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Is Product Patent Protection Necessary in Developing Countries for Innovation? R&D by Indian Pharmaceutical Companies after TRIPS

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Is Product Patent Protection Necessary in Developing Countries for Innovation?: R&D by Indian Pharmaceutical Companies after TRIPS

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Abstract: R&D expenditure has dramatically increased for a segment of the Indian pharmaceutical industry since around the mid-1990s when TRIPS came into effect. It is not only that the amount of R&D expenditure has gone up. There has also been a change in the structure of R&D activities of the Indian companies. While in the past they were primarily engaged with development of new processes for manufacturing drugs, now they are also involved in R&D for new chemical entities (NCEs) and modifications of existing chemical entities to develop new formulations and compositions. Patenting by the Indian pharmaceutical companies has also gone up significantly. But the primary incentive to do R&D has not been the product patent regime in India after TRIPS but the product patent regime in developed countries to which TRIPS has made no difference. While R&D activities have diversified, they are yet to prove their competence in innovating new products. What Indian companies have really demonstrated is the ability to develop generics for the regulated (and other) markets – an ability which they acquired and improved during the pre-TRIPS period.

Key words: R&D, innovation, patent, pharmaceuticals, generics.

I: Introduction

The principal economic rationale for granting patents is that it will stimulate investment for research for innovation. Yet, even if this supposition generally holds true,[1] strong patent protection has traditionally been seen as unnecessary until relatively late in a country's

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development process (Siebeck 1990b, p. 1). The developing countries are net users, not net developers of R&D intensive products. Penrose (1951) and some later studies, including Vaitsos (1972) and Greer (1973) have argued that developing countries lose by granting patent protection. For such countries, these studies contend, the costs of patent protection actually outweigh its benefits. The developing countries suffer from higher prices resulting from patent monopolies. And the benefits of technological progress which are supposed to follow from patent protection take place in developed countries, not in developing countries.

Despite these doubts and despite the lack of empirical evidence that the net benefits are indeed positive (Primo Braga, 1990, p. 87), the 1994 Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) requires all World Trade Organization member countries to provide product patent protection for all products, including pharmaceuticals, within the time specified. Moreover, the United States has used bilateral Free Trade Agreements to promote a "TRIPS-plus" agenda, requiring developing countries to provide patent protection that exceeds the TRIPS minimum standards (Roffe and Spennemann, 2006). Concurrently, an attempt is also being made within the World Intellectual Property Organization (WIPO) to upgrade and harmonize patent standards.

But has the situation changed in recent years to justify stronger patent protection in developing countries? Maskus (2000) contests the traditional view that developing countries do not gain technologically from stronger intellectual property rights (IPRs) such as patents. He argues, in fact, that inadequate protection may stifle technical change even at low levels economic development (p. 147). But a study on Japan by Sakakibara and Branstetter (2001) did not find that stronger patent protection has resulted in more innovation. Moreover, after a review of several other empirical studies, Branstetter (2004) concluded that there is little empirical evidence that stronger IPRs stimulate local innovation. Conversely, a study on China by Maskus, Dougherty and Mertha (2005) suggests that there may be a positive relationship between stronger IPRs and development.

I take up the debate empirically with respect to the Indian pharmaceutical industry. As I have shown elsewhere, the abolition of product patent protection in 1972 was one of the major factors that contributed to the remarkable growth of the pharmaceutical industry in India (Chaudhuri 2005b). Today, India has one of the most advanced pharmaceutical industries among developing countries. With the introduction of the mailbox facility from 1 January, 1995 to receive and hold product patent

applications[2] and the re-introduction of full fledged product patent protection in pharmaceuticals from 1 January 2005 in line with TRIPS, the legal framework is similar to that before 1972.

In the underdeveloped pharmaceutical industry before 1972, the capacity to conduct R&D was limited. But has the situation changed following the rapid growth of the industry since the 1970s? What has been the nature of R&D activities and innovation in the Indian pharmaceutical industry? Does India's experience support the claims of the multinational corporations (MNCs) and their followers that strong patent protection is needed in India for R&D and innovation?[3] During the TRIPS negotiations, it was specifically claimed that TRIPS-compliant patent protection will prompt developing country companies to conduct more R&D for the development of new drugs more suited to local needs.[4] Have those claims been borne out in India? In this paper, I will canvass such questions to cast some light on the relationship between product patents, R&D and innovation in developing countries.

II R&D: Quantitative and qualitative changes

Traditionally, the Indian pharmaceutical industry spent very little on R&D. In the early 1990s, its R&D expenditures amounted to only about 1.5 % of sales (Grace 2004, p. 37). Even larger companies such as Ranbaxy and Dr Reddys Laboratories spent only 2-3% of their sales on R&D in 1992-93.[5] Since then, however, and particularly since the early 2000s, there has been a substantial increase in research spending in a segment of the industry. In Table 1, I have considered the R&D expenditure for two sets of companies – (i) 28 major R&D spenders and (ii) the remaining 81 companies out of the 109 companies for which R&D data have been reported in the data base.[6] For the later group, R&D expenditure as a percentage of sales continues to fluctuate around 1%. In 2005-06, the proportion was only 1.2%. But for the group of 28 major spenders, R&D expenditure has increased steadily from 1.78% of sales in 1992-93 to 3.86% in 2001-02, and then sharply to 7.83% in 2004-05 and 8.79% in 2005-06 (Table 1).

In this paper I focus on this more dynamic segment of the Indian pharmaceutical industry for which R&D expenditure has substantially increased. Ranbaxy is the largest R&D spender in the Indian pharmaceutical industry. In 1994-95, when TRIPS came into effect, it spent Rs 365.8 million on R&D (4.61% of its sales).[7] Initially the increase was moderate with R&D expenditure reaching 5.5% of sales in 2002-03. But thereafter it shot

up to 9.35% in 2004-05 and 17.21% in 2005-06 with an expenditure of Rs 6339.3 million. For Dr Reddys the second largest R&D spender, expenditure increased steadily and sharply from Rs 39.8 million (2.01% of sales) in 1994-95 to Rs 2977.9 (17. 12 %) in 2004-05. The following year, the company's R&D expenditure declined to Rs 2539.5 million, but it still constituted 10.85% of its sales. Among the other major spenders, between 1994-95 and 2005-06, R&D expenditure has increased for Sun from 4.05% to 11.93%, for Torrent from 2.68% to 11.74%, and for USV from 0.73% to 10.74% of sales. There are 9 companies with the R&D proportion exceeding 10% of sales in 2005-06 (Table 2). The larger Indian pharmaceutical companies are among the largest investors in R&D among all industries combined in India. Each of the top five R&D spenders in corporate India are pharmaceutical companies - Ranbaxy, Dr Reddys Laboratories, Sun and Cipla. The only non-pharmaceutical company is the second ranked Tata Motors which spends about 2.3% of its sales on R&D. Ten of the top 20 Indian R&D spenders in India are pharmaceutical companies (*Business World*, 25 December, 2006).

The objectives of R&D conducted by Indian companies can be broadly classified as follows:

- Development of new chemical entities (NCEs)
- Modifications of existing chemical entities to develop new formulations, compositions, combinations (also known as incrementally modified drugs)
- Development of generics (that is, development of processes for manufacturing active pharmaceutical ingredients (APIs) and development of formulations to satisfy quality and regulatory requirements for marketing patent-expired drugs).[8]

A remarkable feature of pharmaceutical R&D in India is that about eleven companies are involved in NCE R&D. In Section III, we will focus on the status and the implications of that activity. We will discuss how Indian companies still do lack the necessary skills and the funds to carry out such R&D independently And how they are partnering with the MNCs and other companies from developed countries. The R&D partnering agreements have typically provided that the developed country partner has commercial rights in designated developed country markets and must pay royalties to Indian companies in the event the product is successful. The Indian company, in turn, holds the commercial rights in remaining countries, including India.

If the product developed under a partnering agreement is successful, the Indian company will typically earn significantly more from the Indian market than during the pre-TRIPS era when India had no product patent protection. Not unexpectedly, therefore, patenting activity has gone up sharply after India started accepting patent applications under the mailbox facility after TRIPS (Mueller, 2006, pp. 158-161).

However, TRIPS has made no difference to the product patent regimes of developed countries. Such countries already recognized product patents before TRIPS. Thus even in the absence of TRIPS, Indian companies would earn royalties on drugs developed in India but marketed and patented in developed countries. And since developed country markets are much larger and more lucrative than the Indian market, Indian companies would have the incentive to do NCE R&D for such pharmaceutical products even in the absence of TRIPS.

In contract, where developing country markets matter--as in the case of neglected diseases--Indian companies are hardly involved in developing drugs. We find in Section III that, contrary to what was claimed during the TRIPS negotiations, the product patent regime has not prompted Indian companies to devote more resources to developing drugs for neglected diseases that exclusively or predominantly affect developing countries.

NCE R&D is not yet a significant part of R&D activities of Indian companies - it constitutes less than a quarter of the total R&D expenditure by the major companies.[9] It should be noted that most of the large R&D spenders are not involved in NCE R&D. Cipla, for example is not yet involved in NCE R&D, but it is the fourth largest spender and its R&D expenditure has increased by more than 50% in 2005-06 (Table 2).

Pharmaceutical R&D conducted by Indian companies has been primarily related to generics and incrementally modified drugs. We will discuss in Section IV how significant R&D efforts are being directed towards developing processes and products to get regulatory approvals for entry and growth in patent–expired generic markets in developed countries. This has nothing to do with TRIPS. It is the result of increasing export orientation of Indian pharmaceutical companies and diversification to the regulated markets, particularly to the US. The US is already the largest export market for India and most Indian companies are trying to enter and grow there. The focus of Section IV accordingly will be on the US.

Most of the Indian exporters in the US operate in the commodity generics market, where entry barriers and prices are low. We will also discuss in Section IV, how to move up the value chain, some Indian companies in the US are targeting value added generics in different ways: challenging patents and developing non-infringing processes and being the first or among the first few to enter the generics market and enjoy higher profit margins. They are also trying to modify existing drugs and develop new formulations. Patenting activity by Indian companies in USA has accordingly gone up sharply. TRIPS permit them to also patent these in India and gain if and when these innovations are commercialized. But even in the absence of TRIPS, they would still be interested in undertaking such innovative activities because of the promise of much higher returns from the United States.

III: R&D for new drug development

The Indian private sector began investing in R&D for new chemical entities when TRIPS came into effect in the mid-1990s.[10] R&D investments were initiated by Dr Reddy's Laboratories followed by Ranbaxy Laboratories. Since then nine other companies - Sun, Cadila Healthcare, Lupin, Nicholas Piramal, Dabur Pharma, Torrent, Wockhardt, Orchid and Glenmark have also joined in.[11] As mentioned above and as can be seen from Table 2, these eleven companies are among the major pharmaceutical R&D spenders.[12] Together they invested Rs 16760.2 million (10.9% of their sales) on R&D in 2005-06. The amount increased by 22.5% from Rs 13676.7 million in 2004-05 (calculated from Table 2). The increase is impressive but it still pales in comparison to what the MNCs spend on R&D. The eleven Indian companies together spent $379 million in 2005-06. Pfizer alone spent $7440 million (*Pharmaceutical Executive*, May, 2006)

It is important to note that none of these companies is engaged in the entire process of drug development. The reason is simple: Indian pharmaceutical companies are not yet ready for a start-to-finish model in NCE research because they do not yet have all the skills and the funds required to develop a drug and put it to the market.[13] The model that the Indian companies have adopted, rather, is to develop new molecules up to a certain stage and then license out to partners from developed countries, primarily to MNCs. There has been a marriage of interests. It is the development of biotechnology companies which has encouraged specialization according to stages of the drug development process. The MNCs seek and contract out specific activities (Nwaka and Ridley, 2003, p. 920). As the NCE pipeline of the MNCs started drying up, they in fact

have intensified efforts to license promising compounds developed by others. In fact most of the major MNCs have opened compound acquisition departments in their companies. There are also specialized companies, which keep track of promising compounds, maintain libraries, catalogue them and offer for sale to prospective clients.[14]

Even at the pre-clinical stage, Indian companies are not engaged with all R&D. Indian companies are not involved in basic research of target identification for new drugs. They rely on the basic research of others and adopt an approach called 'analogue research.' This entails working on certain pre-identified targets for specific diseases to develop molecules that alter the target's mechanism in the diseased person.[15] But even this requires medicinal chemistry and biology skills that are still scarce in the Indian pharmaceutical industry. In the pre-TRIPS era, Indian pharmaceutical industry scientists primarily acquired and developed the organic chemistry skills required for process development. The Indian companies are filling up this gap primarily by hiring Indian scientists who worked in MNC laboratories in India and abroad and in the Indian public sector laboratories.[16]

Dr Reddys commenced drug discovery R&D in 1993. It filed the first patent in the US in 1995 for an anti-diabetic compound. This was out-licensed to Novo Nordisk in 1997. It developed two more anti-diabetic compounds and out-licensed these to Novo Nordisk in 1998 and Novartis in 2001. The deal with Novartis involved upfront and milestone payments up to $55 million depending on the progress and the company received $5 million to start with in 2002-03. These deals were major news and generated tremendous optimism and lured other smaller companies into new drug R&D and one of them, Glenmark has actually struck the best licensing deals.[17]

The initial optimism is reflected in what the chairman of Dr Reddys Laboratories said in its *Annual Report 2002-03* after signing the Novartis licensing agreement:

> When we started our drug discovery program in 1993, industry pundits viewed it with skepticism. This ambition, they said, would not be within the reach of an Indian company. The challenge was, to prove them wrong. And in this last decade, we have done just that.[18]

However, Ranbaxy and Dr Reddys, the two Indian companies that have invested most heavily in R&D (Table 2) and served as prime advocates for new drug R&D in India, have each suffered several setbacks. Novo Nordisk and Novartis discontinued

further development of the three compounds in-licensed from Dr Reddys. Similarly, Schwartz Pharma discontinued the clinical trials of a compound licensed from Ranbaxy. No success at the clinical trial stages have yet been reported from the much publicized Ranbaxy-GSK R&D collaboration.[19] Given that drug development did not progress, as anticipated, the prospect of huge licensing revenue through milestone and other payments failed to materialize.

What the Indian companies initially did not understand is that while their objectives are to earn license fees and royalties from successful commercialization, the MNCs do not necessarily aim to develop the in-licensed compounds for commercialization. In fact where the compound may compete with the MNC's existing or planned products, the MNC's objective may actually be to "kill" the compound.

Indian companies are now aware of this potential conflict. In some cases they are attempting to develop drugs further despite the lack of interest on the part of the MNCs who initially licensed them. Torrent, for example entered into an agreement with Novartis in 2002 for the development of AGE breaker compound for the treatment of heart disease and diabetes. In 2004 the compound was out-licensed to Novartis. The agreement was terminated in 2005 when Novartis decided not to proceed further with the compound. Torrent is now trying to develop it on its own and explore other options. Torrent received only $0.5 million initially and then $3 million from Novartis.[20] This was too small an amount for a large MNC such as Novartis to have any stake in the project.

The later the stage at which a compound is licensed out, the higher the license revenues. The licensor is also in a better position to select the licensee to ensure that the licensee is actually interested in developing the drug for commercializing, so that the licensor can hope to earn royalties. But Indian companies face the predicament that unilaterally developing a drug to that later stage entails considerable cost and risk.

Dr Reddys has suffered several similar setbacks. As a result, that company's R&D expenditure even declined by about 15% in 2005-06 (Table 2). Dr Reddys has now started re-thinking its strategies. Rather than licensing out the molecules to MNCs, Dr Reddys is experimenting with a number of alternative business models. One such is joint development and sharing of costs with smaller specialized research companies, such as Rheoscience and ClinTec. Dr Reddys entered into an agreement with the former in September 2005 to co-develop an anti-diabetic compound (DRF 2593) and with the latter

in September 2006 to co-develop an anti-cancer compound (DRF 1042). Dr Reddys has also sought to de-risk R&D investment by setting up a separate drug development company with equity investment from two leading venture capital companies in India – Citicorp Venture Capital and ICICI Venture Fund. Dr Reddys transferred to the new company four NCEs that it had already developed. The new company will be responsible for the clinical development and out-licensing, co-development or joint commercialization of those NCEs. Currently three of these NCEs are undergoing clinical trails (Table 4).[21]

No NCE developed by Indian companies have yet been approved for marketing in any country. But as Table 4 shows, by the end of 2006-07, 25 NCEs developed by Indian companies were at various stages of clinical trials. Dr Reddys has 5 NCEs under clinical trials followed by Lupin with 4 and Cadila Healthcare, Glenmark and Nicholas Piramal with 3 each. Ranbaxy the largest pharmaceutical company in India and the largest R&D spender has only 2 NCEs under clinical trials.

As Table 4 further shows, the NCEs being developed by the Indian companies are related primarily to "global diseases" such as diabetes, cancer, heart diseases, asthma, and obesity. These are the diseases that offer much larger and more lucrative market in developed countries (though they are also prevalent in developing countries). The "neglected diseases" which primarily or exclusively effect the developing countries and promise much less financial returns are absent from the list except for malaria and TB. In both these cases, public sector or philanthropic funding is involved. Ranbaxy is participating in an international project sponsored and funded by the Medicines for Malaria Venture (MMV), a public-private partnership to develop a synthetic anti-malarial drug. Lupin is involved in developing an anti-TB drug in partnership with some publicly funded research institutions in India (CIPIH 2006, p. 101). The trend towards R&D for drugs for global diseases is unlikely to change in future. A survey on the R&D plans of Indian companies found that only about 10% of the R&D funds are aimed at diseases principally affecting developing countries (CIPIH, 2006, p. 101).

In short, the anticipated benefit of TRIPS that the product patent incentive will prompt local companies to put resources in developing drugs more suited to developing countries has not materialized.

IV: R&D for Exports to the US market

The growth in exports is one of the most outstanding features of the pharmaceutical industry in India. Exports were negligible in the product patent regime before the 1970s. Exports started picking up in the 1970s after the amendment of the Patents Act. Initially the growth was modest. It accelerated in the 1980s. Exports have grown particularly rapid since the mid-1990s. Exports have increased at an annual compound rate of 21.4% from $698.7 million in 1995-96 to $ 4874 million in 2005-06.[22] The export market is larger than the domestic market for a number of Indian pharmaceutical companies. For example for Ranbaxy, 60% of sales, for Dr Reddys Laboratories, 51%, for Orchid, 70%, for Divi's, 85%, and for Shasun, 66% (Table 3). Most of the major R&D spenders (Table 2) are also major exporters (Table 3). The top 6 exporters account for a third of India's total pharmaceutical exports (calculated from Table 3).

The export market can be broadly divided between regulated markets and unregulated markets. In the regulated markets, there are regulatory barriers in the sense that exporters are required to follow an elaborate registration and in some countries, inspection procedure to satisfy the drug control authorities about the efficacy and safety of medicines. Such requirements are absent or are not as elaborate in the unregulated markets. The stricter the regulations, the tougher are the entry barriers and accordingly higher are the prices.

The regulated markets include countries in North America, Western Europe and Japan, Australia and New Zealand.[23] The Indian pharmaceutical industry has been increasingly exporting to the regulated markets. These markets accounted for about 41% of India's total exports in 2005-06. The United States is now India's largest export partner, making up 14.2% of India's total pharmaceutical exports.[24] Larger Indian companies in particular, are increasingly focusing on the US and other regulated markets (CIPIH, 2006, p. 101). The United States is already Ranbaxy's largest market with a 28% share of its global sales of $1178. India is the second largest with a 20% share (Ranbaxy, *Annual Report, 2005*, p. 7).

In this section, we focus on the United States and show how Indian companies must, and are, conducting significant R&D in order to enter and grow in the US generics market.

R&D for DMFs and ANDAs

To get marketing approval for a patent expired drug, generic companies are required to satisfy the quality and regulatory standards of the country.

For selling Active Pharmaceutical Ingredients (APIs) in the US, manufacturers are required to file a Drug Master File (DMF) with the US Food and Drug Administration (FDA) for each such API. A DMF is a confidential document containing information on the manufacturing facility and processes used in the manufacture, packaging and storage of an API. DMFs are kept on file and are reviewed when a pharmaceutical manufacturer files an Abbreviated New Drug Application (ANDA). The latter is required for getting approval to market a formulation. Manufacturing facilities as well as the manufacturing processes and the standards employed must be approved. Generic companies are required to undertake various types of studies, for example bio-equivalence studies, and generate data and submit dossiers to the US FDA. Marketing approval is granted after various types of review by the US FDA including chemistry review, bioequivalence review and plant inspection.

Filing of DMFs and submitting ANDAs involve R&D efforts. Development of processes for manufacturing APIs and product development of formulations, process validation, bio-equivalence testing and generation of other data required for DMFs and ANDAs for getting international regulatory approvals are specifically mentioned as areas where R&D is undertaken by the companies active in the regulated markets.[25]

DMFs and ANDAs by Indian companies

India is now a dominant source of APIs for the US market, either as direct suppliers to US generics companies or processing the APIs in India and exporting formulations to the US (Hoffman, 2005, p. 9). Indian pharmaceutical companies started filing DMFs in the US around the 1980s. But until the late 1990s, only a few DMFs were filed, the largest being in 1993 when 8 DMFs were filed. Since then the rate of filing has accelerated. The number of DMFs filed by Indian companies increased from 17 in 1997 to 33 in 2000, 65 in 2002, 195 in 2004 and 300 in 2006.[26] In relative terms, DMFs filed from India as a percentage of total DMFs filed with the US FDA increased steadily from 18.3% in 2001 to 44% in 2006 (CRIS INFAC 2006, p. A-16). Between January 2001 and March 2006,

India has been by far the largest country, with 738 DMFs filed, way ahead of the second ranked country, China with 250 filings (CRIS INFAC 2006, p. A-17). India has displaced some of the traditional Italian and Spanish API suppliers (Hoffman, 2005, p. 9). Aurobindo and Dr Reddys have filed more than 100 DMFs each as of 2006-07. As can be seen from Table 5, some other major Indian companies also have individually filed a large number of DMFs.

Until recently only a few Indian companies, particularly Ranbaxy and Dr Reddys Laboratories had ANDAs in their own names. The companies such as Cipla which also exported formulations had the ANDAs in the names of their marketing partners in the US. The situation has dramatically changed in the last few years. From 161 ANDAs filed by only 4 companies - Ranbaxy, Dr Reddys Laboratories, Wockhardt and Lupin in the last quarter of 2003, the number has gone up to 701 ANDAs filed by 17 companies by the second quarter of 2007 (Table 5). ANDA approvals by India as a percentage of total approvals, has gone up sharply from about 7% in 2001 to 21 % in 2006 (CRIS INFAC 2006, p. A-8). India now has 75 manufacturing plants approved by USFDA. This is the highest number of USFDA approved plants outside USA. Italy has 55 plants, China, 27 and Spain 25 plants approved. (Ernst & Young, n.d., p. 13).

R&D for value added generics

R&D is required not only for developing the product to get regulatory approvals as described above. R&D is also required to ensure that the products do not infringe on any of the existing patents. An innovator company usually does not obtain a patent only on the active ingredient (NCE) involved in a new drug. Other secondary patents relating to the same NCE which can be obtained are: (i) for new formulations and compositions, such as new dosage forms or routes of administration; (ii) for new salts, esters, etc. of existing ingredients, that is, chemical derivatives of existing active ingredients; (iii) for new uses to treat health problems; and (iv) for the new process of manufacturing the active ingredient. These secondary patents are obtained later and hence typically expire after the basic patent on the NCE expires. Thus by taking such patents, the innovator companies can delay the entry of generics, as for example in the case of the anti-depressant drug, paroxetine. The basic NCE patent expired in mid-1990s. But GlaxoSmithKline could delay the entry of generics by obtaining several secondary patents (Hutchins, 2003, p. 67-68). Studies have shown that the innovator companies use patenting as a matter of strategy to maintain their market dominance.[27] In fact with a

number of drugs scheduled to go off-patent, they have intensified their efforts in recent years to extend the period of patent protection and protect the sales of their branded drugs (Mandi, 2003, p. 3).

Thus it is not enough to just file DMFs and ANDAs. Generic companies must be sure not to infringe the secondary patents in API processes and formulation products. In fact the generic companies which can challenge the secondary patents of the originator companies and can have their own patents can reap huge benefits as I will discuss below.

Most of the Indian companies operate in the commodity generics, where apart from regulatory barriers, there are practically no other entry barriers. These markets are characterized by intense competition among a large number of companies, with low prices and profit margins. Indian companies in fact compete a lot among themselves. The success of one Indian company in a field often induces the entry of other Indian companies in the same field (Chaudhuri 2005b, pp. 198-201). A few Indian companies have lately started targeting these value added segments in different ways. Apart from DMFs and ANDAs, patenting is increasingly becoming important for generic companies desiring to move up the value chain.

Challenging patents

The US FDA provides for two types of applications: (i) the New Drug Application (NDA) for seeking permission to market a new drug and (ii) ANDA for seeking to market a generic drug. When the NDA is filed (for any drug product other than biologicals and vaccines, for which the system is different), the applicant must also provide the FDA with certain information regarding the patents relating to the drug product for which permission is sought. When an ANDA is filed, the application must contain a certification with respect to the patents so listed in what is known as the Orange Book. There are four certification options. One of these is Para IV application. For the latter, the generic company certifies that the patent is invalid or will not be infringed by the generic drug for which the ANDA applicant seeks approval.[28] Para IV certification is relevant because even when the patent on the active ingredient (NCE) expires, there can be secondary patents on formulations and on methods of use, which may still be valid. In almost all Para IV ANDA cases, the generic applicant is sued by the patent holder (Federal Trade Commission 2002). By successfully contesting these patent cases, if a

generic company obtains a Para IV ANDA, it gets market exclusivity for 180 days. During this period no other generic company is permitted to enter the market.

Any successful first to file Para IV ANDA can bring immense returns to the company as the experience of Dr Reddys Laboratories shows. Dr Reddys was the first Indian company to get the 180-day exclusivity for marketing fluoxetine (Eli Lilly's Prozac) 40 mg capsule in August, 2001.[29]

Dr Reddys Laboratories and Ranbaxy are the two Indian companies which have been very active in challenging patents in order to be the first to enter the generics market.[30] These two companies have been the first to file para IV ANDAs in several cases but except the 180-day exclusivity obtained by Dr Reddys as mentioned above and one other by Ranbaxy in June 2006 for simvastatin, 80 mg (Merck's Zocor)[31], they have not yet tasted any success (*Business World*, 15 May, 2006). Patent litigation is a high-risk-high-gain strategy. A failure means a loss of several years of hard labour and huge legal expenses. It is no wonder that other Indian companies are not involved in product patent challenges (Chaudhuri 2005b, pp. 205-6).

Non-infringing processes

Process patents are not required to be listed by the originator companies with the US FDA and hence when a generic company applies for an ANDA, no certification is required for such patents. But originator companies usually have patents for a large number of processes. In fact, the proportion of process patents among all the secondary patents is now higher than before. Originator companies have been relying to a significant extent on process patents to delay generic entry (Leighton 2007). In such cases, a generic player which can develop a non-infringing process and enter the market can earn higher price and margin. Matrix Laboratories of India, for example was the first company to develop a non-infringing process for manufacturing citalopram. With restricted competition it was able to reap huge benefits – sales of the product were Rs 5600 million till 2005-06.[32] Another commercially successful example is the cefotaxime process developed by Lupin.[33] Because of entry barriers, the returns on such bulk drug activities can be significantly higher than that in conventional formulations with a number of competitors.

NDDS

Several Indian companies are increasingly focusing on R&D for modifications of existing drugs. The idea is to develop new formulations, get patents on them and sell at a higher price. The new formulations include novel drug delivery systems (NDDS) such as developing a controlled or extended release formulation of existing oral therapies to reduce side effects or increase patient compliance; developing alternative delivery routes, including oral as opposed to injectables, to increase patient convenience and compliance; and enhancing purification of the product to reduce dosing and side effects (Datamonitor 2001, p. 37).

Commercially the most successful example is that of the NDDS developed by Ranbaxy for ciprofloxacin, whereby patients are required to take the drug once a day against the twice-a-day dosage earlier. It took out a patent and licensed it to Bayer, the innovator of the drug. The latter has put the new dosage form in the market after approval from the US FDA. Ranbaxy receives royalty on the sales of the product though the patent on the original molecule has expired (Singh 2006, pp. 195-6).

Developing NDDS products is now a thrust area for most of the larger Indian companies. They are putting increasing R&D resources into it. Companies which are not yet involved in NCE R&D, such as Cipla, Alembic and J B Chemicals & Pharmaceuticals, have been involved in R&D for NDDS. In the parliamentary debate preceding the amendment of India's patent law to fulfill the TRIPS requirement, a demand was raised that product patenting in pharmaceuticals may be restricted to NCEs only. The Mashelkar Committee (2006) was set up by the Government of India to look into it. Ranbaxy argued in its submission to this committee that NDDS products are less expensive and have lower gestation periods. Indian companies, which have fewer resources than the MNCs, are in fact better placed to benefit from patenting NDDS than patenting NCEs. And hence, Ranbaxy argued, India must permit patenting of NDDS. But in view of the fact that Indian companies are increasingly eyeing the western markets, where NDDS patents are recognized, the Indian companies would continue to invest in R&D for NDDS to move up the value chain even if such patents were not permissible in India. In fact as Cipla has argued, such patenting abroad is required also for defensive reasons – if Indian companies do not patent, others will and may thus block Indian companies from the pertinent market (Mueller 2006, p. 59).

Patenting by Indian companies in USA

Not unexpectedly, efforts of the Indian companies to move up the value chain have been accompanied by increasing patenting in the US as the information provided by the United States Patent and Trademark Office (USPTO) shows.

Patenting by major Indian pharmaceutical R&D spenders (listed in Table 2) started in the US in the 1990s. In 1990 Ranbaxy obtained two patents.[34] Since then, particularly since the late 1990s, there has been an increasing trend. Before 1995, only 7 patents were obtained, all of them by Ranbaxy. Thereafter for the 12 major Indian patentees in USA, the number increased from 40 patents during 1995-99 to 174 during 2000-05. Big companies such as Dr Reddys and Lupin started patenting in the late 1990s. Others such as Sun, Wockhardt, Aurobindo did so in the early 2000s (Table 6). As on July, 2007, 32 Indian pharmaceutical companies have obtained 312 patents in USA. The big three are Ranbaxy (with 79 patents), Dr Reddys Laboratories (73) and Dabur (37). In the next group are Orchid (21), Lupin (17) and Wockhardt (13). Others have less than 10 patents each. Among the major exporters who are not major patentees are Cipla (only 3 patents in the US) and Ipca (1) (Table 5).[35] India has emerged as a major pharmaceutical patentee among the foremost developing countries. India has long had a much higher number of pharmaceutical patents in the US than China, South Africa or Brazil. But the gap has widened in recent times. Between 2001 and 2005, whereas India obtained 572 patents, China obtained only 134, Brazil 32 and South Africa 30 patents (Table 7).

Details are not available from the USPTO about the classification of the patents granted – to what extent the patents are for NCEs; modifications of NCEs and development of generics. But information provided by Ranbaxy to the Mashelkar Committee (2006, pp. 18-19) suggest that patents have been obtained in the US primarily for generics. Out of the 59 patents granted to Ranbaxy in the US, 38 are for new processes and only 21 for new products – 8 patents for NCEs and 13 for modifications of NCEs.[36] For most of the other Indian pharmaceutical patentees in the US which are less involved in new drug R&D, the proportion of product patents would be lower.

V: Conclusions

R&D expenditure has dramatically increased for a segment of the Indian pharmaceutical industry since around the mid-1990s when TRIPS came into effect. It is not only that the

amount of R&D expenditure has gone up. There has also been a change in the structure of R&D activities of the Indian companies. While in the past they were primarily engaged with development of new processes for manufacturing drugs, now they are also involved in R&D for NCEs and modifications of existing drugs to develop new formulations and compositions. Patenting by the Indian pharmaceutical companies has also gone up significantly.

The large Indian pharmaceutical companies who are the major R&D spenders, have been focusing on the larger and the more lucrative developed country markets, particularly that of the United States. In that regard, the primary incentive to invest in R&D, whether for NCEs, modifications or development of generics, has not been the new TRIPS-compliant product patent regime in India but the product patent regime in developed countries that was in place well before TRIPS. TRIPS may have accelerated the trend towards such R&D because of the anticipated shrinkage of domestic opportunities. But in the absence of TRIPS, such R&D activities would still have been undertaken. With the larger domestic operations, Indian companies in fact would have had access to larger resources and would have been better placed to undertake such R&D.

If we focus on the outcome of R&D rather than on the incentives for R&D, we find that even after TRIPS, India's proficiency continues to be in process development. While R&D activities have diversified, Indian pharmaceutical firms have yet to prove their competence in innovating new products. No NCE has yet been developed. There have been several setbacks and the partnership model has not always worked properly. There has been no significant success in new formulations either except for the once a day formulation developed by Ranbaxy for Cipro. What Indian companies have really demonstrated is the ability to develop generics for the regulated (and other) markets – an ability which they acquired and improved during the pre-TRIPS period (Chaudhuri 2005b).

Accordingly, as our case study shows, little has changed to dispute the traditional wisdom that developing countries should not grant product patent protection. In the absence of TRIPS-compliant protection, the impact on R&D for developing country firms is unlikely to be negative because developed countries have such protection anyway and these countries have the largest markets for new drugs. Moreover, there will be significant positive outcome: Generic companies from developing countries such as India will not be forbidden from developing processes for the new drugs innovated abroad and

manufacturing and supplying these at low prices locally and to other developing country markets - as in the case of antiretroviral drugs (ARVs) for HIV/AIDS. The price charged by the originator company for the triple combination, stavudine+lamivudine+nevirapine exceeded $10,000 per person per year and this was beyond the reach of most people in developing countries. Access to ARVs improved substantially after competition from Indian generic companies reduced the price dramatically. By June 2007, the combination was available at less than $100 from India (MSF 2007, p. 6).[37]

But is it not unfair for developing countries to withold product patent protection while enjoying the fruits of such protection in developed countries? As Challu (1991) and Chang (2001) have shown, most developed countries adopted pharmaceutical product patent protection only after they had reached a high degree of economic development. Thus, it is actually morally and historically unfair to deny the developing countries the privileges which developed countries enjoyed at the comparable stages of their development.

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Table 1 R&D Expenditure by Indian Pharmaceutical Industry

	Major spenders: No of cos	Major spenders: R&D exp as % of sales	Other cos: No of cos	Other cos: R&D exp as % of sales
1992-93	7	1.78	40	0.86
1994-95	14	2.42	64	1.15
1995-96	13	2.98	74	1.42
1996-97	16	2.80	73	1.23
1997-98	15	3.06	66	0.94
1998-99	15	3.10	71	0.86
1999-2000	18	3.17	70	0.94
2000-01	21	3.88	68	1.16
2001-02	24	3.86	74	1.33
2002-03	25	4.72	72	1.18
2003-04	28	5.79	81	1.23
2004-05	28	7.83	73	1.40
2005-06	28	8.79	65	1.20

Source: Prowess data base, Centre for Monitoring Indian Economy, Mumbai. All companies in the drugs and pharmaceutical industry which reported positive R&D have been considered here

Notes: Col 2 shows the number of major spenders for which data are available from the above mentioned source. For the list of major spenders, see Table 2.

Table 2 R&D Expenditure of Major Indian Pharmaceutical Companies

	R&D exp 2004-05 Rs million	R&D exp as % of sales 2004-05	R&D exp 2005-06 Rs million	R&D expenditure as % of sales 2005-06	R&D exp 2005-06 $ million
Ranbaxy Laboratories Ltd.	3996.6	9.35	6393.3	17.21	144.40
Dr. Reddy's Laboratories Ltd.	2977.9	17.12	2539.5	10.85	57.36
Sun Pharmaceutical Ind. Ltd.	1159.8	11.09	1614.9	11.93	36.48
Cipla Ltd.	983.8	4.10	1554	5.01	35.10
Cadila Healthcare Ltd.	1032	8.96	1187	8.87	26.81
Lupin Ltd.	836.1	6.86	1080.2	6.29	24.40
Nicholas Piramal India Ltd.	1084.4	8.29	911.5	6.04	20.59
Torrent Pharmaceuticals Ltd.	673.2	12.46	873.6	11.74	19.73
Wockhardt Ltd.	692.8	7.86	810.8	8.73	18.31
Aurobindo Pharma Ltd.	543.1	4.67	770.1	5.22	17.39
USV Ltd.	269.3	5.24	624.6	10.74	14.11
Orchid Chemicals & Pharmaceuticals Ltd.	522.1	7.57	613.6	6.95	13.86
Matrix Laboratories Ltd.	272	4.09	599	7.48	13.53
Panacea Biotec Ltd.	199.5	5.82	490.2	8.87	11.07
Glenmark Pharmaceuticals Ltd.	486.8	9.04	466.9	7.52	10.55
Ind-Swift Laboratories Ltd.	286.5	12.51	458.6	14.18	10.36
Strides Arcolab Ltd.	168.8	6.90	401.9	12.13	9.08
Biocon Ltd.	240.9	3.49	400.8	5.48	9.05
Ipca Laboratories Ltd.	335.9	4.58	378.8	4.62	8.56
Dabur Pharma Ltd.	215	9.12	268.9	9.94	6.07
Alembic Ltd.	311.2	5.44	266.7	4.00	6.02
Shasun Chemicals & Drugs Ltd.	308.2	9.27	263.6	7.14	5.95
Dishman Pharmaceuticals & Chemicals Ltd.	39.7	2.49	245.1	11.18	5.54
Unichem Laboratories Ltd.	153.9	3.64	123.2	2.58	2.78
J B Chemicals & Pharmaceuticals Ltd.	66.1	1.75	121.8	2.53	2.75
Bharat Serums & Vaccines Ltd.	93.6	10.23	114	11.67	2.57
Divi's Laboratories Ltd.	94.6	2.58	100.6	2.55	2.27
Natco Pharma Ltd.	52.2	3.04	74.3	4.30	1.68
TOTAL	18096	7.83	23747.5	8.79	536.38

Source: Same as in Table 1. Figures in rupees have been converted to US $ figures by using the average exchange rates for the relevant financial years obtained from Reserve Bank of India, *Handbook of Statistics on Indian Economy* (accessed from www.rbi.org.in).

Table 3 Export Intensity of Major Indian Pharmaceutical Companies, 2005-06

Company	Exports Rs million	Exports as % of sales	Exports as % of total exports of India
Ranbaxy Laboratories Ltd.	22243.4	59.89	10.31
Cipla Ltd.	15136.4	48.77	7.01
Dr. Reddy's Laboratories Ltd.	11966.6	51.11	5.55
Aurobindo Pharma Ltd.	8163.3	55.32	3.78
Lupin Ltd.	7611.0	44.32	3.53
Orchid Chemicals & Pharmaceuticals Ltd.	6210.1	70.32	2.88
Matrix Laboratories Ltd.	3902.7	49.50	1.81
Ipca Laboratories Ltd.	3857.7	47.02	1.79
Sun Pharmaceutical Inds. Ltd.	3652.1	26.97	1.69
Biocon Ltd.	3577.2	49.10	1.66
Divi's Laboratories Ltd.	3348.0	84.91	1.55
Wockhardt Ltd.	3201.7	34.49	1.48
Strides Arcolab Ltd.	2624.1	79.22	1.22
Shasun Chemicals & Drugs Ltd.	2452.8	66.41	1.14
J B Chemicals & Pharmaceuticals Ltd.	2447.1	50.87	1.13
Nicholas Piramal India Ltd.	2201.5	14.59	1.02
Cadila Healthcare Ltd.	2073.0	15.48	0.96
Ind-Swift Laboratories Ltd.	1507.1	46.60	0.70
Unimark Remedies Ltd.	1468.2	44.39	0.68
Dishman Pharmaceuticals & Chemicals Ltd.	1431.6	65.31	0.66
Glenmark Pharmaceuticals Ltd.	1408.1	22.68	0.65
Torrent Pharmaceuticals Ltd.	1344.2	18.06	0.62
Alembic Ltd.	1192.5	17.91	0.55
Dabur Pharma Ltd.	1158.5	42.84	0.54
Ajanta Pharma Ltd.	1116.3	52.56	0.52
Claris Lifesciences Ltd.	1039.0	36.47	0.48
Neuland Laboratories Ltd.	1037.5	60.80	0.48
Total	117371.7	44.93	54.39

Source: Same as in Table 1. These are the 27 largest Indian exporters in 2005-06 for which data have been reported. Each of these companies exported more than Rs 100 million in 2005-06. Only one MNC (Aventis Pharma) is a major exporter from India, exporting Rs 2222 million (24.9% of its sales).

Table 4 NCEs under Clinical Trials, Indian Pharmaceutical Companies as on 2006-07

Company	NCE	Indication	Development stage
Cadila Healthcare	ZY11	Anti-inflammation, pain	Phase I
Cadila Healthcare	ZYH2	Diabetes	Phase I
Cadila Healthcare	ZYH1	Dyslipidemia	Phase II
Dabur	DRF 7295	Anti-cancer	Phase II
Dr Reddys Labs	DRF2593	Diabetes	Phase II completed (partner Rheoscience, Denmark)
Dr Reddys Labs	DRL11605	Obesity	Phase I (assigned to Perlecen)
Dr Reddys Labs	RUS3108	Atherosclerosis	Phase I (assigned to Perlecen)
Dr Reddys Labs	DRF10945	Dyslipidemia	Phase II (assigned to Perlecen)
Dr Reddys Labs	DRF1042	Anti-cancer	Phase II (partner Clintec International. UK)
Glenmark	GRC8200	Diabetes	Phase II
Glenmark	GRC6211	Osteoarthritis, pain	Phase I
Glenmark	GRC3886	Asthma/COPD	Phase II
Lupin	LL3348 (herbal)	Anti-psoriasis	Phase II
Lupin	LL4858	Anti-TB	Phase I
Lupin	LL2011	Anti-migraine	Phase II completed
Lupin	LL4218	Anti-psoriasis	Phase I completed
Nicholas Piramal	P276	Anti-cancer	Phase II
Nicholas Piramal	PP04 (herbal)	Anti-fungal	Phase II
Nicholas Piramal	PP05 (herbal)	Arthritis	Phase II
Orchid	BLX1002	Diabetes	Phase II
Ranbaxy Labs	RBx9841	Urological disorders	Phase I
Ranbaxy Labs (jointly with MMV)	RBx11160	Antimalarial	Phase II (In India, Thailand and Africa)
Sun Pharmaceutical Industries	NCE	Anti-allergy	Phase II (in USA independently with a CRO)
Wockhardt	WCK771	MRSA, resistant infection	Phase II
Wockhardt	WCK1152	Respiratory infections	Phase I

Source: Company annual reports and websites, accessed February, 2007.

Table 5 R&D Output of Major Indian Pharmaceutical Companies as on 2006-07

Name of companies	No of DMFs	No of ANDAs	No of patents issued in USA
Aurobindo Pharma Ltd	105	70	9
Dr Reddys Laboratories Ltd	103	84	73
Cipla Ltd	88	4	3
Matrix Laboratories Ltd	80		
Ranbaxy Laboratories Ltd	77	204	79
Cadila Healthcare Ltd	73	50	3
Lupin Ltd	55	49	17
Sun Pharmaceutical Ind. Ltd	53	78	8
Orchid Chemicals & Pharmaceuticals Ltd	44	36	21
Hetero Drugs Ltd	35		5
Wockhardt Ltd	35	51	13
Divi's Laboratories Ltd	29		1
Glenmark Pharmaceuticals Ltd	26	29	5
Neuland Laboratories Ltd	25		
Ipca Laboratories Ltd	24	1	1
USV Ltd	19		8
Jubilant Organosys Ltd	19	18	3
Shasun Chemicals and Drugs Ltd	17		1
Cadila Pharmaceuticals Ltd	17		2
Biocon India Ltd	16		6
Alembic Ltd	16		5
Wanbury Ltd	15		
Natco Pharma Ltd	13	2	1
Sekhsaria Chemicals Ltd	11		1
Ind Swift Laboratories Ltd	10		1
Unichem Laboratories Ltd	8	2	
Nicholas Piramal India Ltd	6		3
Unique Chemicals	6	10	2
Torrent Pharmaceuticals Ltd	5	9	2
Dabur India Ltd	5	4	37
Panacea Biotec			13

Sources: (i) For DMF, www.fda.gov/cder/dmf/, accessed 15 July, 2007 - list updated till 15 May, 2007; (ii) For ANDAs, Electronic Orange Book, accessed on 10 July, 2007 from www.fda.gov and searched by applicant holder for both prescription and OTC drug products; (iii) For patents data, www.uspto.gov, searched issued patents by assignee name, accessed July 24, 2007.

Notes: Sun Pharmaceuticals includes Caraco; Dr Reddy's Laboratories includes Dr Reddys Research Foundation; Dabur India includes Dabur Research Foundation.

Table 6: Patenting by Indian Pharmaceutical Companies in USA

First name assignee	Before 1989	1990-94	1995-99	2000-05	Total
Ranbaxy Laboratories Ltd	0	7	13	45	65
Dr Reddy's Laboratories Ltd	0	0	10	33	43
Dabur India Ltd	0	0	1	27	28
Orchid Chemicals & Pharmaceuticals Ltd.	0	0	0	18	18
Panacea Biotec Ltd	0	0	6	8	14
Lupin Ltd	0	0	9	3	12
Torrent Pharmaceuticals Ltd.	0	0	0	8	8
USV Ltd	0	0	1	7	8
Biocon India Ltd	0	0	0	7	7
Wockhardt Ltd	0	0	0	7	7
Aurobindo Pharma Ltd	0	0	0	6	6
Sun Pharmaceutical Industries Ltd.	0	0	0	5	5
Total	0	7	40	174	221

Source: Company and year patent data obtained from, “Patenting by Geographical Region (State and Country), Breakout by Organization: Count of 1969-2005 Utility Patents Grants by Calendar Year of Grant” accessed from www.uspto.gov on 21 June, 2007. The list includes all organizations with 5 or more patents. Some discrepancies have been observed between this source and patent data obtained from direct search (Table 5). The numbers of patents granted to Panacea Biotec and Biocon, for example are 13 and 6 respectively in Table 5.

Notes: Dr Reddy's Laboratories includes Dr Reddy's Research Foundation; Dabur India includes Dabur Research Foundation

Table 7 Pharmaceutical Patenting by India, China, Brazil and South Africa

Country	Before 1995	1995-2000	2001-2005	Total
India	161	189	572	922
Brazil	20	19	32	71
South Africa	59	37	30	126
China	30	60	134	224
Total	270	305	768	1343

Source: "Patenting In Technology Classes Breakout By Geographic Origin (State and Country): Count of 1963 - 2005 Utility Patent Grants, By Calendar Year of Grant With Patent Counts Based on Primary Patent Classification," accessed from www.uspto.gov on 21 June, 2007. I have considered Class 424, Drug, Bio-Affecting and Body Treating Compositions (includes Class 514) and Class 532, Organic Compounds (includes Classes 532-570).

Notes

[1] The positive impact of patents on R&D is being increasingly questioned and alternatives are being talked about (see Baker 2004 for a review of some of the proposals).
[2] Such applications could be taken up for granting patents not before 1 January, 2005. But Exclusive Marketing Rights (EMRs) could be obtained for the application if a patent were granted in some other WTO member country and the application were not rejected in the country as not being an invention.
[3] Such claims have re-surfaced after an Indian court rejected Novartis' challenge of India's patent law (see, for example the editorial of the *Wall Street Journal*, "Drug Patents in India." August 14, 2007). Section 3(d) of India's Patents Act which Novartis challenged provides for conditional grant of patents for modifications of existing chemical entities (see below).
[4] See Velasquez and Boulet (1999, p.37), for a reference to such views.
[5] Prowess data base, Centre for Monitoring Indian Economy, Mumbai (CMIE). It provides company level data culled from company annual reports and other sources. Since 1992-93, R&D expenditure data are available for a sizable number of companies from this data base. In 1992-93, R&D expenditure was only 1.1% of sales for a sample of 47 companies considered by the Prowess database.
[6] Our sample of 28 pharmaceutical companies (see Table 2) includes each of the 27 largest R&D spenders in 2005-06 each with R&D expenditure above Rs 100 million in the year. We have also added in the sample Natco (R&D expenditure Rs 74.3 million), which is a major DMF filer in the US, the focus of our discussion in Section IV below.
[7] The source of R&D and sales data reported in this para is Prowess data base, CMIE.
[8] The companies get a handsome benefit of weighted deduction of 150% for expenditure relating to in-house research and development for income tax purposes (Mani, 2006). And this could be one of the factors explaining the rapid rise in R&D expenditure.
[9] Ranbaxy, Dr Reddys Laboratories and Cadila Healthcare spend about one-third of their R&D budget on NCE R&D (Singh (2006, p. 198); Dr Reddys Laboratories, *Annual Report, 2005-06*, p. 75; Cadila Healthcare, Investor Presentation, October, 2006 accessed from company website. www.zyduscadila.com. Assuming that other Indian pharmaceutical companies involved in NCE R&D, maintain a similar proportion (and this may be an overestimate for the smaller companies), total R&D expenditure for NCE is about Rs 5531 million in India in 2005-06. This constitutes only 23% of the total R&D expenditure by the 28 major companies.

[10] In the Indian private sector, Sarabhai Research Centre was the first one to be set up in the 1960s for developing new drugs. But it was wound up in the 1980s.
[11] Among the large Indian companies, a notable absentee is Cipla.
[12] Few other companies have also initiated or are in the process of initiating new drug discovery R&D. Panacea Biotec has announced that it is setting up a new centre for such R&D (www.panacea-biotec.com, accessed 28 July, 2007). Biocon is involved in R&D for development of novel biotherapeutics (*Annual Report, 2006-07*). Suven Life Sciences has diversified from contract research to collaborative research. It has started collaboration with Eli Lilly in 2006 for pre-clinical molecule R&D (www.suven.com accessed 28 July, 2007). Similarly Dr R Barbhaiya ex-chief of Ranbaxy R&D has set up Advinus Therapeutics in collaboration with the Tata group. It is involved in new drug discovery services (www.advinus.com accessed 28 July, 2007).
[13] See, Chaudhuri (2005a), section V and Chaudhuri (2005b), chapter 5.
[14] Personal discussion with B Gopalan, then with Glenmark Research Centre, Navi Mumbai, 11 February, 2005.
[15] Glenmark Pharmaceuticals Ltd, *Annual Report, 2003-04.*
[16] In the pre-TRIPS regime too some R&D for new drug development were undertaken in India primarily by Central Drug Research Institute (CDRI) (public sector), Ciba Geigy, Hoechst and Boots (all MNCs). As a result of these efforts not many drugs have come to the market. But it generated skills – see Chaudhuri (2005a).
[17] Glenmark has developed a compound for the treatment of asthma/COPD and entered into a licensing agreement with Forest Laboratories of the US. Forest has paid the former an upfront amount of $10 million on signing the agreement and depending on development and commercialization of the product, other

milestones payment will be paid totaling $190 million. In addition, Glenmark will get "mid-teens" royalty from Forest on net sales of the product in North America if the product is commercialized.

[18] Similarly, the Chairman said in its *Annual Report 2000-01* that "Our achievements in drug discovery are testimony to our belief that there is little correlation between innovation and size" and in its *Annual Report 2001-02* that "Even today, I am often inundated by various "facts and figures" … Our response to such data has been that in the area of discovery research we cannot be a prisoner of averages. The test of successful R&D driven pharmaceutical company should be its ability to consistently beat these so-called averages. Your Company exemplifies this tenet."

[19] Unlike the other product specific licensing deals, the second largest MNC in the world, GSK and the largest pharmaceutical company in India, Ranbaxy announced on October 2003 that they have entered into an R&D collaboration agreement covering a wide range of therapeutic areas. The agreement has been revised and the scope enlarged in February 2006 (see press releases in company website, www.ranbaxy.com).
[20] "Novartis Acquires Rights in Torrent's AGE Compound", Press Release, October 31, 2002 and "Torrent Licenses AGE Compound to Novartis, " Press Release, July 29, 2004**,** Torrent Pharmaceuticals Ltd (accessed from website: www.torrent-india.com).
[21] Similarly, Sun Pharmaceuticals has de-merged the company and has set up a new company to exclusively deal with NCE R&D, the investment requirements, risk profile and skill sets for which are different (Sun Pharmaceuticals, *Annual Report, 2005-06*, p. 5).

[22] Updated Table 2.5 of Chaudhuri 2005b, p. 45.
[23] We have considered as regulated markets, all the OECD countries except the recent members (Czech Republic, Korea, Mexico, Poland and Hungary).
[24] Calculated from export data compiled by the Directorate General of Commercial Intelligence & Statistics and obtained from CMIE India Trades data base.
[25] See, for example, Dr Reddys Laboratories, *Annual Report, 2005-06*, p. 85; Ranbaxy, *Annual Report, 2005*, p. 46. Mani (2006) has suggested that DMFs and ANDAs also should be used as indicators of research output of Indian pharmaceutical companies.
[26] Information on DMFs has been obtained from the website of US FDA (http://www.fda.gov/cder/dmf/). For APIs/intermediates to be manufactured in a location outside USA, FDA mentions the country. The data on DMFs for India have been compiled for all the DMFs for which India has been mentioned as the country.
[27] See, for example, Federal Trade Commission 2002, which did a detailed study on patents and generic entry in the US.
[28] The other certifications known as para I, II and III respectively are: (I) the required patent information has not been filed; (II) the patent has expired; (III) the patent has not yet expired and approval is sought after patent expiration.

[29] The total sales of generics of Dr Reddys increased from Rs 304 million in 2000-01 to Rs 4066 million in 2001-02, driven largely by the success of fluoxetine 40 mg, which contributed 81 per cent of the total generics sales. About half of Dr Reddy's operating profits in 2001-02 came from this product alone –see Dr Reddy's Laboratories Ltd, *Annual Report, 2001-02*.
[30] Another way in which a generic company can be the first to enter is to directly challenge the existing patents as Ranbaxy did in the case of cefuroxime axetil (Chaudhuri 2005b, p. 204).
[31] Ranbaxy, *Annual Report, 2006*.
[32] Matrix Laboratories Ltd, *Annual Report, 2005-06.*
[33] Lupin Ltd, *Annual Report, 2002-03.*
[34] Company-wise and year-wise patent data obtained from, "Patenting by Geographical Region (State and Country), Breakout by Organization: Count of 1969-2005 Utility Patents Grants by Calendar Year of Grant", accessed from www.uspto.gov on 21 June, 2007. The list includes all organizations (first name assignees) with 5 or more patents.
[35] The number of Cipla's published patent applications not yet issued in the US is however 14. Moreover, the number of patents filed in USA is much less than what Indian companies do worldwide. In 2006 alone,

Cipla had 49 patent applications published worldwide (European Patent Office website: http://ep.espacenet.com). See also Li (2007).

[36] The period for which these patents refer to has not been mentioned.

[37] These ARVs being pre-1995 drugs are not required to be patented in India under TRIPS.