial systems can all lead to

[14] Abbreviated New Drug Approval refers to an application for a license to market a generic version of a drug that has already met the statutory standards for safety and effectiveness.

changes in the qualities or properties associated with the biopharmaceuticals. Ultimately such changes could lead to alterations in the safety and efficacy profile, which calls for expensive clinical trials to get the regulatory approval. The stability aspect of biopharmaceuticals also warrants that establishing bioequivalence is difficult. Generally, estimates of a pharmaceutical's shelf life are based on "accelerated" testing, in which the temperature and humidity are considerably higher than the temperature and humidity recommended for commercial storage. Since heat can affect protein structure, the utility of accelerated testing for expiration-dating biotech pharmaceuticals is very limited. To establish expiration dates for protein-based pharmaceuticals, manufacturers necessarily have to conduct real-time stability studies on such preparations under recommended storage conditions. This will prove to be a constraint for manufacturers planning to enter the biogenerics sector since clinical trails are expensive. In new product development, clinical trails account roughly for 40 per cent of the total cost. That is why in the recent years due to inadequate resources to invest and insufficient expertise in clinical trials, pharmaceutical companies license out the new molecules to multinationals for further development on agreed milestone payment basis[15], which may happen with the biopharmaceuticals also.

Another factor that has the potential to hamper biogenerics is the Material Transfer Agreement (MTA)[16]. MTA governs transfer of tangible materials between two organizations 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.

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

[15] Dr. Reddys initiated licensing in 1997 when it developed a molecule for the treatment of diabetes and sold it to Nova nordisk the world leader in the field. Since then other companies which have made some progress in new drug development for example Ranbaxy, Torrent, Glenmark followed the same model' (Choudhury, 2005).

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

Institutional Biosafety Committee and will have to be approved by the Review Committee on Genetic Manipulation and Genetic engineering Approval Committee. According to Bindu Dey, Director, Department of Biotechnology, Government of India, the approval procedure followed for biogenerics so far are a mix of the ones required for new biological entity (NBE) and generics. `The molecules/vaccines have been cleared through three-tier mechanism adopting special abbreviated procedures and by constituting special committees. This has been possible as the gold standard in the form of original products was available to evaluate the physico-chemical and bioequivalence properties of these entities. How far these procedures may apply to new molecules is still to be seen. The first NBE that is going to face the approval system would be the anthrax vaccine. Hence, despite a large number of biogenerics being produced indigenously, the regulatory mechanisms are not very clear as to what has to be followed in case of biogenerics vis-à-vis NBE'[17]. Implicitly, if the properties of the original products are not available in public domain or if they are protected by `data exclusivity' measures, examining the generic products could be difficult in the Indian situation. In the case of research on stem cells is concerned, no progress has been made on the recommendations of a high level committee that was set up three years ago to frame a policy for genomic research including stem cells. The draft guidelines formulated by the Indian Council of Medical Research is also with the government. But no progress has been made on it yet [18].

4.1 IPR and Tragedy of Anticommons

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

[17] Pharmabiz, May 2006.
[18] Pharmabiz, December 27, 2005.

lead to the abandoning of the project altogether. Such a situation could lead to underutilization of research (resources) and thereby deprivation of benefits to the society, which would have otherwise occurred. Popularly referred to as the `tragedy of anticommons', when it happens in the case of pharmaceuticals it means access to new drugs is curbed in the initial stages itself. In future it is extremely unlikely that the situation of anticommons is overcome without legal intervention. Here it may be worth mentioning the controversies concerning the university research in the US, where IPR protection was used as an entry barrier.

4.2 Biotech and University Research[19]

Columbia university on Feb 25, 1980 filed a patent application popularly known as Axel patent or 216 patent (short form of US patent no 4399216). This 216 patent describes an invention as a process for inserting DNA into Eukaryotes to yield transformed cells with foreign DNA integrated into chromosomal DNA that can generate functional proteins. This patent lists 73 claims.

The Axel patent was instrumental in facilitating the development of a number of modern protein based drugs expressed in Eukaryotic vectors. This research was funded by the government. Since Columbia's patent preceded Bayh Dole Act[20] by 10 months, it had to enter into an separate agreement with Columbia to `license the technology provided that these licenses specifically included adequate safeguards against unreasonable royalties and repressive practices and guaranteed that royalties not in any event be in excess of normal trade practice'. Columbia licensed the Axel patent to 30 companies contributing directly to successful development of at least 29 drugs. Between 1983 and 2000, Columbia had collected $400 million by way of license fees. The Association of University Technology Managers Survey (2001) observed that North American Universities, research institutes and hospitals had collected $1.071billion by way of royalties from 13,000 patents and Columbia topped the list for getting nearly

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19 This section draws from the Axel patent litigation appeared in Harvard journal.

20 In the 60s and 70s there was disagreement within the US government to come to a conclusion on whether inventions by private entities carried out with public subsidy can be property of private entity. The Bayh Dole Act enacted on Dec 12, 1980 was designed to encourage commercialization of research by allowing universities to take title to inventions even if the government funded them.

ten per cent of the total amount. Further, as Table 12 shows Columbia filed patents in such a manner that it resulted in prolonging the life of the patent and ensured that it would earn from licensing. Hence, in 2002, eight pharmaceutical and biotech companies filed a suit against Columbia University for prolonging patent protection like a pharmaceutical company thus questioning the doctrine of university commercialization. While the case is going on, the point is such sub-marine patents in biotech prevent further development and the monopolization of the investor continues for a long time.

4.3 Cost of Biotherapuetics

One issue that would bother the public health providers is the enormous cost of the biothreapuetics which are emerging with new therapies in the life threatening diseases segment but mostly involve relatively smaller number of patients. A study carried out by Rijkom et al (1999)[21] on the efficacy and the cost of three biopharmaceutical product indicate interesting results. Nebacumab is a human monoclonal antibody and said to be effective in the treatment of cases of gram-negative bacteramia and cost $3000 a dose. Filgratism is a member of the family of hemetopoietic growth stimulating factors (GCF) (acts against the side effects of chemotherapy). It basically reduces the risk of febrile neutropenia in patients undergoing chemotherapy. It was calculated that the use of GCF would cost $19,567 per case of febrile neutropenia avoided. Recombinant human growth hormone (GH) is administered for children with growth hormone deficiency. According to Rijkom et al (1999), cost considerations have been left out as GH is considered as a substitution therapy and there is no alternative exists. These authors observe that relatively higher cost of the therapy and targeting a relatively smaller number of patients attracts more attention on biopharmaceuticals.

Nicole and Nielson (2003) have studied cases where the patented diagnostic tests are covered under public health schemes. For example in the US, diagnostic tests of haemochromatosis, factor Vleiden, protein C or S deficiencies, antithrombin 3 deficiency and fragile x syndrome are covered in public health benefit schemes. These authors discuss cases where the patent holders

[21] We have not discussed the scientific details such as cost and utility, efficacy and safety of the drug here.

exercise their rights over laboratories providing genetic tests. Implicitly, when such diagnostic tests are provided by the public health schemes, it is going to have a telling effect on the public health budget because of their higher costs (especially in cases where the license fee has to be paid to the patent holder). They also observe that a few of their respondents noted that 50 per cent of their time is spent in identifying how not to get into any patent infringement while another said 90 per cent of the time is spent in inventing around the innovation (p.226).

In India, while entry of Shantha biotech reduced the cost of hepatitis B vaccine, in the case of other recombinant products that are available, we are not sure about the cost and accessibility of these drugs. The note of caution is that, in the absence of biogenerics and lack of competition, price of such products may prevent access. In developed countries, it could affect the public spending on health if these were provided through public health system. Though, in India such medicines may not be provided by common public health system, but may be brought under specific agency dealing with control of specific diseases like National AIDS Contorl or the Direct Observatory Treatment System to control TB. Also since health cover is limited to a small segment of the population, patent protected diagnostic tests and kits would deny access to treatment and the diseases may remain untreated and undetected. The Department of Biotechnology has recommended that the prices of all biotech medicines to be kept of price control for a specific period of time till the biotech companies gather `momentum'[22]. If this suggestion is accepted all the biopharma products would be out of price control where accessibility due to the limited purchasing power of the people could be an issue.

5 Conclusion

The contribution of biotech drugs is in the field of finding the root cause of some of the life threatening diseases. The West is leading the research in this field and India is emerging as a major player by offering its services in the area of diagnostic kits, vaccines and recombinant drugs. This paper discussed the status of biopharmaceutical industry in India and addressed a few areas where patent

[22] Pharmabiz, May 11, 2006 `Pharma Policy May Exclude Biotech Products from Price Control'

production could have adverse effects in delaying generics and accessibility in the case of diagnostic services.

In India, with some of the leading pharmaceutical companies also venturing into biopharmaceuticals, the scope for collaborative efforts, contract manufacturing and marketing is brighter. The strength of the Indian biopharmaceuticals appears to be in biogenerics. Resources are the major constraints for entering new product development. In the area of biogenerics, though there are numbers of medicines that would go off patent in the near future, yet, the generic development in those segments appears to be limited. While regulations governing these biogenerics are yet to evolve, number of patents protecting each product also complicates the biogenerics development besides the inherent problem in establishing equivalence between two biopharmaceutical products. Conducting clinical trials involves lot of resources and the Indian companies will have to nurture their talents in this area. The reports of the two expert committees that are working on the definition of patentability criteria and data exclusivity could have significant implication on the existing biogeneric manufacturers as well as new research and investment in this area. While the therapies suggest enormous scope for medical field, the cost of such treatment may not provide wider access to patients deserving such treatment. Hence the focus of research in this sector in emerging economies should also aim at reducing the cost and make such therapies accessible.

Table 1: Biopharmaceutical Industry Investment in R&D 1980-2004

(in $ billions)

	PhRMA Member Companies			Non-PhRMA member cost	Total Bio-pharmaceutical R&D
Year	Domestic R&D	R&D abroad	Total R&D	Non Pharma Member biotech R&D	
2004@	30.6	8.2	38.8	10.5	49.3
2000	21.4	4.7	26.0	Na	Na
1990	6.8	1.6	8.4	Na	Na
1980	1.5	0.4	2.0	Na	na

Notes: Total value may be affected by rounding. R&D abroad indicates expenditure outside the US by US owned PhRMA member companies and R&D conducted abroad by the US division of foreign owned PhRMA member companies. R&D performed abroad by the foreign division of foreign owned PhRMA member companies is excluded. Domestic R&D includes R&D expenditure in US by all PhRMA member companies.

@ estimated figures

Source. PhRMA (2005).

Table 2: Top Ten Global Biopharma Companies

Company	Revenues in 2003 (US$mn)
Amgen	7868
Genentech	2621
Serono	1858
BiogenIdec	1852
Genzyme	1141
Chiron	1117
Medimmune	993
Gilead	836
Millennium	244
Intermune	154

Source: An Analytical Report on the Biotechnology Sector in Gujarat, Government of Gujarat (not dated) P19

Table 3: Sales of Biotherapeutics Globally (US$mns)

Product	1990	1995	1997	1999	2000	2005
EPO	225	776	1212	1535	1703	3337
Alpha-interferon	182	582	673	837	946	1939
Insulin	310	655	673	816	918	1720
G-scf&GM-CSF	19	194	586	746	823	1542
Growth hormone	221	492	444	5469	592	1011
Hepatitis b vaccine	124	233	299	380	421	987
Monoclonal Ab based products	19	155	216	294	329	674
Factor VIII	136	465	300	306	310	581
TPA	163	78	82	61	115	215
Streptokinase			31	35	39	122
Interleukin 2			34	46	51	105
Gamma interferon			30	35	39	80
Follicle stimulating hormone			20	26	29	59
Beta interferon			24	28	31	57
Others	39	105	153	301	377	705
Total	1439	3812	4778	5992	6743	13134
New products being introduced	0	0				32959
Grand total	1439	3812	4778	5992	6743	46093

Source: Table 8 of Maria et al (2004)

Table 4: Public Private Collaborations for the Development of Recombinant Products in India

Product	Institution	Industrial Partner
Streptokinase	Institute of Microbial Technology (IMTECH)	Cadila, Bharat Biotech
Follicle stimulating hormone	Indian Institute of Science, Bangalore	Cadila
Human Growth Hormone	Indian Institute of Science, Bangalore	Shantha Biotechnics
Hepatitis B Vaccine	M S University of Baroda ICGEB, New Delhi	Biological E ltd
Epidermal Growth Factor	Centre for Biotechnology, New Delhi, MS University of Baroda, Baroda	Bharat Biotech Biological E

Source: Maria, et al (2004)

Table 5: Top Ten BioPharma Companies in India

Company	Revenues in 2003-04 (US $ mn)
Serum Institute of India	123.3
Biocon Ltd.	96.74
Panacea Biotec	33.23
Nicholas Piramal	28.88
Novo Nordisk	24.44
Venkateshwara Hatcheries	0.18
Wockhardt Ltd	18.66
Glaxo SmithKline	17.77
Bharat Serems	17.07
Elilliy	14.99

Source: An Analytical Report on the Biotechnology Sector in Gujarat, Government of Gujarat (not dated)

Table 6: Indian Market for Recombinant Therapeutics (US $mns)

Product	1997	2000	2005
Insulin	7.1	16.7	26.9
Streptokinase	3.1	52.7	9.0
Erythropoitein	2.0	4.1	6.5
Hepatitis B	30.6	45.9	92.3
Human Growth Hormone	1.0	2.3	3.7
Granulocyle colony stimulating factor	4.1	15.3	24.7
Alpha interferon	12.2	16.3	26.5
Gamma interferon		0.1	0.2
Blood factor VIII		0.2	0.3
FSH		3.1	4.9
TPA			
Total	60.2	109.3	195.4

Source: Maria et al (2004)

Table 7: Investment in R&D

Company	Year	R & D	% of revenue	Notes
Biocon	FY 04	$ 3.3	2.6%	Biocon also had capital expenditure on R&D of Rs89.9M ($2.1M). Total excludes $5.3M in R&D and $1.2M in R&D capital expenditures at the Syngene and Clinigene subsidiaries.
Cadila Healthcare	FY 04	$ 14.6	4.4%	
Dr Reddy"s Laboratories	FY 04	$ 46.0	10.0%	$17M allocated for drug discovery.
Lupin	FY 03	$ 5.4$	2.3%	
Nicholas Piramal	FY 04	$ 7.0	2.2%	
Ranbaxy Laboratories Limited	FY 03	$53.2	5.4%	Ranbaxy plans to increase R&D to 10% of revenues.
Sun Pharma	FY 03	$6.2	3.0%	About 30% of the research budget is allocated to innovation-based projects, expected to exceed 70% over the next three years. In addition, capital expenditure on R&D was Rs363.4M ($7.7M).
Torrent Pharma	FY 03	$5.5	5.8%	Half of the R&D budget was spent on discovery projects. In addition, capital expenditure on R&D was Rs52.2M ($1.1M).
Wockhardt	FY 03	$10.3	6.1%	Wockhardt also had capital expenditure on R&D of Rs135.5M ($3M).

Source : BioCentury, August 2, 2004, Vol 12, No 34

Table 8: 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 9: Details of Patent Application by Companies

Name of the Company	No of Patents
American Cyanamid Co	25
Avestha Gengraine tech	23
BAS Aktiengesellschaft	88
CSIR	202
F Hoffman La Roche	36
Hindustan Lever Ltd	28
Nova Nordisk	79
Pfizer	21
Smithkline Becham	35
Proctor and Gamble	55
Zeneca Inc	22
Biocon*	Over 100
Serum Institute of India*	-
Panacea Biotechnology*	93 (48 in black box)
Shantha Biotech*	14 (granted)
Nicholas Piramal*	142
Wockhardt*	150 (3 biotech based)

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

Table 10: Outsourcing Trends by System 2003-08

(figures in %)

Details	2003	2008
All systems	35	47
Yeast	17	33
Microbial Fermentation	42	52
Mammalian Cell culture	21	44

Note: Figures in percentages show the share of biopharma of the West who out source

Source: Business world, December 12, The BioBottleneck

Table 11: Patent Details of a Few Bio Pharmaceuticals

Brand	Active Substances	Marketer	Year of Approval	Biogenerics 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 insulinisophane 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	Epoeitin beta	Roche	1991	No	998
Cerzyme/ Cerdase	Glucocerebrodidase	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	Etanercapt	Amgen	1998	No	1300

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

Table 12: Summary of History and Description of Columbia's Co-Transformation of Patents

Patent	Issue date	Expiration	history	claims
'216	Aug 16,1983	Aug 16, 2000	Application for patent filed on feb 25, 1980	Co-transformation process with selected marker; unlinked and linked DNA1 and DNA 2; protein production and recovery; transformed eukoryotic or mammalian cell
'665	Jan 6, 1987	Aug 16, 2000 Terminal disclaimer	Divisional application filed on august 11, 1983	Co-transformation process using phage or plasmid vehicle
'017	Jan 12, 1993	Aug 16, 2000 Terminal disclaimer	Divisional application filed on June 18, 1991	Transformed CHO Cell with DNA 1 stably integrated in to chromosomal DNA
'275	Sept 24, 2002	Sept 24, 2019	Continuation application filed on June 7, 1995	DNA construct of DNA 1 and DNA 2: DNA 1enclodes glycoprotein of interest; transformed CHO cell with DNA construct incorporated

Source: Harvard Journal of Law and Technology (2004)

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