

## **TRIPS-COMPLIANT NEW PATENTS ACT AND INDIAN PHARMACEUTICAL SECTOR: DIRECTIONS IN STRATEGY AND R & D**

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*With the much awaited amendment in the Patents Act in March 2005, retroactive to Jan. 1, 2005, India has finally met its obligations under the TRIPS agreement. However, this has set a new debate not only in India but also in other developing countries, especially from the African subcontinent, regarding its fallout on the affordability of drugs to poor nations. Within India, the opinions are divided regarding its implications for the survival and growth of the pharmaceutical industry. This article traces the history and the current profile of the Indian pharmaceutical industry, taking note of the prominent changes in the new Act over the last Patents Act of 1970 and presents an analysis on the impact of such changes on the Indian pharmaceutical sector in terms of strategy choices and R&D directions. The study concludes that most dynamic Indian pharmaceutical players are likely to adopt a combination of 'cooperate and compete' strategies to ensure a smooth transition from reverse engineering based to research-based pharmaceutical firms. The analyses also suggest that there may be considerable inflow of outsourcing business to India in the realms of clinical trials, contract research and manufacturing.*

### **INTRODUCTION**

With the substantial amendment in the Indian Patents Law in March 2005 in compliance with the TRIPS (Trade Related Aspects of Intellectual Property Rights) agreement, much debate has centered around the impact of the product patent on the survival and growth of the otherwise booming Indian pharmaceutical sector and its implications for the overwhelming proportion of the poor population's access to medicines in India and other developing countries. It may be noted here that under the TRIPS agreement of WTO, all the signatory states are obliged to provide strong intellectual property rights (IPR) protection to both domestic and foreign entities, and the latest Indian Patents Act is a move towards compliance of TRIPS obligations within the agreed upon timeframe. It may be further pointed out that the importance of IPRs is not universal in nature. They are especially valued in regard to dynamic knowledge sectors such as pharmaceutical and biotechnological products that are costly to develop, easy to replicate and where market spin-off is not considered to be fast enough to ensure a reasonable reward (Mansfield 1994). In the absence of alternative means of appropriation of the benefits of innovation in the pharmaceutical sector and weak patent laws in most of the

countries, global production of medicines turned into a geographically highly concentrated activity, with around 93% of world production located in a few high-income countries where the patent protection has been strong. In fact, five countries—the USA, Japan, Germany, France and the UK—account for two-thirds of the value of all medicines produced (WHO 2004). It may be further pointed out that not only is the learning process involved in the development of pharmaceutical products much more complex (Nogues 1990), the success rate is low as drug discovery is purely a process of trial and error, thereby adding uncertainty regarding the magnitudes of investment as well as returns. The emergence of multiple drug resistant strains of diseases has further added to the unease of policy makers as the discovery and development of new drugs have become the issues of vital concern for national governments and international agencies such as WHO.

The basic objective of this article is to assess the impact of the Indian Patents Act 2005 on the structure and direction of commercial operations of the Indian pharmaceutical industry. Since the latest amendment has much to do with the pharmaceutical sector, the article exclusively focuses on the impact of the latest amendment on this sector. The article is divided into two main sections. Section I deals with the history and current profile of the Indian pharmaceutical industry. It also discusses, though in brief, the points highlighting the fundamental changes in the new patent law over the old one. The Section II assesses the on-going and prospective changes in the pharmaceutical industry in order to ascertain the direction it may take in the future.

## SECTION-I

### THE INDIAN PHARMACEUTICAL INDUSTRY AND RECENT DEVELOPMENTS IN THE INDIAN PATENTS LAW

#### 1. Historical Perspective and Current Profile of the Industry:

The major growth of the Indian pharmaceutical industry can be attributed to the enactment of the Indian patents Act 1970, which came into force in 1972, and was part of a wider set of policies of the Government of India to develop a “self-reliant” pharmaceutical industry. This Act provided for product patents for all inventions except for food, medicine, drugs and substances produced by chemical process. For the latter category, only the process patent was accorded. The patent term was also reduced from 16 years to 5 years from the date of patent approval or 7 years from the date of application, whichever is earlier. The provision of compulsory licensing which provided for the opening of the patented drug for the generic replication by others if the drug was found to be unnecessarily ‘highly priced’ was also made after three years from the date of approval of the patent. This particular provision considerably weakened the patent strength and as a consequence, Indian firms were able to introduce life saving drugs much earlier than what the global strategies of the multinationals would have otherwise permitted (Queen 2005). The cases of immediate replication of proprietary drugs such as Ranitidine (Zantac), Viagra and Antiretrovirals (ARVs) by the Indian pharmaceutical firms can be cited as examples in this regard.

With the amended patents act in place in 1970, the number of drug manufacturing units grew from 2,257 (in 1970), to 5,156 (in 1980), to 16,000 (in 1990) and to over

23,000 (in 2005) with 349 units in the formal sector. In the 1980s, the industry had grown at a rapid rate of 11 percent per annum, which further accelerated to 17 percent per annum during 1990s (Pradhan 2004). The average growth of the industry in the last few years has been about 12%, compared with the growth of the fast-moving consumer goods sector, which has grown approximately at 4.7% (Ganguli 2003). The amount of investment which stood at Rs. 2250 million in 1973, rose to Rs.6000 million by 1982, an almost three times increase over a period of nine years. It further increased to Rs. 18400 million and Rs. 45000 million in 1997-98 and 2002-03 respectively. This industry, which produced only formulations in the pre-1970s era, now manufactures more than 400 bulk drugs making up around 6% of the international bulk drug market. In terms of volume, the composition of the formulation and the bulk drugs has been around 80:20 over the period with only minor fluctuations. More than 85% of the formulations produced in the country are sold in the domestic market. The number of brands in the domestic market, with varying levels of credibility, vintages and therapeutic effectiveness, are over 6,500 in 77 therapeutic segments. Due to such fast growth of low cost domestic producers of the drugs, the market share of multinational companies in the Indian market declined from 75% in 1971 to 27.2% in 2003 (FICCI Report 2005). Essential drugs comprising antibiotics, antibacterial, anti-TB, anti-parasitic, and cardiovascular constitute a major portion of turnover of the industry. This spectacular growth can be attributed mainly to the exemption of this sector from product patents and also to the industry's low capital requirement. Table 1 provides an overview of progress of the Indian pharmaceutical industry.

**Table 1**  
**Indian Pharmaceutical Industry: Growth Indicators (In Rs. Million)**

<i>Particulars</i>	<i>1965-66</i>	<i>1980-81</i>	<i>1997-98</i>	<i>1999-00</i>	<i>2000-01</i>	<i>2002-03</i>
Capital Investment	1,400	5,000	18,400	25,000	29,000	45,000
Production:						
Formulation	1,680	14,400	146,910	197,370	228,870	392,547
Bulk drugs	1,500	12,000	120,680	159,600	183,540	238,659
Trade						
Export	180	2,400	26,230	37,770	45,330	63,908
Import	30.5	464	53,530	72,300	87,340	128,260
R & D expenditure	82	1125	28,680	16,160	29,800	28,650
	30	147.5	2,200	3,200	3,700	6,600

*Source:* Pharmaceutical and Drug Manufacturers. Downloaded on June 16, 2005 from the website: <http://www.pharmaceutical-drug-manufacturers.com/pharma-industry-statistics/growth-indicators.html>, and CII, 2003.

As is evident from Table 1, the pharmaceutical related R&D investment in India has been very low and started picking up only in the early '90s. Prior to the '90s, government R&D was much higher than private R&D, which started changing by the early '90s (Bowonder 1998). On average, most Indian companies spend less than 0.2% of their sales on R&D, although this stands around 4-8% for larger firms. This is insignificant when compared to 10-16% in case of foreign research-based pharma companies. The overwhelming dominance of generic and copycat drugs in the Indian market supports the contention that this investment was primarily reverse engineering

in nature and aimed at process improvements and adaptation of technology (for longer shelves life, maintenance of the effectiveness even without continuous refrigeration facilities etc.), rather than at new product development. This observation is further corroborated by the poor patenting activities of Indian pharmaceutical firms over the same period of time. For instance, during 1975-95, Indian firms sought only 65 out of approximately 100,000 patents approved by US patent office (quoted in Lanjouw 1998). However, while the ease of reverse engineering led to intense competition among Indian firms for market share, it had also effectively blocked the possibility of the development of a collaborative web of networks of research institutes, academia and industry (Ramani 2002).

Another notable feature of the Indian pharmaceutical industry is its capacity to produce drugs at the lowest prices. It is estimated that Indian firms have lower costs—estimated to be one-eighth (in R&D) to one-fifth (in manufacturing) compared with Western firms (Grace 2004). The drug prices in India are among the lowest in the world for several reasons:

- (a) Due to the existence of the process patent since 1972-2004, Indian manufacturers could make bulk drugs and formulations by “reverse engineering” the overseas patented medicines without any obligation of the payment of royalty, license fee or spending much on R&D. As a consequence, drug prices, which were amongst the highest in the world in 1961 (quoted in Hamied 1993), fell substantially after 1972.
- (b) Labour and capital costs are lower (capital costs 50-75% lower) compared with developed countries’ market levels (Ghemawat and Kothavala, 1996).
- (c) The exemption of small-scale units from the Drug Price Control Order (DPCO) and payment of excise duty, led to further reduction in the prices, and to the proliferation of small scale units as the large players in the organised sector started outsourcing their requirements from small-sized companies through loan-licensing arrangements, thus further boosting their growth.
- (d) With the existence of a three tiered *price* control system—on Bulk Drugs, Formulations and Overall Profitability—placed certain drugs (known as scheduled drugs, as they are listed in the first Schedule to the Drug Price Control Order, 1995 (DPCO), 76 in number and accounting for 50% of Indian retail sales) under price controls.

The fast expansion of this sector also resulted in increasing pharmaceutical exports growing at a much higher rate than total exports as is evident from Table 2. It brings to the fore that while there is not much of a difference in the compound growth rate of pharmaceutical imports and aggregate imports, the growth rate of pharmaceutical exports has been far above the aggregate exports. As a consequence, the ratio of pharmaceutical products to the total exports grew from a mere 0.6 percent in 1970-71 to 4.9 percent by 2000-04. The ratio of pharmaceutical imports to total imports, on the other hand, came down from 1.5% in 1970-71 to 0.8 percent in 2003-04. India had moved from the position of net importer to that of net exporter in 1981-82, and had started earning regular trade surpluses in these commodities groups, in increasing magnitude, from the year 1987-88 and is therefore contributing substantially to the trade balance.

**Table 2**  
**Compound Annual Growth Rates (CAGR) of Indian**  
**Pharmaceutical Exports and Imports (%)**

<i>Period</i>	<i>India's Pharmaceutical Exports</i>	<i>India's Total Exports</i>	<i>India's Pharmaceutical Imports</i>	<i>India's Total Imports</i>
1970-71 to 1980-81	26.43	17.85	15.63	22.23
1981-82 to 1994-95	26.48	17.89	18.92	13.70
1995-96 to 2003-04	20.39	14.10	12.32	14.79

*Note:* CAGR has been calculated from semi-log regression model.

*Source:* Calculated from RBI's foreign trade data.

The composition of India's pharmaceutical exports has also radically changed over this period of time. Exports constitute almost 40% of the total production of pharmaceuticals and approximately 30% of total revenues of pharmaceutical companies. India's pharmaceutical exports were to the tune of US \$3.1 billion in 2003-04, a substantial achievement when compared to the figures of US \$11.2 million, US\$85.2 million, US\$565.2 million in 1970-71, 1980-81, and 1990-91 respectively. Of total exports in 2003-04, formulations contributed nearly 54% (down from 76 percent in 1980-81) and the rest 46% (up from 24% in 1980-81) came from bulk drugs. While formulation exports are mainly to the developing countries, bulk drugs are exported to developed nations. Almost 90 percent of the exports are in the off-patent domain. On a region-wide basis, India's biggest export markets are the developing countries with 56% share in 1996-99 followed by developed nations with 29% share, in sharp contrast to China which primarily caters to the markets of developed economies (WHO 2004). Within developing countries, Asia and Pacific countries stand as the most important export destinations for Indian drugs claiming a 36 percent share, followed by Africa with 14.6% share of the total pharmaceutical exports. Among the developed countries, Western Europe and the US are the major destinations. On the import front, despite a decline in the ratio of bulk drugs to the total pharmaceutical imports from 78 percent in 1980-81 to 59 percent in 1998-99, bulk drugs (which are technology intensive, as opposed to manufacture of formulations) continue to overshadow the imports.

India, at present, ranks thirteenth in world production by value but ranks fourth in the volume of pharmaceuticals produced. In volume terms, Indian drugs are estimated to account for more than 20% of global consumption (Goldman Sachs 2004, page 1). The large difference between value and volume arises out of the kind of segment – the high-volume, low-price - that Indian firms cater to. With overall production of \$7.3 billion (finished product domestic consumption, plus exports), Indian firms produce approximately 1.5% of the global pharmaceutical market of \$480 billion (Goldman Sachs 2004). It is a truly amazing turnaround for an industry, which until the sixties was dominated by foreign companies with domestic manufacturing largely limited to two public sector companies.

Apart from having a strong manufacturing base, the Indian pharmaceutical sector also has the largest number of U.S. FDA approved (61 in number) manufacturing facilities outside the U.S. They also have the largest number of Drug Master Files (DMFs) with 74 filings (cumulative total 198) with the US food and drug administration as of March 2005 (37% share of the total), which gives it access to the high-growth international

generic bulk drugs market (*The Financial Express*: June 7, 2005). Major filers from India include Cipla, Dr Reddys', Ranbaxy, Wockhardt, Lupin, Cadila and Aurobindo.

## **2. Patenting in India: Synchronising With the World Order**

The most notable amendment in the Patents (Amendment) Act, 2005 is the deletion of the controversial Section 5 (which granted process patents to the innovators of new food, medicine, drugs and substances produced by chemical process) of the Indian Patents Act, 1970. The new Act also provides protection for 20 years for all categories of inventions except those excluded under Section 3 of the Act. The Act further affirms that the sellers of already-approved generic drugs in India will now have to pay licensing fees. Under the new regime, local drug makers will have to apply for a license to manufacture patented drugs after paying "reasonable" royalty to patent holders if they had been making them after Jan. 1995. The Act stipulates that a patentee who gets a patent through the Mail Box cannot institute procedural changes implemented by the Act including those at both pre-grant and post-grant opposition and reduces the time limit to request examination to 3 years. The Act also curbs "ever-greening" (lengthening the commercial life of a drug through incremental inventions) of patents.

### **SECTION-II**

#### **SHAPING DESTINY: THE INDIAN PHARMACEUTICAL SECTOR IN THE POST-JAN. 1, 2005 ERA**

There are wide ramifications of the latest amended Indian patents law ranging from the domestic to the international drug markets. In an increasingly competitive and rapidly changing economic environment, there is a high likelihood of a radical restructuring of the Indian pharmaceutical industry resulting in mergers, acquisitions, liquidation, creation of brands images and forging strategic in-licensing and/or co-marketing partnerships nationally and globally. The Indian firms may also take a fundamentally different strategic business approach that may help them to refocus so as to adequately respond to current challenges as well as future uncertainties. There are, however, two areas that merit urgent attention for a smooth transition. The first is that there is a strong trend towards globalisation of regulatory and scientific requirement pertaining to safety, efficacy and quality issues where Indian firms may have to be proactive to avoid threat of denial of export markets to them on these bases. The second is that being relatively novice to the generics business in highly regulated markets of developed countries, Indian firms may face difficulties, at least in the transition period, in managing large product portfolios, regulatory filings, scaling up manufacturing, forging alliances, and handling the legal proceedings against them (Grace 2004).

In this regard, it may be pertinent to assess the impact of the changed patents regime on the business behaviour of foreign as well as Indian firms separately so as to develop a better perspective of the overall scenario.

#### **1. Impact on the Business Behaviour of Foreign Pharmaceutical Firms**

Substantial impact of the new Indian patents law is expected to be felt on the willingness of foreign pharmaceutical players to invest in India either through FDI, technology/

product licensing, contract R&D or manufacturing (CRM). However, the choice of the investment instrument largely depends on the quality of enforcement of the law in this regard. If enforcement is found to be weak, there is every probability that foreign direct investment (FDI) will be undertaken but that companies will confine their technologies to their affiliates rather than outsourcing. On a world-wide scale, there is also an increasing trend to in-source the sensitive technologies/product. If enforcement of the IPRs laws is found to be reasonably strong, business and patenting activities of the foreign drug companies are expected to grow. Licensing arrangements for manufacturing and marketing drugs in specific market segments could be one major strategy in this regard. Research studies using data from the European Patent Office have reported that strong enforcement of the patent laws also induces substantial increases in the filing of patent applications by nonresidents in the highly advanced technological areas (Branstetter et al 2004, Lerner 2001, 2002). This is also supported by the fact that foreign entities are seeking an increasing number of patents in India. For instance, out of a total of 8,926 patent applications received by the Indian patent office during 1995-2005 (WTO implementation transition period) a majority of them (i.e., 7,520) belong to foreign entities, while the rest are applications from Indian establishments. However, this is not to say that such an investment may lead to new drug development in India as can be seen from the fact that out of 8,926 patent applications, only 3.6% were related to new drug development. It only implies that with the stronger patent regime in place, the foreign firms will have better incentives to invest in India. They may also be interested in using the potential of the dynamic Indian drug companies by outsourcing R&D jobs to them for the development of new chemical entities (NCE), developing alternate process for manufacturing a particular drug at the expiry of the patent, low-cost API or dosing formulations. In view of the fact that most of the US FDA approved pharmaceutical facilities outside the developed world are located in India, the Indian potential for high product quality at lower costs are likely to be commercially exploited by these firms.

The trends in the recent past also suggest that due to a sharp decline in R&D productivity. This is suggested by the fall in the number of newly approved medicines from an average of over 60 a year in the late 1980s to 52 in 1991 and only 31 in 2001, despite a three fold rise in R&D expenditure between 1990 and 2000 (NIHCM Foundation 2002, Ogg et al, 2000, Pollack 2002, Taylor 2003). Because of rising drug prices and competition from generic drugs, pharmaceutical companies, all over the world are under intense pressure to contain R&D expenses. It may be noted that investments in R&D had reached a whopping \$ 26.4 billion in 2000, close to an average of over 14-20% for the leading companies. These rising R&D costs are prompting manufacturers to develop strategic alliances with small research-based companies. Another important issue that has increased the possibility of R&D outsourcing to India, is the emergence of relatively new fields of genomics and proteomics that have enabled the firms to have multiple drug targets, not all of which the firm would be able to do in-house. In this regard, it may be pointed that the global market for outsourced pharmaceutical research stands at \$60 billion, of which the non-clinical segment accounts for \$21billion and the clinical segment accounts for \$39bn. Given the cost advantage of the Indian firms coupled with the changed IPRs scenario, India may become one of the important destinations for contract research.

The generic firms of the developed world, on the other hand, may pursue strategies to take away major cost advantages from Indian firms by subcontracting the manufacturing of generic drugs to many Indian low cost producers. This trend, in fact, has become visible, with US based generics companies such as Watson, Ivax, and Apotex already involved with such kinds of arrangements with Indian firms (Grace 2004). Although there are still apprehensions about government price controls and bureaucratic delays, the liberalized global economic environment offers better operating leverage to firms investing in India more than ever before.

## **2. Impact of the Changed Patents Regime in India on the Indian Pharmaceutical Industry**

### *2.1. Possible Strategies and Present Trends*

The impact on Indian pharmaceutical sector is, undoubtedly, going to be large enough to push it towards fast restructuring and consolidation. Building upon some studies which have already been conducted to assess the possible impact of the changed scenario (CII 2002, Chaudhary 2003, Dhar and Rao 1992, Grace 2004, Kumar and Pradhan 2003, Lanjouw 1998, Mashelkar 2001, Mishra 2001, Nayyar 1992), we may proceed with the hypothesis that Indian firms, in pursuance of their business objectives, are faced with three new strategic choices: to cooperate, to compete, or to follow a combination of both. It is expected that that Indian firms may not opt for the aggressive competitive mode with established international players, though some of them, especially with relatively deeper pockets, better infrastructure and visionary leadership, may strategize for a combination of 'cooperate (through licensing arrangements, contract R&D, manufacturing and co-marketing) and compete'. Such alliances are also expected to be formed with other Indian firms (e.g., Ranbaxy teaming up with Cipla for marketing Carvedilo). The combination strategy appears to be one good option because India's leading pharmaceutical firms already have achieved a reasonable level of sophistication (Karmali 2004, Kripalani 2004, Merchant 2004, Slater 2003, The Economist, Sept. 6, 2003).

One important question is why Indian firms may prefer some kinds of alliance with the established international firms, at least for the time being. The first and foremost point is that the presence of large international firms gaining further leverage with regard to resources and expertise as a result of mergers and acquisitions, are making it almost impossible for the newly emerging Indian players to compete with them on even terms. Approximately 67.5% of the revenues in this industry is accounted for by the world's top 15 companies, making them highly resource rich (KPMG 2003). The second issue is that Indian pharmaceutical companies have a serious lack of resources and infrastructure needed for conducting animal and human trials for the toxicity and efficacy of drugs under development. However, even if they do have access to the resources through some means, then one confronts a fundamental question: do Indian firms, habituated to the quick and certain returns, have the necessary attitude and patience to wait for such a long period of time where there is no certainty about the return? The considerable gestation lag (ranging from 12 to 16 years) between initiation of research and discovery, development and commercialisation of one's own proprietary products as compared to almost insignificant time period involved in reverse engineering of the

drugs is another most important issue. What are the alternatives available to them? These are the considerations for understanding the probable strategies of Indian firms in the short as well as long term.

Looking at the Indian pharmaceutical scenario, one finds that Indian pharmaceutical firms have traditionally been investing little in R&D as there was no big requirement of funds for process engineering. Though, of late, especially after the signing of the TRIPS agreement, they have become conscious of the need to pump more money into R&D, their investment in R&D is still meager as compared to what the established global firms are spending. For instance, at present, R&D expenditure of the Indian Pharmaceutical industry is around \$ 74 million (0.003% of global R&D) and the spending by the largest Indian company on R&D is around \$ 17 million (0.006% of the largest R&D spending by an MNC). Though these firms have the potential for getting output even with a relatively low level of R&D spending because of lower costs of doing so in India, they may have other problems such as lack of necessary expertise in the basic areas (such as biomedical research, chemical synthesis, process development, clinical testing) and new tools (such as combinatorial chemistry, structure based molecule design and high throughput screening), to smoothly switch over from reverse engineering. Reverse engineering and generic R&D both require much less communication of knowledge across disciplines or therapeutic areas as compared to the innovative pharmaceutical R&D (Henderson et al 1999). Product development research, on the contrary, is just not the development, screening and selection of promising lead compounds of the new drug molecules, it is also about conducting a series of tests to determine safety, efficacy and proper dosage strength and form. It involves huge funds as well as 'out of the box' thinking (Kale 2005). Recent studies indicate that 1 out of 5000-10,000 compounds synthesized during applied research eventually reaches the market (PhRMA, 1995).

Industry estimates also reveal that most of the R&D budget of the major companies is invested in the different stages of clinical evaluation of new products. Pharmaceutical Research and Manufacturers of America (PhRMA) data for the USA in 1998 indicated the breakdown as: Clinical evaluation: 40%, Basic research: 27%, Development of production process: 19%, Implementing regulatory requirements: 7%, Others: 7%. Existing estimates indicate that of 100 drugs that enter the first clinical testing phase, about 70 complete phase I, 33 complete phase II, and 25-30 clear phase III. Only two-thirds of the drugs that enter phase III are ultimately marketed (Lalitha 2003). This suggests that attrition rates are especially severe in earlier research stages. However, as phase III is the more costly R&D stage, one failure out of three produce may still imply a considerable loss of resources (Gambardella 1995). Because of such magnitude of investment involved, even the bigger global players have not been able to come up with many new products and innovations over the last two decades. According to a US FDA report, 84 per cent of new drugs placed on the market by large US firms during the period 1981-88 had little or no potential therapeutic gain over existing drug therapies. Similarly in a study of 775 New Chemical Entities introduced between 1975 and 1989, only 95 were rated to be truly innovative (Lanjouw 1998).

In such an environment there is a high probability that drug firms disadvantaged with resources, experience and research, may opt to orient their R&D towards preparing

and producing generic copies rather than developing/discovering NCEs. Therefore, the short term R&D focus of an Indian firm, having expertise in reverse engineering, is likely to be on building upon the existing research, and consequently opting for line extensions, combination drugs and improved dosage forms of drugs. These are the areas where the existing research infrastructure can be effectively utilized to achieve productive outcome. Consistently increasing R&D and patenting activity (pharmaceutical firms shared 25% of all U.S. patents granted to Indian inventors during 1990-2002) of some of the Indian pharmaceutical firms, as is evident from the doubled share (9% in 1997 to 18% 2002) of pharmaceutical products patents in total patents, (Business Today Jan. 2004), without coming up with any new drug, suggests that the major focus is not on developing NCEs.

The strategy of Indian companies to form strategic alliances with global players, therefore, makes perfect business sense under the given scenario as it considerably reduces the degree of uncertainty for them. In the medium term, the strategy of these firms may be to seek alliance with global firms for conducting clinical trials as it would be difficult for them to do it independently due to resource constraints. The case of two leading Indian drug companies testifies to this difficulty. For example, due to severe resource constraints, Ranbaxy had to out-license one of its urology molecules to Schwarz Pharma and Dr Reddy's also out-licensed one new molecule to Novo Nordisk for clinical development.

The increasing attractiveness of the generic market for the low-cost yet quality conscious producers is another important factor that may keep relatively smaller players across the globe, away from undertaking R&D investment for developing new proprietary products. For example, larger global corporations have pulled out of the low-margin vaccine business (Mercer Management 2003). As a consequence, the number of players in this segment declined from 26 in 1967 to 4 in 2003 (Rao 2003). The stated reasons are: price controls, liability fears and opportunity costs. Despite this declining interest of global pharmaceutical giants, there is a constant increase in the demand for vaccines, more so in developing countries. As a result, 60% of UNICEF's requirement for Expanded Programme on Immunisation vaccines is now being met by India, Indonesia, Cuba, and Brazil. This gives promising leverage to existing Indian players to focus on this niche market.

It can, therefore, be presumed that Indian pharmaceutical firms are likely to avoid direct competition with the established global players and may enter into some kinds of strategic alliance to maximize their benefits. In fact, there appear to be three ways in which the Indian pharmaceutical industry may respond to the change: A) a combined compete and cooperate strategy; B) outsourcing; and C) the formation of alliances.

A. The bigger Indian concerns such as Dr Reddy's Laboratories, Ranbaxy, Sun Pharmaceuticals, Cipla, Wockhardt etc. may follow both the strategies viz., cooperate and compete, simultaneously. There are indications that they are already following a multi-stage strategy of moving up the product value chain and firmly establishing themselves in the global markets (Grace 2004). These strategies are:

- (i) Target plain vanilla generic exports to developed countries' markets in the immediate future by leveraging upon the lower costs.

- (ii) Develop generics with manufacturing complexity such as injectables and lower-risk New Drug Applications (NDAs) in the medium term. They may also concentrate on the value added formulations and newer versions of existing chemical entities facilitating new drug delivery technologies
- (iii) Stepping into the area of New Chemical Entity (NCE) or proprietary drugs in the long term.

The fact that Indian companies who had initiated lawsuits against the MNCs (Ranbaxy with GSK and Matrix lab. with Novartis) have entered into collaboration with them indicates that they are adopting cooperative as well as competing strategies. The established Indian players are also setting up bases in the US as well as crucial European markets such as the UK, France, and Germany either through acquisitions or by setting up greenfield ventures in order to improve customer acceptance in those markets. While Ranbaxy has manufacturing and marketing operations in over 26 countries (including France, China, Netherlands, Ireland, Nigeria), Matrix Laboratories has also taken initiative in this direction as is evident from its acquisition of 22% stake in Belgium's Docpharma for \$263 million. Other Indian firms such as Dishman (Synprotec of UK), Cipla etc. have also made similar kinds of acquisitions. The export-led growth strategy of the Indian pharmaceutical firms also appears to be appropriate given that the Indian market is very low in value terms (1% of the global market) though it produces 8% of the drugs available in the global market in terms of volume. However, this strategy while offering them greener pastures in the larger international markets, may also expose them to tough competition from firms such as Teva (an Israeli firm with a manufacturing facility in India), Sandoz, Watson and Ivax, apart from the fast emerging low cost producers from China, Argentina, Mexico and Brazil. They may also face severe competition from other generic drug producers and MNCS getting their supplies through contract manufacturing in India and China.

Besides penetrating the generic markets further, the most dynamic Indian firms have also been investing in R& D for quite some time with a positive outcome in sight. Indian pharmaceutical Industry sources have reported that currently there are 37 research leads for NCEs, 28 of which are in pre-clinical development, and 9 in Phase I/ II trials. It may, nevertheless be pointed out that around two-thirds of Indian R&D expenditure is directed towards API and formulation work, with only one-third dedicated to new chemical entities (Grace 2004).

- B. Other Indian pharmaceutical firms who have a relatively different orientation are likely to be more interested in the outsourcing business. At present India shares only \$470 million of the US\$ 50 billion world outsourcing business (Business Week Online 2004). With the strengthening of IPRs across the globe, and rising costs of conducting clinical trials, R&D and manufacturing, global pharmaceutical and biotechnology firms are actively scouting for cheaper options available elsewhere. Many of these MNCs may look for outsourcing deals spanning all stages in the drug development pipeline, in particular initial R&D, clinical trials, custom synthesis, technical services and manufacturing with the Indian pharmaceutical firms having such a potential. These trends have important implications for the possible content of the outsourcing business in India. There are two areas—contract research and contract manufacturing—where outsourcing is most plausible, as suggested by existing trends:

## **Contract Research (Clinical Trials and Drug Discovery Related R &D)**

### *(i) Clinical Trials*

Cost considerations and the existence of a genetically diverse population coupled with the homogenization of the patent laws and dismantling of national barriers facilitating free movement of capital and technology, are the most powerful factors that may make India one of the attractive destinations for clinical research and administering clinical trials (Slater 2004, Gombar 2004). According to an estimate by CII, clinical trials cost approximately \$ 300–350 million abroad, while they cost about \$ 20 million in India (CII 2003). Taking advantage of this competitive edge, some of the Indian pharmaceutical firms have taken early initiatives in this regard. For instance, one Indian company (Nicolas Piramal Group) has set up a subsidiary named Wellquest to provide clinical trial services on a contract basis. Similarly, one of the most prominent drug companies i.e., Novartis, is investigating clinical trial opportunities in India and China while big pharmaceutical companies such as Eli Lilly, Pfizer and Roche have already established clinical trial programmes in India. In 2002, the industry for clinical trials in India was estimated at \$ 70 million. This market is growing at a rate of 20% per annum, which implies that this industry will be worth anywhere between \$500 million to \$1.5 billion by 2010. In terms of Indian prices, this translates into \$7 billion (at 1/3<sup>rd</sup> of US/EU costs) and \$7.8 billion (at 1/5<sup>th</sup> of US/EU costs) respectively. This constitutes a total potential of \$14.8 billion for the Indian pharmaceutical companies (FICCI 2005).

Despite these favourable considerations, experts in the business world are, however, skeptical about the confidentiality of shared intellectual property. Similarly, doubts are also cast about the efficacy of such tests owing to relatively limited experience of Indian agencies in conducting clinical trials as per FDA norms. Moreover, keeping in view the serious implications of unrestricted clinical trials for national health and safety, restrictions have also been put in place through an amendment of the Schedule Y of India's Drugs and Cosmetics Act. According to the amendment, foreign companies are not permitted to conduct clinical trials solely in India, though conducting simultaneous clinical trials in India and other countries may be permitted in the near future. Apart from this, the Ministry of Health (MOH) has the power to set up a special group to monitor clinical trials.

### *(ii) Drug Discovery Related R&D*

R&D in India is also much less expensive than in the developed world (CII 2003). With the kind of clear cost and competency advantages over other competitors and increasing consolidation of Indian pharmaceutical firms, as is evident from several mergers taking place since 1995, the R&D related potential of Indian drug companies has further increased. Indian pharmaceutical companies at present are carrying out limited preliminary screening to identify lead molecules. They are also identifying candidate drugs for further in vivo screening, pre-clinical pharmacology, toxicology, animal and human pharmacokinetics and metabolic studies before taking them up for human trials. Due to this level of competency, drug MNCs entered into 700 such alliances with Indian pharmaceutical companies during 1997-98 as compared to 319 in 1990 and 428 in 1992 (Moses 2002). One of the biggest Indian pharmaceutical firms, namely

Ranbaxy, has already entered into an agreement with GlaxoSmithkline for drug discovery and clinical development collaboration covering a wide range of therapeutic areas such as infection, inflammation and diabetes. In addition, contractual outsourcing of some research and product testing is also being used. For example, Nicholas Piramal has launched a \$25 million R&D facility in India; Wockhardt has commissioned a \$50 million biopharmaceutical complex—India's largest—in Aurangabad; Sun Pharma and Lupin Limited have also expanded their R&D operations; smaller Indian firms like Shantha Biotechnics are producing enzymes for U.S. clients like Calbiochem, an affiliate of Merck KGaA of Germany; and Ocimum Biosolutions, another Hyderabad-based company, has developed bioinformatics software for Dow AgroSciences, and set up a contract research arm in Indianapolis. Here India has a clear edge over China due to improvement in product and market positioning (Dolan 2005).

### **Contract Manufacturing**

The availability of conducive infrastructure almost equaling U.S. complexity and quality, low labour costs, FDA regulations and ISO and other international standards in place, has made India one of the favoured destinations for contract manufacturing. Keeping an eye on the rapid globalization of pharmaceutical trade, many Indian companies have made their plants cGMP compliant. The Indian Pharmaceutical companies are going for compliance with International regulatory agencies like USFDA, MCC etc. for their manufacturing facilities. India, with 61 FDA approvals, has already replaced Italy (60) in the largest number of FDA approvals outside the US, while other players such as Spain (25), China (22), Taiwan (9), Israel (7) and Hungary (5), are far behind. Currently, Indian pharmaceutical firms are performing three kinds of contract manufacturing (Grace 2004):

- (i) Contract Manufacturing for Patented Drugs and Custom Synthesis & Scale Ups,
- (ii) Contract Manufacturing for Specialized Generics, and
- (iii) Contract Manufacturing for Old Generics/ Old Molecules.

Indian companies are also expanding their state-of-art manufacturing facilities for contract manufacturing. For instance, Divi's Laboratories (Hyderabad, India), a manufacturer of active pharmaceutical ingredients and advanced intermediates built up a 1000m<sup>3</sup> GMP fine chemicals plant for US\$25 million in the mid-1990s. In the US, the same facility would have cost US\$250-\$400 million. Similarly, Actavis, an Icelandic pharmaceutical company, purchased Lotus Laboratories in Bangalore, India for approximately \$25 million. Top MNCs like Pfizer, Merck, GSK, Sanofi Aventis, Novartis, Teva etc. are largely depending on Indian companies for many of their APIs and intermediates. Indian pharmaceutical Industry estimates suggest that the Indian companies bagged manufacturing contracts worth \$75 million in 2004 (Quoted in FICCI 2005). It may be pertinent to mention here that the contract manufacturing market for global companies in India is expected to touch \$900 million by 2010 (The Boston Consulting Group estimation).

- C. Under the changing environment, smaller players are expected to form manufacturing and co-marketing alliances with the bigger Indian and foreign firms

for the production and supply of generic drugs and specialty chemicals on a contract basis. This strategy may help them to coexist with the bigger players and enjoy economies of scale. However, the road ahead will be tough if they do not ensure better quality control and international packaging specifications and resort to international norms in the drug production.

In sum, generic drugs are expected to remain at the core of almost all the Indian pharmaceutical industry players. Recent trends also suggest that the use of generic drugs world-wide is growing annually by 14%, which is 8% faster than prescription, or branded, products. The generic drug market is important for India (India accounted for around 22 percent of the world generics market valued at \$27 billion in 2001) and shall remain so in the future given the attractive projections for this drug segment. (US, the biggest drug market in the world, is expected to soar from \$15 billion in 2002 to \$38 billion in 2010.) The year 2007, when patents of generic drugs worth US\$ 50-60 billion expire, is going to be very important for generic medicine producers all over the world and more so to Indian firms. Preparation for manufacturing and marketing such drugs in 2007 through alternative process is on and the Indian firms having expertise in this are likely to get a bulk of such business on contract from MNCs and foreign producers. In order to keep the costs of health care services down in the face of rising cost, the healthcare systems in developed countries are increasingly resorting to generic drugs (WHO 2004). The generic market today forms 75 per cent of the US pharmaceutical industry compared to 5 per cent in 1984. Generic prescriptions as a percentage of total prescriptions stand at 47 per cent in the US (up from 18.6% in 1984), 49 per cent in Germany, 52 per cent in the UK, 40 per cent in Canada, 11 per cent in Japan, and 5 per cent in France (WHO 2004).

In the light of these developments, it appears logical to think that with the new IPRs regime in place, more dynamic Indian pharmaceutical firms, as a long term strategy, shall have a strong inclination to keep serving the larger generic drugs market to survive and mobilise funds for the discovery of the new drugs as well as to grow into research-based entities. These firms may start with discovering new molecules to manufacture low-cost yet far more effective drugs with fewer side effects for which relatively inconvenient generic substitutes are available. The demand for such drugs may also increase many fold if they are also able to substantially cut down the treatment time. These areas could also emerge as strong 'cash cows' to finance R&D for further discoveries. Due to the rapidly expanding Indian economy and increasing incomes in developing countries generally as a consequence of growth in recent years, demand for both kinds of drugs viz, 'tropical diseases' and the most profitable 'life-style related' is increasing in these countries. This offers a good opportunity to Indian firms, though they would be amongst a plethora of drug companies positioning themselves to capitalize upon this fast emerging market segment. The emergence and potential of biotechnology, genetic engineering and nanotechnology to develop relatively inexpensive equivalents of drugs and vaccines against disease-causing microbes may (Lanjouw and Cockburn 2000) also give advantage to the Indian firms due to the availability of a vast pool of scientific and technical expertise in the country. The path, however, does not appear to be very smooth. Apart from the regulatory hurdles (Hatch-Waxman Act) in the markets of developed countries, there is a problem in determining the bio-equivalence as biotech firms will have to collect their own data regarding safety and efficacy of the drug.

Though comparing China and India is not the focus of this paper, it may be mentioned that both of them, by and large, have distinct areas of expertise with innovative capabilities (Ballance et al, 1992). Till now, the target markets for both of these Asian giants have been different. While China had been focusing more on the developed countries' markets and is a major supplier of ingredients for antibiotics, India, on the other hand, enjoys a predominant position with regards to API and finished products' supplies, most notably vaccines and ARVs across the globe. A good number of Indian firms also source cheaper drug ingredients (especially in regard of ARVs) from China. However, China's big potential as a source of cheaper drugs in the future and the Indian pharmaceutical firms opting to explore the developed world's markets bring to the fore the strong possibility of fierce competition between these two Asian giants in the future for shares in the generic drug market (Einhorn et al 2004; *The Economist*, December 11, 2004; *Wall Street Journal*, November 22, 2004). Currently China is meeting around 50-60% of the world demand for penicillin, vitamin C, terramycin, doxycycline hydrochloride and cephalosporins (Pharmaceutical Business News 2004) and its cost of production is lower than that of Indian drug companies. China appears to be ahead of India particularly in the development of biotech drugs as it has developed excellent expertise already in gene mapping, transgenic technology for animals and plants, gene therapy technology, stem cell research, gene chips, and gene research of some major diseases. Owing to large state investment, Chinese companies now produce much cheaper hepatitis vaccines, recombinant insulin, interferon and other generic therapeutic biologics. India's biotechnology sector is also growing rapidly, however, with an emphasis on biogenerics, transgenic plants, building research platforms and bioinformatics (Maria et al. 2002, Vaishampayan and Chen, 2004). India also enjoys many other advantages over the Chinese pharmaceutical sector that are not discussed here.

## *2.2. Possible Directions of R&D Investment by Indian Pharmaceutical Firms*

Existing evidence suggests that drug inventive firms across the world orient their research programs toward products and technologies for which they expect a large global demand. It is, therefore, natural for them to invest in high cost-high returns rather than high cost-low returns pharmaceutical products. Since developed countries' markets are most profitable because of high income and the existence of health insurance coverage, a huge portion (estimated at 90%) of the R&D investment goes towards diseases, mostly life-style related ailments, which afflict these nations (Global Forum for Health Research, 2000, 2002, WHO 2004). As a consequence, tropical diseases such as pneumonia, diarrheal diseases, TB, malaria, Schistosomiasis, chagas disease, tetanus, and lymphatic filariasis etc., receive only 10% of the global R&D and most of it comes from the governments and international agencies.

Indian firms have, so far, focused more on anti-infections than on the life-style related diseases as the domestic market had sufficient demand for such drugs. Around 85% of the current domestic demand for formulation comprise: Analgesics and Anti-pyretics, Antacids and anti-ulcerants, Antibiotics, Anti-tuberculoses, Anti-parasitics and Anti-fungal cardiac therapy, Corticosteroids, NSAIDs, Anti-rhematic respiratory system, Vitamins and other therapeutic segments. However, the emerging Indian market trends suggest that old and mature categories like anti-infectives, vitamins, analgesics

are slowing (with growth rate less than 9%) while new lifestyle categories like Anti-Diabetic Cardiovascular, Antacids, Central Nervous System (CNS), are expanding at double-digit growth rates ranging from 15-17% for antacids and cardio-vascular diseases to 40% for anti-diabetes (SCOPE Report on Pharmaceuticals, quoted in KPMG 2003), making the life-style diseases segment the most attractive for investment. A 2003 survey of Indian firms also indicated that only 10 percent of R&D expenditures (down from 16% in 1999) was targeted at tropical diseases (Lanjouw and Cockburn 2000, Lanjouw and MacLeod 2005). As a consequence, there is heavy concentration of Indian pharmaceutical patenting in the US and Europe in the area of life-style related diseases (Lanjouw and MacLeod 2005). This trend is also evident from the R&D strategy of the two prominent Indian firms viz., Ranbaxy and Cipla, which have set R&D priorities in favour of cardiovascular diseases, diabetes, and cancer precisely because even a moderately innovative drug may have significant payoff.

These trends suggest that any discovery research would be on global diseases and on products for the worldwide market. In India and other developing countries too, the most profitable market segment comprise upper and upper middle income groups that are more afflicted by the life-style related diseases prevalent in the developed countries. Even if one assumes 30% (over 300 million) of the Indian population falls into the upper and upper-middle income ranges, it constitutes a market even larger than US for life-style drugs. In such a situation, developing new drugs for this segment could be the major area of focus as such drugs could also have a profitable global market.

In terms of affordable access to the most needed medicines for poor countries, however, a ray of hope lies in the fact that some of the Indian pharmaceutical companies may still be interested in investing R&D funds on 'tropical diseases' primarily because these areas would be characterized by low competition as MNCS or relatively bigger domestic firms may not be interested in these market segments. Another area which is likely to experience a renewed interest is the herbal-based traditional Indian medicines systems such Ayurveda and Unani. Some of the innovative Indian pharmaceutical firms may try to separate the molecules from the traditional medicines known for their healing properties.

In the light of the above discussion, it is clear that while there may be some setbacks during the period of restructuring and consolidation, the Indian pharmaceutical industry as such may gain more, as compared to the past, in terms of better product portfolios, access to the global market, improved productivity and expanding technical base. There are other possibilities as well. For instance, relatively smaller and non-innovative players without a global perspective may withdraw from the market. Though it is difficult to estimate at this juncture, the extent of the net impact of either of the business strategies discussed above on the employment scenario, it appears, at least prima facie, that the employment profile of this industry may only be affected in the short term while the industry is under the immediate impact of restructuring and consolidation. In the medium and long term, further expansion of the industry may lead to increase in employment. On the balance of trade front, existing trends in the contribution to the trade surplus from this sector should continue as the export scenario is more firmly rooted in generics than in copies of the on-patent drugs.

## CONCLUSIONS

The preceding discussion amply demonstrates that there may be significant impact of the changed patent regime on the business behaviour of foreign as well as Indian pharmaceutical firms. Foreign firms may exercise various options to utilize the potential of the Indian market as well as its technically well-equipped pharmaceutical firms through outsourcing alliances and competition. Indian firms, for their part, may also prefer to follow a combination of the strategy 'Cooperate and Compete' precisely to take advantage of increasing attractiveness of the global generic market and also to buy time till they become reasonably resource rich to conduct expensive R&D. There also appears to be a strong possibility that Indian firms may experience a large influx of outsourced jobs such as clinical trials, drug discovery related R&D and contract manufacturing. Indian pharmaceutical firms appear to be readying themselves for this situation. The discussion above shows that the focus of the Indian industrial sector R&D is likely to focus more on drug discovery with regards to life-style related diseases than 'tropical diseases. Further, even if product patents result in significantly higher prices, much of the pharmaceutical market is not likely to be affected for the simple reason that over 97% of the drugs sold in India are off-patent. However, there could be significant effects on the accessibility of essential medicines mainly to HIV/AIDS afflicted poor African countries that at present are getting their supplies of a cheaper copy version of ARVs from India.

Thus to sum up: Under the emerging scenario, internal networking and co-ordination amongst different constituents of the innovation chain comprising academia, industry, public funded labs (such as ICMR, CDRI, CSIR etc.) has become imperative to substantially improve the efficacy of the system relating to new drug discovery and its introduction in the market place. On the health care front, there may not be much impact immediately but the new law certainly has serious long term implications, which will vary considerably depending on how the Indian pharmaceutical sector, international agencies such as WHO and other stakeholders respond to the needs of health care around the world.

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