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The R&D Scenario in Indian Pharmaceutical Industry

Reji K Joseph*

Abstract: A set of policy reforms have been introduced in the Indian pharmaceutical sector since mid-1990s, aimed at incentivizing the private sector R&D. Patent reforms was the most significant policy reform. An implicit assumption that the Indian pharmaceutical firms have become capable of developing new drugs underlined these reforms and it was expected that both the Indian firms and MNCs would invest in R&D on new drugs not only for diseases that are prevalent globally but also for diseases that are specific to India and other tropical countries. This discussion paper provides an analysis of the impact of these reforms on pharmaceutical R&D in India. It looks into the context in which the reforms were introduced, the nature and trends of R&D efforts and emerging R&D strategies.

Key Words: Indian pharmaceutical industry, R&D, policy reforms, patents, neglected diseases.

Introduction

One objective of the post-1994 policy regime was the incentivisation of pharmaceuticals research and development (R&D). Innovative products were given exemption from price control; a number of financial schemes were made available to firms for undertaking R&D; technology collaborations were brought under the automatic approval route; and most importantly, patent rights were granted for a period of 20 years for products as well as processes. What were the outcomes of these measures? Who are the major players? What are the therapeutic areas in which the R&D efforts are focused? This discussion paper makes an analysis of the R&D profile of the Indian pharmaceutical industry.

The Context

An important aspect of the policy reforms in the Indian economy since 1991 has been the change in the perception on the respective roles of the

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public and private sector industries. In the pre-liberalisation phase, public sector industry in the pharmaceutical sector was assigned the leadership role and the private sector was required to support the efforts of the State. In the liberalisation phase the public sector is assigned with inferior position and the leadership role is assigned to the private sector firms who are also expected to make commercially sensible decisions.

The 1948 Industrial Policy Resolution viewed foreign knowledge and technology as important instruments for the industrialisation of the country. The Resolution read that "it should be recognized that participation of foreign capital and enterprise, particularly as regards industrial technique and knowledge, will be of value to the rapid industrialisation of the country" (Para.10). Pharmaceuticals and drugs was one of the 18 industries which the Resolution recognised as industries requiring "investment of a high degree of technical skill". When Government of India observed that in the pharmaceutical sector the multinational companies (MNCs) were behaving just like trade agents, i.e. importing drugs and marketing in India and were not engaged in activities that would build domestic competence, a new strategy with the lead role assigned to the public sector firms was devised for building up the pharmaceutical industry. The Industrial Policy Resolution of 1956 classified industries into three categories based on their priorities. "Schedule A" industries were exclusively reserved for the public sector and "Schedule B" consisted of industries, where the public sector would play a lead role and the private sector was expected to supplement the efforts of the State. "Schedule C" consisted of the remaining industries whose future development was left to the private initiatives. The pharmaceutical industry fell under Schedule B. Private industry was also encouraged, though strictly regulated through industrial licensing. The leadership role of the public sector was further emphasised in the Industrial Policy Statement of 1977, which stated that "the public sector will be charged with the responsibility of encouraging the development of a wide range of ancillary industries, and contribute to the growth of decentralised production by making available its expertise in technology and management to small scale and cottage industry sectors." It also provided the perspective on technology capability building. In those priority areas where Indian skills and technology were not adequately developed, "preference would be for outright purchase of

the best available technology and then adapting such technology to the country's needs", subject to the conditions of setting up of indigenous R&D facilities to enable appropriate adaptation and assimilation of such technologies and of Government monitoring through the national registry of foreign collaborations in the Secretariat of the Foreign Investment Board.

In pursuit of these policies, the Government of India established five public sector companies in India of which two played very important roles - Hindustan Antibiotics Ltd. (HAL) and Indian Drugs and Pharmaceuticals Ltd. (IDPL).[1] IDPL was established with technical assistance from USSR and HAL with the technical assistance of World Health Organisation (WHO) and United Nations International Children's Emergency Fund (UNICEF). The two companies played a major role in building up technical competence in the industry as well in establishing a strong bulk drug industry in the country. According to Anand (1988), IDPL and HAL created a new environment and confidence that India could manufacture bulk drugs in a major way. The university system in India at that time did not provide the specialised training required by the pharmaceutical industry. IDPL and HAL not only encouraged the university system to impart specialised training required for the pharmaceutical industry by creating a demand for skilled labour but also sparked industrial developed in upstream and downstream business by generating demand for specialised capital and other services (Smith 2000). It was this dynamism that led to the creation of a bulk drug manufacturing industry in Hyderabad where the synthetic drug plant of IDPL is located (Chaudhuri 2005).

These two companies also made considerable efforts in the adaptation and assimilation of technologies supplied by their sponsors to meet Indian requirements. Modifications were required due to technological imperfections and due to the physical and economic climate in which the technology was being implemented (Joshi 1977). Efforts were also made for the exchange of technologies between the two firms. The government insisted that the technologies developed in the laboratories of IDPL and HAL from time to time, be shared with each other (Parthasarathy 2007). When it was found that the technology agreements with their sponsors were prohibiting the transfer of technologies between the two firms, the government found a way out by

making scientists from each company work in the other. When Merck & Co. of United States (US), which provided the technology to the streptomycin unit of HAL, objected to the sharing of the technology with IDPL and the USSR strongly objected to the application of technology of Merck & Co. in IDPL, the Government appointed a senior technologist of HAL to work in IDPL's antibiotics plant (Parthasarathy 2007). The technologies available in these firms were spilled over to the private sector by way of movement of scientists and technicians from public sector companies to the private sector. Some of the founders of private sector bulk drug manufacturing companies had earlier worked in public sector or companies, for example Dr. Anji Reddy, the founder of Dr. Reddy's Laboratories, had worked in IDPL.

The public sector research laboratories under the Council for Scientific and Industrial Research (CSIR), especially Central Drug Research Institute (CDRI), Indian Institute of Chemical Technology (IICT) and National Chemical Laboratory (NCL) also contributed considerably to the growth of the Indian pharmaceutical industry. Their contribution has been in the form of development of laboratory level processes that were transferred to private industry, which scaled up the technologies at the industry level. These laboratories also conducted research on the problems referred to them by the Indian companies. The process technologies developed by the CSIR laboratories includes technologies for ciprofloxacin, omeprazole, salbutamol, vitamin B6, lamivudine, diclofenac sodium and azithromycin. Almost all the top pharmaceutical companies in India have used the services of the CSIR laboratories (Chaudhuri 2005).

The Patents Act 1970 recognised only process patents in pharmaceuticals and Indian companies were required to invent new processes for the manufacture of patented drugs. The Patents Act 1970 came as a response to the recommendations of various pharmaceutical enquiry committees and the Government's own experience of product patents blocking technology capacity building during the implementation of the 'penicillin project'. The innovator companies usually patent a large number of processes so as to prevent others from manufacturing the product. Eli Lilly protected its anti infective drug Cefaclor through 32 processes and Ranbaxy managed to develop a new process which gained Ranbaxy international fame. Indian

companies were required only to prove the bioequivalence of their drug to market the drug in India.[2] The technologies developed in these laboratories also spilled over to the private sector through the movement of R&D personnel. J M Khanna and Bansi Lal, who headed the R&D divisions of Ranbaxy and Nicholas Piramal respectively, had been with CDRI before joining these firms (Chaudhuri 2005).

The outcome of all these concerted efforts was the emergence of a strong domestic pharmaceutical industry, which could tread an independent path to growth, making the country self-reliant in the production of the entire range of formulations that are required to meet the healthcare needs of the country[3] including drugs for the neglected diseases, transforming the drug prices scenario in the country from one of the highest in the world to one of the lowest in the world[4], reducing the time lag for the introduction of a drug in India after its launch in the global market from more than 15 years to less than 5 years[5], and earning the nation foreign exchange by way of a positive trade balance.[6] By the beginning of the 1990s, Indian pharmaceutical industry was globally recognised as a powerhouse in reverse engineering.

What is unique in the reform era is that the internally induced policy reforms and externally induced reforms, i.e. change in the intellectual property rights regime, have complemented each other. The Industrial Policy Statement of 1991, while assigning the leadership role to the private sector, called for the withdrawal of the government from exercising control, limiting its role to "providing help and guidance by making essential procedures fully transparent and by eliminating delays" (Para 21). As opposed to the earlier Industrial Policies, the 1991 Industrial Policy viewed foreign investment and technology collaborations involving MNCs as important channels for the technology competence building. The new intellectual property rights regime in the country would ensure that the intellectual property created (both process and product) would be protected and competitors would be prevented from taking undue advantage. With a strong patent regime in place, the pharmaceutical firms are expected to invest more in R&D. It has been argued by proponents of the product patent regime that stronger patent protection would stimulate innovation in pharmaceutical products (Levin 1987; Prasad and Bhat 1993; Prasad 1999).

What are the likely implications of these reforms on the future development of the Indian pharmaceutical industry? This industry has already mastered skills in reverse engineering and now needs to step into new drug development. The study of Balance *et al.* (1992) which analysed pharmaceutical industries in 27 countries classified Indian pharmaceutical industry in the group that is not active in discovering new chemical entities, but has the necessary technological capabilities to reverse engineer existing drugs. Do Indian firms possess the required skills and other resources for developing new drugs? If they do not possess these resources, it is very likely that they will be collaborating with MNCs as foreign investment and foreign technology collaborations are viewed as important means for competence building in the Indian industry. What will be the position of Indian firms in such alliances? Will they be collaborators on equal terms that would enable an independent path to growth or will they be subordinate collaborators which will lead to a dependent path to development?

One other issue of concern is whether the firms would find commercial opportunities in all therapeutic segments. If allying with MNCs, the R&D strategy of Indian firms is likely to be placed on global diseases, resulting in the neglect of diseases which are more prevalent in developing and least developed countries. There are two views on this. According to Aggrawal and Saibaba (2001) and Prasad and Bhat (1993), firms would find opportunities in all therapeutic areas including those predominantly prevalent in developing countries. They argue that it was the lack of product patent rights in pharmaceuticals in India that discouraged Indian firms, which are capable of developing new drugs, from venturing into new drug development. This line of argument is not convincing to all and another group of scholars maintain a contrary view. They make a careful distinction between diseases where the new patent regime would likely incentivise the firms and where it would not. According to them, R&D decisions are guided by commercial considerations and neglected diseases or diseases prevalent mostly in developing countries do not make an attractive market for the pharma majors. Keayla (1994) and Dhar and Rao (1993) argue that developing countries have very low purchasing power and hence diseases which are predominantly prevalent in them do not offer market incentives for R&D. The UK Commission on Intellectual Property Rights (CIPR 2002) reported that large companies

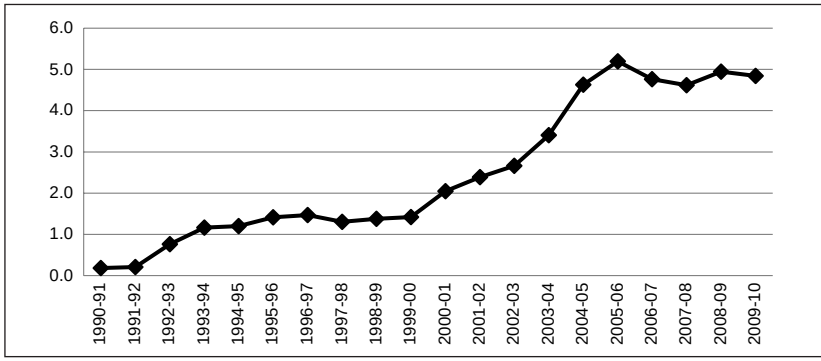
are unwilling to pursue a line of research unless the potential outcome is a product with annual sale of the order US$1 billion. Studies have shown that MNCs are not interested even in filing for patents in those countries where the market is not attractive. A study conducted in 53 African countries for 15 antiretroviral drugs found that patenting prevalence was only 21.6 per cent (Attaran and Gillespie 2001). How is the R&D scenario in pharmaceutical sector unfolding in the Indian context?

The paper aims to answer these questions by analysing the issues of: (a) emerging trends in R&D in pharmaceutical sector in India; (b) strategies adopted by domestic firms in technology competence building; and (c) therapeutic areas in which R&D investments are made.

Changing Trends in R&D

The global pharmaceuticals industry is highly research intensive and innovative firms spend on average about 15 per cent sales turn over in R&D.[7] However, R&D expenditure as percentage of sales turnover (R&D intensity) of Indian pharmaceuticals industry remained less than 2 per cent throughout the period till the beginning of the new millenniums. The report of the Hathi Committee (Government of India 1975) observed that R&D intensity was only 1.1 per cent in 1973. Perhaps the low R&D intensity is explained by the fact that Indian companies were engaged primarily in the manufacture of generics and development of non-infringing processes and not in new drug development, which involves huge investments. The process patent regime under the Patents Act 1970 enabled Indian companies to manufacture and market patented drugs using non-infringing processes. With the change in the Government's approach to the private sector and the creation of new incentive mechanisms (product patent rights), the R&D intensity began to increase from 2000-01 and reached its peak in 2005-06 (Figure 1). This increase has entirely been accounted for by the private sector and the R&D intensity of the public sector industry still remains below the 2 per cent mark. Since the R&D intensity of public sector industry is very low and its share in total industrial investment in R&D (public industry and private industry combined) is negligible[8] our focus of analysis in the following sections will be on private industry.

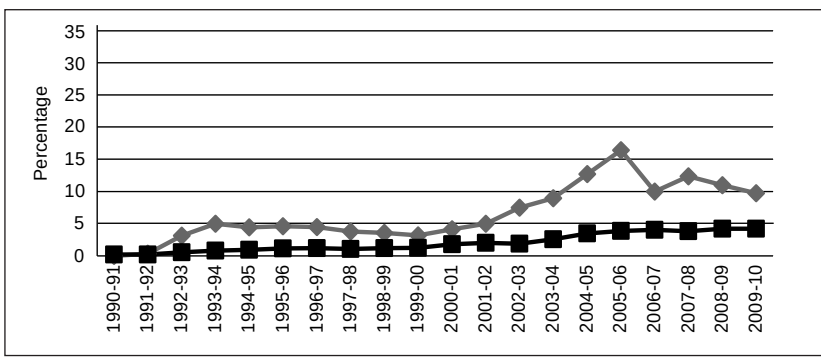
Figure 1: R&D-Sales Ratio in Pharmaceutical Industry in India (percentage)



***Source*:** Prowess.

Figure 1 shows that the R&D intensity began to decline after reaching its peak in 2005-06. The R&D intensity should have shown further acceleration in the post 2005-06 period especially because it was only in 2005 that India fully implemented the product patent regime in the country. Further, there were other incentives like tax benefits, grants and soft loans awaiting firms engaged in R&D[9]. Why did the R&D intensity decline after 2005-06? The firm-wise analysis using the Prowess data shows that the decline can be explained by just two firms - Dr. Reddy's and Ranbaxy (Figure 2).

Figure 2: R&D Intensity of Dr. Reddy's, Ranbaxy and Other Firms



Source: Prowess.

The R&D investment of all other firms while hovered around 4 per cent of sales, Ranbaxy and Dr. Reddy's invested 16 per cent of sales turn over in R&D in 2005-06. The R&D intensity of DR. Reddy's reached 18 per cent in 2004-05 and Ranbaxy's 20 per cent in 2005-06. But this came down to 9 per cent for Dr. Reddy's and 11per cent for Ranbaxy by 2009-10. What prompted these two companies to invest heavily in R&D and later forced them to reduce the allocation? Analysis of the entry of Indian pharmaceutical industry into new drug development shows that these two companies were the pioneers. Dr. Reddy's developed an anti-diabetic molecule (DRF 2593), which the company out-licensed to Novo Nordisk in 1997 for pre-clinical and clinical development. Dr. Reddy's also out-licensed two other anti-diabetic molecules - DRF 2725 and DRF 4148 - to Novo Nordisk and Novartis, respectively, in the following years. Similarly, Ranbaxy out-licensed its first compound (RBx 2258, for the treatment of benign prostate hyperplasia) in 2002 to Schwarz Pharma. When a molecule is out-licensed, the subsequent expenditure is incurred by the licensee and the license holder gets upfront and milestone payments and in some cases royalty payments upon commercialisation of the product. These deals brought substantial financial returns to both the companies. Dr. Reddy's deal with Novartis contained a package of $60 million of which $5 million was upfront and $55 million was to be milestone payments. Ranbaxy's deal with Schwarz Pharma provided for $48 million returns to the company of which $6.3 million was upfront and the remaining was in the form of milestone payments.[10] Ranbaxy was also to receive royalty payments on the commercialisation of the drug. Out-licensing seemed to be highly lucrative business model as the cost of development of molecules till the pre-clinical stage was relatively cheaper and prospects of returns from out-licensing were huge. It is reported that the cost of developing the first eight molecules of Dr. Reddy's till the pre-clinical stage was only $57 million (Chaudhuri 2005), and on average per molecule cost was only $7 million. Excited by the initial few out-licensing deals, both the companies boosted the allocations on R&D, resulting in R&D intensity growing many times as compared to the late 1990s.

But the trouble began when the licensees found problems at the pre-clinical and clinical development stages. In 2003, Novo Nordisk suspended the trials on DRF 2725 after finding tumours in the pre-clinical studies. In the same year Novartis also decided to discontinue the development of DRF

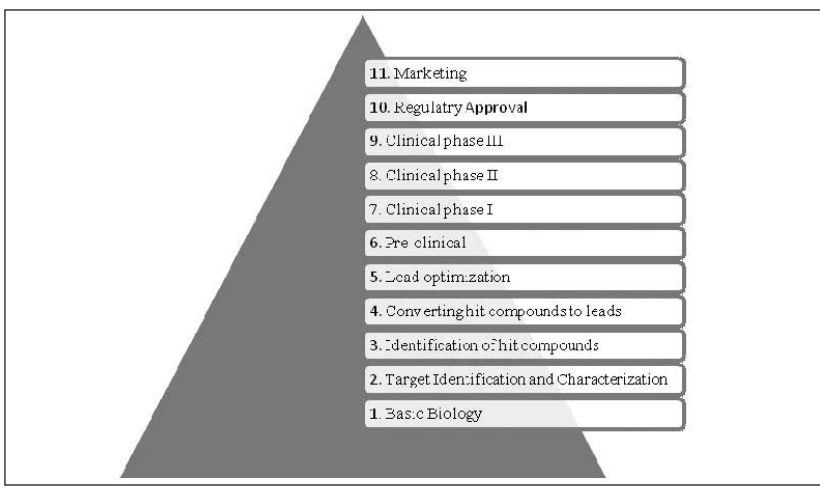
4148. In 2004, Novo Nordisk decided to terminate further clinical development of DRF 2593, as the phase II results did not suggest a sufficient competitive advantage for the molecule (Balaglitazone) compared to existing products. Schwarz Pharma in 2004 discontinued Ranbaxy's molecule (RBx 2258) due to disappointing results in phase II. These setbacks forced the two companies to review their R&D strategy and the direct outcome was pruning of R&D expenditure. The failure of the so-called "out-licensing business model" also manifested in other forms. Dr. Reddy's removed the line "discovery led global pharmaceutical company"[11] from its grandiose vision statement and replaced it with "the viable vision" to transform the company into an "ever flourishing company."[12] In 2009, Dr. Reddy's shut down its R&D office in Atlanta, US. In the same year, the company transferred its research division based in Hyderabad to a Bangalore based subsidiary Aurigene, which offers research services to pharma firms. Dr. Reddy's has now only 30 scientists working on new drug development compared to 280 in the early years of the last decade.[13]

Why did these companies out-license the molecules instead of developing them in-house till the last stage? Do they have the science and technology (S&T) skills and other resources required for developing new chemical entities (NCEs)? Analysis of the stages involved in the development of new drugs and the skills required in each stage would give some clues as to where the Indian pharma industry stands in terms of its ability to develop new drugs. Figure 3 gives the stages involved in the R&D process for new drugs.

In stages 1 and 2, biology studies are conducted to understand how a disease works and this leads to identification of the specific targets, inhibition of which plays a crucial role in treating the particular disease. In stages 3 to 5, teams of chemists, pharmacologists and biologists are engaged in screening thousands of compounds or chemically or genetically engineering new ones to generate potential compounds. Those molecules that have desirable properties are further modified to enhance the activity or minimize side effects (this process is known as lead optimization).[14] Pre-clinical testing (on animals; stage 6) and clinical trials (on humans; stages 7, 8 and 9) are conducted to determine the efficacy and safety of the molecule. During the pre-clinical phase, the study of how the drug moves through a living organism is conducted by examining four key processes - absorption, distribution, metabolism and excretion. The preclinical studies also involve chemistry tests to establish the purity of the compound, manufacturing tests to determine what will be involved

in the production of drug in a large scale and pharmaceutical tests to explore dosing, packing and formulation (for example pill, inhaler, injection, etc.). Pre-clinical studies take 3 to 6 years.[15] Phase I clinical trials are conducted on a small group of healthy volunteers of 20 to100 to determine the safety profile of the drug. Phase II trials involve volunteer patients of 100 to 500. The studies in this phase aim to establish the efficacy of the drug. Phase III involves a larger group of patients of 1000 to 5000 and the volunteers are closely monitored at regular intervals to confirm that the drug is effective and to identify side effects. During the phase III studies, toxicity tests and long-term safety evaluations are also carried out. Clinical trials take about 2 to 6 years. Once all the three phases of clinical trials are completed, the company applies for regulatory approval. Only one in every 10000 potential compounds investigated gets regulatory approval, which in turn takes efforts of about 15 years and involves R&D expenditure of $1 billion.[16] The clinical phase is the most expensive stage in new drug development. Forty per cent of the R&D expenses are incurred during this phase. On average, basic research accounts for 27 per cent, development of production processes 19 per cent, implementing regulatory requirements 7 per cent and other expenses 7 per cent.[17] Adequate skills in biology and medicinal chemistry are fundamental prerequisites for venturing into new drug development.

Figure 3: R&D Process for Developing New Drugs



Source: Kettler, White and Jordan (2003).

In a study for the Commission for Intellectual Property Rights, Innovation and Public Health (CIPIH) of the World Health Organisation, Chaudhuri (2005) analysed in detail the preparedness of the Indian pharmaceutical industry for new drug R&D. He found that this industry lacks the biology skills required in stages one and two and medicinal chemistry skills to carry out research from stage three to nine. The capabilities which Indian companies have in new drug research from stage six are in the manufacturing aspects of the compounds including process chemistry, scaling up, manufacturing process development and formulation development of proper dosage forms.

How did the leading Indian firms like Dr. Reddy's and Ranbaxy manage to develop new molecules till the pre-clinical stages, before out-licensing, if they did not have the skills to conduct R&D from stage one to five? The molecules developed by these firms do not fall under a completely new family of drugs, but are new molecules within an existing family of drugs that have already been well discovered. By working on targets that are already established and developing a new drug within a family that has been extensively researched, the company reduces some amount of uncertainties involved in new drug research (Chaudhuri 2005; Abrol *et al*., 2011). This model of R&D is known as 'analogue research'. The Japanese pharma firms had resorted to this strategy very successfully when they ventured into new drug development.[18] Dr. Reddy's anti-diabetic compound DRF 2593 (balaglitazone) is under the family of glitazone. Glitazones are the only approved anti-diabetic agents that are known to act as insulin sensitisers. Glenmark's GRC 3886 (oglemilast) belongs to the family of PDE4 inhibitors.[19] Similarly, Wockhardt's WCK 771/2349 is within the family of antibiotics fluroquinolines.[20] Fluroquinolines are broad spectrum antibiotics used in the treatment of a number of bacterial infections.

This shows that the argument that the Indian firms are capable of innovating NCEs and are in a position to take advantage of product patent rights is misplaced. PhRMA estimates suggest that out of 10000 molecules synthesized, only 20 reach the preclinical stage and 10 the clinical trials stage and ultimately only one gets the approval for marketing.[21] Going by this estimate, a company should have a minimum of 20 molecules at the pre-clinical stage if a successful one is to be expected. Since Indian firms

are using the analogue research strategy they also carry the additional risk of proving enhancement of efficacy over existing ones; in their efforts to develop molecules in the same family of drugs it is possible that they might be developing some molecules with certain therapeutic activities for which other drugs already exist in the market. So, the failure of the out-licensed molecules cannot be attributed as individual cases but is to be expected in the process of new drug development.

Indian companies also lag behind in the ability to invest in R&D. There have been reservations about the $1billion benchmark.[22] R&D costs in India can be much lower. McKinsey & company estimated that R&D in India would be only 40 to 60 per cent of similar costs in the US. CDRI estimated that it would cost only 30 per cent of expenses in US (Chaudhuri 2005). But the fact is that the R&D investments made by India's largest R&D spenders are way below the R&D spending of MNCs. The R&D investment of India's top three pharmaceutical R&D spenders' (Ranbaxy, Dr. Reddy's and Sun) in the last 12 years is way behind the $1 billion benchmark, with Ranbaxy at $728 million, Dr. Reddy's at $509 million and Sun at $232 million.[23] And this investment is inclusive of R&D expenses for the production of generics and new drug delivery systems (NDDS). While Pfizer, the largest pharma firm in the world, invested $7945 million in R&D in 2008 alone, even the combined R&D investment of India's top 10 pharma R&D investors during the last 10 years amounts to only $3172 million, 40 per cent of Pfizer's investment in just one year (2008).

The myth about the capacity to innovate new drugs also resulted in the failure to form dedicated R&D companies. By hiving off R&D units and creating new R&D companies, parent firms are expected to raise more funds. This would insulate the parent firms from the risks associated with the failure of research projects. Dr. Reddy's established India's first integrated drug development firm "Perlecan" in 2005 in collaboration with Citigroup Venture and ICICI Venture, putting together $52.2 million. Dr. Reddy's shifted four of its experimental drugs to Perlecan. Out of the four molecules, the development of three drugs had to be stopped due to the potential side effects. The remaining one did not prove to be more effective than drugs already existing in the market. In 2008, Citigroup and ICICI pulled out of Perlecan and Dr. Reddy's had to buy back their shares. The Perlecan

debacle need not come as a surprise because the success of such venture would require a large number of experimental drugs. Further, the financial outlay of the company was also very small. The failure of the out-licensed molecules further inhibited private venture capital from coming forward in supporting pharma R&D initiatives. A few companies like Nicholas Piramal also established separate R&D companies, but are now in the process of remerging the R&D company with the parent firm. Though Ranbaxy, Torrent and Wockhardt earlier had plans for spinning off R&D units, they have not gone ahead with the implementation,[24] possibly due to a late realisation which came in the wake of the Perlecan debacle.

The above discussion raises a number of questions. Does the paucity of skills and resources indicate a bleak prospect for the Indian pharmaceutical industry? Does the strategy of Indian drug firms really contribute to strengthening the innovative capability of Indian pharmaceutical industry? What do the Indian firms do to overcome their constraints? The following section analyses the emerging R&D strategies in the pharmaceutical sector in India.

Emerging R&D Strategies in the Pharmaceutical Sector

Unlike in the pre-reform era when the government provided the direction and necessary support, now the firms are expected to be standing on their own feet and are required to take decisions based on commercial considerations. Indian pharmaceutical firms have been engaging in various kinds of business collaborations in R&D with MNCs. Such collaborations are to be expected in the new environment where the foreign technology and capital have been viewed favourably in accelerating the process of competence building. But the important issue is whether such alliances result in actual competence building. There are broadly three kinds of alliances involving MNCs: contract research and manufacturing services (CRAMS), collaborative research projects (CRPs) and out-licensing and in-licensing.

Contract Research and Manufacturing Services

CRAMS are essentially outsourcing arrangements. CRAMS include manufacturing of active pharmaceutical ingredients and formulations;

chemistry and biology research for new drug compounds; pre-clinical trials; and clinical trials. The CRAMS market in India was estimated at $2.5 billion in 2009[25] and is expected to reach $6.6 billion by 2013.[26]

There are many factors forcing MNCs to outsource their production to India. Cost of manufacturing is substantially low in India – as low as 35 per cent of US costs and 28 per cent of cost in Europe (ICRA 2011). India also has the largest number of US Food and Drug Administration (FDA) approved manufacturing plants outside the US.[27] MNCs like AstraZeneca and Eli Lilly have already announced their plans to outsource substantial part of their manufacturing activities to firms in countries like India. In 2010, the contract manufacturing market in India was estimated at $2.3 billion.[28] Top global pharma firms like Pfizer, Merck, GlaxoSmithKline, Sanofi-Aventis, Novartis, Teva, etc., largely depend on Indian firms for the supply of many of their active pharmaceutical ingredients (APIs) and intermediates (FICCI, 2005). Table 1 gives the list of leading firms engaged in contract manufacturing in pharmaceuticals and the type of products.

Foreign companies are keen to outsource their production for containing their cost. India has become a favourable destination as it has the largest number of USFDA approved plants outside the US. India has more than 160 FDA approved plants in India whereas its competitor China has only about 30 (ICRA 2011). We do not have information on how many of the outsourced APIs are under patent protection so as to draw some conclusions on the impact of new IP rules on outsourcing.

Earlier, it was the smaller Indian firms who were into contract manufacturing, but lately larger firms like Dr. Reddy's are also into this business as part of much wider alliances such as marketing collaborations. The alliance between Dr. Reddy's and GlaxoSmithKline (GSK) provides that latter would have exclusive access to Dr. Reddy's diverse portfolio and future pipeline of more than 100 formulations in therapeutic segments such as cardiovascular, diabetes, oncology, gastroenterology and pain management. The drugs will be manufactured by Dr. Reddy's and licensed and supplied by GSK in various developing countries in Africa, the Middle East, Asia Pacific and Latin America. In some markets, the drugs will be co-marketed by both companies.[29] Revenues will be shared with Dr. Reddy's as per the agreement.

Similar kinds of contract manufacturing alliances involving marketing tie-ups exist between AstraZeneca and Torrent; Pfizer and Aurobindo; Pfizer and Biocon; and Boehringer Ingelheim and Cipla. The financial terms of these deals are often not disclosed and hence it is not possible to gauge the actual size of the contract manufacturing business as part of wider alliances. Glenmark is in agreement with Napo pharmaceuticals of US, as part of its alliance to develop Crofelemer compound for its diarrhoea indication, for the exclusive supply of Napo's global requirement of the API for Crofelemer drug.[30]

Table 1: Outsourcing by MNCs

Indian Partner	**MNC**	**Outsourced Products**
Cadila Healthcare	Altana (Germany)	Two intermediates for Altana's under patent molecule Protonix (pantoprazole)
	Boehringer Ingelheim (Germany)	Gastrointestinal and cardiovascular products
	Mayne (Australia)	Intermediates for oncology products
Hikal Ltd.	Degussa	Pharmaceutical intermediates and APIs
Nicholas Piramal	Advanced Medical Optics (USA)	Neutralising tablets and sterile FFS packs (product name not disclosed)
	Allergan (USA)	APIs For Levobunolol (Betagen) And Brimonidine (Alphagan and Alphagan-D)
	AstraZenica (Sweeden)	APIs
	Pfizer (USA)	APIs
Dishman Pharma	Solvay (Belgium)	6 projects. Main one being for starting material and advanced intermediate for Tevetan (eprosartan maleate)
	AstraZenica (Sweden)	intermediate for Nexium (esomeprazole)
	GSK (UK)	Intermediates and APIs
	Merck (USA)	Intermediate for Losartan (to be supplied to its contract manufacturer in Japan)
Shasun Chemicals	GSK (UK)	API for Ranitidine
	Eli Lilly (USA)	APIs for Nizatidine, Metohexital and Cycloserine
	Reliant Pharma (USA)	APIs
	Alpharma (USA)	APIs and generics
	Boots (S. Africa)	APIs
Lupin Labs.	Fujisawa (Japan)	Cefixime
	Apotex (Canada)	Cefuroxime Axetil, Lisinopril
	DMS (USA)	APIs for cephalosporings
IPCA labs.	Merck (USA)	APIs
	Tillomed (UK)	Atenelol
Biocon	Bristol Myers Squibb (USA)	APIs

***Source*:** KPMG (2005) and Linton and Nicholas (2007).

The contract research business in India was estimated at $1.5 billion in 2010.[31] The contract research market in India is growing at a more rapid pace as compared to the global contract research market. Between 2007 and 2010 when the global contract research market grew at CAGR 19 per cent to reach $25 billion in 2010, this market in India grew at CAGR 65 per cent to reach $1.5 billion. The low cost of conducting research in India is an important factor for the outsourcing of research to India. R&D activities in India are estimated to be 60-65 per cent cheaper as compared to the costs in the US. Labour cost in India is in the range of 10-15 per cent of similar costs in the US. There is 25-50 per cent reduction in the upfront capital requirements in setting up R&D projects in India due to locally fabricated equipment and high quality local technology/engineering skills.[32] The cost advantage of conducting clinical trials in India is more than 50 per cent during phase I studies and more than 60 per cent during the phase II and phase III studies.[33] More than half (52 per cent) of the contract research in India takes place in clinical trials.[34] There are other factors which make India an attractive destination for clinical trials. India provides a large population which is ethnically and genetically diverse and suffering from various ailments (Grace 2004). India has six out of the seven genetic varieties of human race and a large size of treatment-naive population (untreated) who are looking for cure and better treatment (Srinivasan and Sachin 2009). English speaking population and a well developed communication network with information technology capabilities are also advantages in favour of India in clinical trials. Contract research organisations (CROs) have grown in number in India from 20 in 2005 to 100 in 2008 and are expected to number 150-200 by 2012. Table 2 lists leading CROs in India.

Contract research arrangements are for fixed periods on an identified therapeutic area. The service provider receives research funding and milestone payments. Those Indian companies that have proven strengths in selected areas of drug discovery but are not prepared to step into new drug development enter into this type of collaborations. The risk of the failure of the project is entirely borne by the outsourcing company and the compound developed under the partnership will be owned by it. A number of mid level Indian firms are actively engaged in this business. Jubilant Organosis, a Bangalore based company, has research collaborations with two leading

MNCs and a foreign university. It has a five year contract, starting in 2009, with AstraZeneca to add to its pre-clinical pipeline in neuroscience. Jubilant is expected to earn $220 million in upfront and milestone payments. Of this, $20 million is upfront with an annual payment of $3 million coming in during the first two years. The company could potentially earn up to $200 million as and when it meets certain targets in developing drugs under the deal. This deal also provides for royalties from AstraZeneca on successful sale of any drug.[35] Jubilant also has a similar arrangement with Eli Lilly for a period of nine years starting in 2005. In this deal, however, Jubilant will receive only upfront and milestone payments and not royalties.[36] The company has entered into a multi faceted partnership with Duke University in 2009. In this partnership, Jubilant and Duke University would jointly select a set of research projects that synergize on the research capabilities of Duke University and the development capabilities of Jubilant.[37] Jubilant is expected to translate discoveries of Duke scientists into clinical therapies.[38]

Table 2: Leading CROs in India

Companies in Contract Research (excluding clinical trials)	**Companies in Contract Research (in clinical trials)**
Aurigene (Dr. Reddy's)	Clingene (Biocon)
Syngene (Biocon)	Jubilant Clinsys (Jubilant Organosys)
GVK Biosciences	WellQuest (Nicholas Piramal)
Jubilant Organosys	Synchron
Divi's Laboratories	Vimta Labs
Vimta Labs	Lambada (Intas)
Suven Life Sciences	SRL Ranbaxy
Dr. Reddy's Laboratories	Reliance Life Sciences
Nicholas Piramal	Asian Clinical Trials (Suven Life Sciences)
Shasun Chemicals	Metropolis
Avra Labs	Quintiles
Procitius Research	Manipal Acunova

Source: Abrol, *et al.* (2011); Rao (2007); Planning Commission of India (2006).

GVK Biosciences, a Hyderabad based contract research firm offering drug discovery services, started with bioinformatics and then moved into providing medicinal chemistry services. According to the Report of the Working Group on Drugs and Pharmaceuticals for the Eleventh Five Year

Plan (Planning Commission of India, 2006) GVK Biosciences is planning in future to begin a collaborative research programme where they can partner with virtual companies not having any fixed assets. Virtual companies work with specialist service providers and sell off the molecule whenever they get the optimum price. Contract research arrangements provide a source of revenue for Indian partners but their contribution in terms of competence building is doubtful. In this arrangement, the Indian firms are expected to perform piecemeal jobs in drug research and they are not exposed to the whole process of new drug development. Further, the products developed out of the partnership are exclusively owned by the outsourcing firm, denying Indian firms an opportunity to benefit from the future gains accruing to the product.

Firms offering clinical trial services, unlike those offering drug discovery services, essentially perform the administrative work of the clinical trials (Srinivasan and Sachin 2009). They recruit researchers and train them, provide them with supplies, coordinate study administration and data collection, organize meetings, ensure that the trial is in compliance with clinical protocol and ensure that the sponsor receives clean data from all trial sites. It is the responsibility of the sponsor to monitor the study results coming from different study sites.

Clinical trials in India are regulated under the Schedule Y of the Drugs and Cosmetics Rules, 1945 and are monitored by the Drug Controller General of India (DCGI). For new drugs developed in India, clinical trials have to be conducted in India from phase I. For obtaining marketing approval for a drug that is already approved in other countries, phase III trials have to be conducted in India on 100 people to assess the impact on the Indian ethnic population. Till 2005, the year in which the Schedule Y of the Drugs and Cosmetics Rules was amended, clinical trials of drugs developed outside India were permitted only with a “phase lag”, meaning phase III would be permitted only when phase III was completed outside India (Srinivasan and Sachin 2009). This restriction served the twin purposes of safeguarding against the initiation of unnecessary clinical trials in India and also forcing the companies to conduct R&D in India if they are to conduct clinical trials here from early stages. The amended Rules enabled parallel global clinical

trials where firms can conduct clinical trials in India without the phase lag. In just one year period from 1 April 2009 to 31 March 2010, the DCGI has granted 237 permissions for global clinical trials in the country.[39] With effect from 15 June 2009 registration of applicants in the clinical trial registry maintained by Indian Council of Medical research (ICMR) has become mandatory for conducting clinical trials in India.

Do Indian pharmaceutical firms benefit from the liberalised clinical trial regulation in the country? The pharmaceutical industry would benefit if the clinical trials offer an opportunity for it to build competence. The recent study of Abrol *et al*. (2011) finds that clinical trials by MNCs are concentrated in phase III where the gains of competence building are extremely limited and domestic firms are just starting to enter into phase I trials. Phase III trials are designed just to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication by conducting trials on a larger population, and no new safety and effective assessments are done. The study argues that the health infrastructure and the healthcare personnel India has created during the past more than 60 years are increasingly being utilised for the benefit of MNCs. In the process, patients in India have been misused in clinical trials. In June 2011, the DCGI suspended the clinical trial of an anti-cancer drug conducted by Hyderabad based Axis Clinicals on account of its violating the Schedule Y requirement of obtaining informed consent of the people on which trials are conducted. The illegal trial came to light when at least nine women from Guntur district of Andhra Pradesh reported health problems to a local doctor.[40] Not informing the people involved about the trials and not documenting their informed consent is a means for huge costs saving for the company. Schedule Y and the Indian Good Clinical Practices Guidelines require the sponsor to meet compensation requirements in case any harm is caused to the people during the trials.

Another aspect of business related to clinical trials is clinical data management. Managing clinical trial data requires multi-disciplinary skills – information technology, clinical terminology and physician skills (Rao, 2007). A number of leading information technology firms like Tata Consultancy Services (TCS), Cognizant, Satyam, HCL, Infosys and IBM and

clinical trial companies like Quintiles and Manipal Acunova are engaged in this business. Pharmaceutical MNCs like GSK has established clinical data management units in India. The Clinical Data Management Centre India (CDMCI) established in 1996 and Biomedical Data Sciences India (BDSI) established in 1999 are under the management of GSK.[41] The services offered by this category of firms range from protocol development to data management, analysis and reporting to manuscript writing. In 2007, this business was estimated at $100, million growing at 80 per cent per year (Rao 2007). Clinical data management services have not been included in the above discussion on CRAMS. If we include this business also in the CRAMS, this may be perhaps the fastest growing business category under the CRAMS.

The contract research arrangements taking place in India *per se* do not result in any technology transfer and in that sense does not amount to competence building. However, they provide an opportunity for firms to improve their skills in specialised areas of new drug discovery and development and to strengthen their finances. In the long run those companies which offer integrated drug development, research, clinical trials and manufacturing outsourcing services like Dr. Reddy's, Nicholas Piramal, Suven Life Sciences and Biocon (Table 2) would be able to synergies the strengths accumulated in various stages of drug discovery and development. For those firms engaged in providing services in the initial stages of drug development, the opportunity is open to synergise from the skills developed and profits accumulated and move into higher levels of new drug R&D, an example being Suven Life Sciences (discussed below).

Collaborative Research Projects

There is only a thin line differentiating contract drug discovery and development services and CRPs. In contract drug discovery and development services, the firm provides discovery services in a number of therapeutic areas, whereas in CRPs the Indian firm's focus is in selected therapeutic areas. But the firm may have collaborative tie-ups with more than one MNC. In CRPs, the MNC and Indian partner jointly discover drug molecules and develop them. In CRPs, unlike in CRAMS, risk is shared proportionally. The

MNC works closely with the Indian partner in the discovery process and the clinical development is the responsibility of the MNC. The Indian company gets upfront payments and milestone and royalty payments depending on the progress and commercialisation of the drug. However, the compound is owned by the MNC. A few mid-level Indian firms are involved in CRPs. Suven Lifesciences, which started off as a generic company and then moved on to CRAMS and finally reached CRPs, provides the best example. Suven Lifesciences focuses its research on central nervous system (CNS) disorders. Research in CNS disorder like Alzheimer's disease or depression is very difficult as quantitative measurements are not possible, unlike in the case of diseases like hypertension. This requires expertise and Suven has brought in Eli Lilly as its collaborator in CNS research. The company now has 13 molecules in various stages of pre-clinical development.[42]

In CRPs, royalty is an essential component of the arrangement, unlike the CRAMS. This would ensure a steady stream of income to Indian firms. As for CRAMS, in CRPs also Indian firms are subordinate allies, who are entitled only to a fraction of the total benefits accruing to the product. Since the Indian firms work jointly with the MNC partners, the chances are better for building up specialised skills as compared to CRAMS. The royalty payments involved often are in double digit percentages and this is a major incentive for Indian firms to enter into CRPs.[43]

Out-licensing and In-licensing

Out-licensing

Discovery and development of new drugs require huge financial resources and expertise. As a result, in most cases, Indian companies have collaborated with MNC partners at the more advanced stages of drug development - clinical development. Outlicensing is the most widely adopted strategy of major Indian firms. They independently develop the molecule up to a certain stage and then license it out to an MNC partner for further development. Indian firms receive upfront and milestone payments and royalty (depending on the terms of the contract), on successful marketing of the drug. In some cases of out-licensing, Indian firms have been entitled to marketing rights and to contract manufacturing opportunities. The Ranbaxy-Schwarz Pharma

deal on RBx 2258 compound provided that Schwarz Pharma would retain exclusive marketing rights in Europe, Japan and the United States, while Ranbaxy would retain the rights for rest of the markets. The deal also provided for Ranbaxy to manufacture and supply finished formulations of the drug to Schwarz Pharma.[44] Outlicensing was considered a win-win strategy because on the one hand it augments the scarcity of resources in finance and research skills of the Indian firms and on the other it gives the MNCs access to promising compounds at considerably lower prices. With the NCE pipeline of MNCs drying up and the profit margins hitting the bottom due to competition from generic firms, the MNCs are forced to look for new compounds. In fact, many of these companies have started compound acquisition departments in their companies. The out-licensing business was initiated in the country by Dr. Reddy's and Ranbaxy. They were later joined by others like Glenmark and Torrent.

With consecutive setbacks in out-licensing deals, Indian firms became more careful in outsourcing deals and in selecting partners. Dr Reddy's entered into an agreement with Rheoscience, a subsidiary of Denmark based Nordic Bioscience, for the development of Balaglitazone (DRF 2593) which was abandoned by Novo Nordisk. The molecule currently is at an advanced stage of phase III trials. And in many cases the companies are pursuing the development of drugs independently. When Merck decided to shift away its focus from anti-diabetic research, it returned to Glenmark a molecule (GRC 8200, Melogliptin) it had licensed in 2006. Glenmark was paid $31million upfront for this deal in 2006. When Merck pulled out from the deal in 2008, Glenmark decided to develop the drug on its own and now the molecule is in phase III trials. Piramal Lifesciences also follows a similar strategy in the case of cancer drugs. The company is striving to develop its own cancer drugs which are less expensive to develop at about $100 million. At present the company has one molecule (for a head and neck cancer) in phase II clinical trials. Piramal Lifesciences' strategy is that it would go for out-licensing only in non-cancer drugs, and that too after the compound passes phase II. The company has learned that MNCs are not willing to pay much for compounds out-licensed in the initial stages of development.[45] Whenever out-licensing is required, most Indian firms now pursue the strategy of developing the molecule till phase II. Valuation goes

up considerably when the molecule passes phase II. Suven Lifesciences also pursue the same strategy in its in-house developed CNS candidates.[46] This strategy, at the same time, raises the risks also as failures at higher levels of R&D means more loses. The growing confidence among the Indian firms may be an indication to the growing innovative as well as financial capabilities of Indian pharmaceutical firms.

How will Indian firms be able to develop further in-house molecules, if they do not have the required S&T skills? The non-resident Indians (NRIs) having experience in new drug development projects of MNCs are increasingly becoming resource persons. A number of new drug development projects of Indian companies are headed by NRIs with experience in pharma MNCs. Dr. Rajinder Kumar and Dr. Rashmi H. Barbhaiya, who earlier headed R&D division of Ranbaxy, had worked at GlaxoSmithKline and Bristol Myers Squibb, respectively (Chaudhuri 2005). Dr. Uday Saxena, the President and Chief Executive Officer of Reddy US Therapeutics, Inc., a subsidiary of Dr. Reddy's group since 2002 has earlier worked with AtheroGenics, Inc. a biopharmaceutical company located in Georgia, US, where he directed several drug discovery and early development programmes. He was also associated with Parke-Davis Research Division in Michigan, US, where he was responsible for establishing a discovery programme in inflammation and atherogenesis.[47] Similarly, Dr. Somesh Sharma, Managing Director of Piramal Life Sciences is also an NRI who worked with Monoclonal Antibody and Vaccine Unit at Anosys Inc., USA before joining Piramal Lifesciecnes.[48] It has been estimated that 15per cent of those working in the laboratories of pharmaceutical companies in US and Europe are of Indian origin (Chaudhuri 2005).

In-licensing

There are also a few cases of in-licensing of molecules for clinical development, though these are very few in number. Glenmark has an in-licensing deal with San Francisco based Napo Pharmaceuticals for Napo's proprietary anti-diarrheal molecule Crofelemer. Diarrhea is the most commonly reported gastrointestinal symptom in HIV infected patients. About 15-30 per cent of HIV/AIDS infected population is affected with diarrhea.

Napo has granted development and commercialisation rights to Glenmark in 140 countries including India (outside US, Europe, China and Japan).[49] Glenmark has successfully completed phase III clinical trials in the US last year and is working towards regulatory approvals for the marketing of the drug.[50]

What is important in this deal is that the intellectual property rights over composition of matter and formulation of the compound are with the Napo. Glenmark has been given the license to develop and commercialise the drug in certain geographical areas. It also contained a contract manufacturing provision wherein Glenmark would exclusively supply Napo's global API requirements for the manufacturing and sale of Crofelemer drug.[51] Glenmark also received $15 million for upgrading its Crofelemer API manufacturing unit. As in the other collaboration models, in-licensing is also more of a business opportunity for Indian firms than means for competence building through joint ownership of the technologies generated out of the partnerships.

In all kinds of partnerships involving MNCs, Indian firms always have a subordinate status which may in the long run result in a dependency relationship of Indian firms with the MNCs. This can have deleterious consequences to the country in many ways. Being trusted allies in the global strategy of MNCs, Indian companies may lose interest in those therapeutic areas which do not have global presence (for example, tropical country diseases). These allies might also withhold themselves from exercising compulsory licensing provisions, the TRIPS instruments to counter any abuse of monopoly rights of the patents.

The R&D efforts of Indian companies are not just confined to new drug development. Substantial efforts are into the development of generics and NDDS.

Other Areas of R&D

Development of generics

The most important factor leading to the expansion of the Indian generic industry has been the acceptance of its low priced drugs by consumers the

world over. The share of exports in sales turnover has grown from 15 per cent to 41 per cent between 1993-94 and 2009-10. The approvals obtained by Indian firms in regulated markets, especially in the US give the best illustration of R&D put into the generics business.

Firms are keen to enter the regulated markets, despite the stringent standards, as they offer better economic prospects. The doors of the generic drugs market in the US opened in 1984 with the 'Drug Price Competition and Patent Restoration Act' (better known as the Hatch-Waxman Act). This legislation facilitated the entry of generic versions of previously approved innovator drugs to be brought into the market. There are two sets of data indicating the extent to which Indian firms are seeking opportunities in the US market – approvals of abbreviated new drug applications (ANDAs) and drug master files (DMFs). Generic drug applications are termed 'abbreviated' because they are generally not required to include pre-clinical and clinical data to establish safety and efficacy and are only required to demonstrate the bioequivalence of the product. When filing an ANDA, the company is required to certify that its product is not infringing any patent rights or the patent is invalid (para IV certification). If the company successfully proves that the patent is invalid or if it is the first one to get approval for the generic version, it gets market exclusivity for 180 days during which no other generic company is permitted to enter the market. DMF, on the other hand, is a package of proprietary information that is voluntarily filed by a firm with the USFDA, which indicates the future intention of the company to market the product in the US. There are five types of DMFs: *Type I* relating to manufacturing site facilities and operating procedures; *Type II* relating to drug substance, drug substance intermediate, and material used in their preparation or drug product; *Type III* relating to packaging material; *Type IV* relating to excipient (material carrying the active ingredient), colorant, flavour, essence or material used in their preparation, and *Type V* on FDA accepted reference information. Type II DMF applications would give indication on the number of drugs on which a firm is interested in the US market. Table 3 shows the ANDA approvals including the first time generic approvals with 180 day exclusivity and DMF filings in the US by leading Indian firms.

Table 3: ANDA Approvals, First Time Generic Approvals (180 Day Exclusivity) and DMF Filings in the Us by Leading Indian Firms

Company	2001		2002		2003		2004		2005		2006		2007		2008		2009		2010		Total	Total	DMF#
Aurobindo	0	0	0	0	0	0	2	1	7	2	9	1	27	1	19	3	18	3	17	0	99	11	144
Dr Reddy's	5	1	4	2	3	0	3	3	6	2	14	4	13	2	13	1	17	4	11	6	83	31	153
Ranbaxy	3	1	11	3	15	9	14	5	15	5	6	2	14	6	3	1	7	3	3	1	81	46	101
Sun	0	0	0	0	0	0	0	0	0	0	7	0	10	3	21	2	17	5	12	0	67	10	70
Wockhardt	0	0	0	0	4	0	0	0	4	1	6	0	13	1	18	0	14	1	5	0	64	3	43
Glenmark	0	0	0	0	0	0	0	0	0	0	4	0	9	2	5	0	9	1	19	3	46	6	45
Lupin	0	0	0	0	3	0	2	2	5	0	6	3	7	2	4	1	1	0	12	3	40	11	100
Orchid	0	0	0	0	0	0	0	0	9	0	9	0	4	1	3	0	3	2	2	0	30	3	77
Matrix	0	0	0	0	0	0	1	0	0	0	0	0	1	0	2	1	3	1	10	1	17	3	139
Cipla	0	0	0	0	0	0	0	0	0	0	0	0	2	0	4	0	3	1	1	0	10	1	90
Total	8	2	15	5	25	9	22	11	46	10	61	10	100	18	92	9	92	21	92	14	537	125	962

Note: Figures in the shaded columns indicate first time generic approvals; # Type II DMF.
Source: US FDA.[52]

The leading 10 firms in India got 537 ANDA approvals in the last decade, of which one-fourth carried 180 day market exclusivity. The bulk of these activities were carried out by three firms – Aurobindo, Ranbaxy and Dr. Reddy's. Ranbaxy and Dr. Reddy's stand out distinctly for their aggressive approach to challenging patents and obtaining the market exclusivity. Fifty-seven per cent of Ranbaxy's and 37 per cent of Dr. Reddy's ANDA approvals carry market exclusivity as against the average 23 per cent for all the leading firms. An illustrative list of innovators' exclusive markets thrown open to Indian generics with 180 day exclusivity is given in Table 4.

Table 4: Selected Drugs for which Indian Companies Have 180 Day Market Exclusivity in the US

Indian Company	Year of launch	Brand	Innovator	Innovator Sales/ Year ($Mn)
Sun & Glenmark	2007	Trileptal	Novartis	700
Dr. Reddy's	2008	Imitrex	GlaxoSmithKline	1000
Sun	2008	Protonix	Altana	2300
Lupin	2008	Ramipril	Bayer	800
Sun	2009	Effexor XR	Wyeth	2300
Ranbaxy	2009	Flomax	Boehringer Ingelhiem	1300
Ranbaxy	2010	Lipitor	Pfizer	8000
Ranbaxy	2010/11	Aricept	Eisai	1600
Glenmark	2010/11	Zetia	Schering-Plough/Merck	1200
Glenmark	2010/11	Tarka	Abbot/Sanofi Aventis	72
Glenmark	2010/11	Cutivate	Nycomed	37

Source: Compiled from Company Reports and Media Reports.

Only few companies, particularly Ranbaxy and Dr. Reddy's, had ANDAs in their names till recently. Companies like Cipla had ANDAs in the names of their marketing partners in the US. This situation has changed dramatically in recent times and more companies are engaged in securing ANDAs. From 161 ANDAs filed by four companies-Ranbaxy, Dr. Reddy's, 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 (Chaudhuri 2007). ANDA approvals held by Indian firms as percentage of total approvals have gone up sharply from 7 per cent in 2001 to 21 per cent in 2006 to 30 per cent in 2008.[53]

Companies also engage in developing non-infringing process for ANDA filing. Matrix Laboratories was the first Indian company to develop a non-infringing process for manufacturing citalopram. The company was able to reap huge benefits with its sales of the product amounting to Rs. 5600 million till 2005-06. Another commercially successful example is the cefotaxime process developed by Lupin (Chowdhuri, 2007).

India has approximately 119 FDA approved plants;[54] the largest number outside the USA and approximately twice the amount that China presently has. Recent market estimates indicate that there would be further acceleration of Indian exports to the USA. It is estimated that about 250 Indian generics products have been launched in the US market in 2008, as opposed to 93 in 2003.[55] Up until the end of the 1980s, Indian firms focused extensively on the rest of the world markets, especially USSR where there was little patent protection coupled with lax registration requirements. The accumulation of enhanced technologies and production capabilities coupled with the change in the global patent regime led to a gradual shift of focus to the highly lucrative US generics market while retaining the old markets.

'Para IV filings' involving patent litigations are a high risk high return strategy. A failure would bring huge losses of years of hard work and of huge legal expenses. The leading firms also have a large number of DMF filings, an indication of their interest in the US market. These 10 firms account for nearly half of DMF filings made by all pharmaceutical firms in India.[56]

Novel drug delivery systems

Developing NDDS for existing drugs has been a priority area of research for most leading firms in India. Developing an NDDS is relatively much easier and involves less investment; it can be developed in 3-4 years with an investment of $20-50 million (Dhar and Gopakumar 2008). A regulatory requirement with NDDS involves only the establishment of its bioequivalence with the 'normal' brand. This essentially means that the drug in its new mode of delivery provides similar concentration in the blood as the original drug would do and hence has the same effect in the body. Several Indian firms are working in this line – JB Chemicals, Cadila Healthcare, Zydus Cadila, Morepen Laboratories, Neuland Laboratories and Aurobindo.

Ranbaxy has exhibited the most remarkable success in the development of NDDS. It developed an improved version of ciprofloxacin, which was developed by Bayer AG and was under patent protection until 2003. Ranbaxy developed a once-a-day formulation instead of the multiple-dose a day offered by the Bayer. The Ranbaxy formulation assured better patient-compliance and was hence considered to be a major step forward. Bayer recognised the improvement and entered into a licensing agreement with Ranbaxy for its version of ciprofloxacin. Under the agreement, Ranbaxy Laboratories received US$ 65 million from Bayer over a four-year period, with an initial payment of US $ 10 million (Dhar and Gopakumar 2008). The agreement allowed Bayer AG to have the worldwide marketing rights over ciprofloxacin, except in India and the CIS countries where Ranbaxy Laboratories had the marketing rights.

Alembic's once-a-day NDDS for Belgium-based UCB's anti-epileptic drug Keppra is yet another success story. In 2007, Alembic entered into a licensing agreement with UCB for US$11 million. Alembic would also continue to receive royalty payments.[57] The Dabur pharma developed a nanotechnology based anti-cancer NDDS, Nanoxel for the widely used anti-cancer treatment drug Paclitaxel. This NDDS entered clinical trials in Europe and US in 2007.[58] Nanoxel is currently under the portfolio of Fresinus Kabi (Singapur), a unit of European health care company Fresenius SE, which took over Dabur Pharma in 2008.

We have seen that from the beginning of last decade Indian pharmaceutical industry has been become more R&D intensive. Has the new patent regime been the driver for R&D? The data on R&D spent on new drug development is not available separately and hence it is not possible to make any conclusion based on R&D expenditure. However, a few studies have attempted to address this question by means of analysing information accessed by pharmaceutical companies and their patenting behavior. Chaudhuri (2005) who interacted with senior officials of leading pharmaceutical companies in India concluded that the increase in the R&D intensity has been the outcome of the fear of shrinking market opportunities as they will no longer be able to reverse engineer and produce new drugs rather than induced by the incentives of the new patent regime. The recent

study of Abrol *et al.* (2011) which analysed the patenting behaviour of Indian pharmaceuticals firms in the US Patents and Trademark Office (PTO) finds that the chemistry driven process research resulting in non-infringing processes for APIs, introduction of cost effective routes, reduction of impurity levels, new dosage forms and formulations and NDDS are the main priorities of Indian firms. Of the 1159 patents granted to 35 firms from India between 2000 and 2007, product patents constituted only 5 per cent; dosage forms constituted 44 per cent, new form of substance 24 per cent and processes 18 per cent. This study also concludes that the Hatch-Waxman Act of 1984 still continues to be "the most important stimulus for domestic pharmaceutical firms to invest in the process of learning, competence building and innovation making activity."

Another way to address this question is to analyse the therapeutic areas of new drug R&D of Indian firms. If the patent regime in India is the driving force, firms would find market opportunity in diseases that are relevant in the Indian contexts. On the other hand, if the patent regime in developed countries (that was there before the TRIPS) is the driver, we expect that Indian firms to invest more on drugs for global diseases. Following section provides a therapeutic area wise analysis of new drug R&D of Indian firms.

Therapeutic Areas of New Drug R&D

Table 5 gives the list of new molecules of leading pharma firms in India which are at different stages of development.

Table 5: Compounds of Indian Companies at Different Stages of Development

Compound	Therapeutic Area	Status
Dr Reddy's[59]		
DRF 2593	Metabolic disorders	Ongoing. Phase III
Several Compounds	Respiratory disorders	Ongoing. Phase I
DRL 17822	Metabolic disorders / Cardiovascular disorders	Ongoing. Phase I
Ranbaxy[60]		
RBx 11160 (Arterolane)	Anti-malaria combination drug	Ongoing. Phase III Studies in India and Thailand

Table 5 continued...

Table 5 continued...

Unnamed	Respiratory problems	Ongoing. Completed Phase I in collaboration with GSK and received related milestone payment from GSK
Glenmark[61]		
GRC 10693	Naturopathic Pain, Osteoarthritis & other Agonist inflammatory pain	Ongoing. Entered phase II trials
GRC 8200 (Melogliptin)	Diabetes type-2	Ongoing. Entered phase III
GRC 3886 (Oglemilast)	COPD, Asthma	Ongoing. Phase II completed.
GRC 4039 (Revamilast)	Rheumatoid arthritis, multiple sclerosis and other inflammatory disorders	Ongoing. Entered phase II
GBR 500*	Multiple Sclerosis and inflammatory disorders	Ongoing. In phase I
GRC 15300	Osteoarthritis pain, Naturopathic Pain, Skin Disorders	Ongoing. In phase I
GBR 600*	Anti-platelet, Adjunct to PCI/ Acute Coronary Syndrome	Ongoing. Completed preclinical trials
Crofelemer	Anti-diarrhoeal	Successfully completed phase III. In-licensed from Napo Pharmaceuticals, USA.
Biocon[62]		
PEG-GCSF*	Oncology	Ongoing. Pre-clinical
Bmab 100*	Oncology	Ongoing. Pre
Bmab 200*	Oncology	Ongoing. Pre
BVX-20*	Oncology	Ongoing. Pre
IN 105 (Oral Insulin)*	Diabetes	Ongoing. Phase III
T1h*	Inflammation	Ongoing. Phase II
BIOMAb EGFR (Glioma, NSCLC)*	Oncology	Ongoing. Phase III
Wockhardt [63]		
WCK 771	Anti infective	Ongoing in phase II
WCK 2349	Anti infective	Ongoing in phase I
Piramal Healthcare[64]		
P 276	Oncology (head and neck cancer)	Ongoing. Entered phase II. Trials are going on in India, US and Australia.
P 276 combination with Gemcitabine	Oncology (pancreatic cancer0	Ongoing. Phase I.
P 276 combination with Radiation	Oncology (head and neck cancer)	Ongoing. Phase I.
P 1446	Oncology	Ongoing. Phase I in India and Canada.
NPB-001-05-Bcr-Abl	Oncology (chronic myeloid leukemia)	Ongoing. In phase II.

Table 5 continued...

Table 5 continued...

P 13 Kinase	Oncology	Ongoing. Lead selection.
Microbial leads	Oncology	Ongoing. Lead selection.
Target X - Merck	Oncology	Ongoing. Lead selection.
Target Y - Merck	Oncology	Ongoing. Lead selection.
NPS 31807-TNFa	Inflammation (rheumatoid arthritis)	Ongoing. Phase II completed.
P 979-TNFa	Inflammation	Ongoing. In preclinical.
P 3914	Inflammation	Ongoing. In preclinical.
IL 6	Inflammation	Ongoing. Lead selection.
TNFa	Inflammation	Ongoing. Lead selection.
P 1736 – Non PPARy	Diabetes and metabolic disorders	Ongoing. Phase I.
P 1201 - Lilly	Diabetes and metabolic disorders	Ongoing. Phase I.
P 2202 - Lilly	Diabetes and metabolic disorders	Ongoing. Phase I.
DGAT1	Diabetes and metabolic disorders	Ongoing. Lead selection.
NPH30907# - Dermatophytes	Anti-infective	Ongoing. Phase I completed.
PP 9706642# – Anti-HSV2	Anti-infective	Ongoing. Preclinical.
PM 181104 – MRSA/ VRE	Anti-infective	Ongoing. Toxicity studies.
Lupin[65]		
LL 2011#	Anti-migraine (Amigra)	Ongoing. In phase III.
LL 4218	Anti-psoriasis (Desoside-P)	Ongoing. In phase II
LL 3858/4858#	TB (sudoterb)	Ongoing. In phase I
LL 3348	Anti-Psoriasis (Herbal Desoris)	Ongoing. In phase II
Unnamed	Diabetes type 2	Ongoing. In preclinical
Unnamed	Rheumatoid arthritis	Ongoing. In preclinical
Torrent Pharmaceuticals[66]		
Unnamed	Diabetic heart failure	Ongoing. Completed phase I.

Note: * Biologics; # these molecules are phytopharmaceuticals (origin from plants).

Table 5 shows that R&D efforts are concentrated in global chronic disease conditions such as cancer and diabetes. Though there are two molecules on malaria and tuberculosis (TB), it should be noted that they have not been completely the outcome of corporate considerations. Ranbaxy's anti-malarial compound (Arterolane) came out of its partnership with Medicines for Malaria Venture (MMV), a global public health funding agency. Ranbaxy has obtained approval from DCGI to initiate Phase III human clinical trials in India. It also plans to seek regulatory approval in other countries outside India to the Phase-III clinical trial.[67] However, MMV pulled out of the project in 2007 after the review of the preliminary data and

Ranbaxy has been looking for other international collaborators for further development of the drug.[68] MMV, which has financed the bulk of the anti-malarial project cost, is estimated to have spent about $13-15 million on this project.[69] When MMV pulled out, DST, Government of India came out willing to collaborate in the project with an offer of Rs. 11 crore.[70]

Lupin, the only company engaged in the development of TB drugs, has been the world leader in the production of TB drugs. It is also a preferred supplier to the Global Drug Facility (GDF), which supplies the drugs to more than 50 countries. For the development of the TB drug, Lupin has been in partnership with public funded research institutions (Chaudhuri 2005). Under the New Millenium Indian Technology Leadership Initiative (NMITLI) programme of CISIR, the expertise of 12 institutional partners and Lupin were synergised in the TB research for the development of new targets, drug delivery systems, enhancers and therapeutics. Lupin's TB candidate is the first success achieved in developing a new TB therapy in the last 40 years globally.[71] Unfortunately, the company now is in the process of shedding its TB research programme. "We were not satisfied with the way the programme was running" says Nilesh Gupta, President the Executive Director of Lupin. "Our focus will now be on diabetes and anti-inflammatory research. Globally these are hot areas".[72] Until recently Lupin had focus on TB and psoriasis drug research. As the R&D strategy is being reviewed, those molecules which do not qualify for western markets have progressed very slowly over the past five years. Globally there has been a decline in the interest of pharmaceutical companies in doing R&D on tropical diseases and the withdrawal of Indian firms should also be seen in that context. Out of the four TB molecules in different stages of clinical development in the world, all the three with the exception of Lupin's molecule (LL3858) came out of sponsorship from public institutions and global health initiatives.[73]

The policy initiated in the country in pharmaceuticals since the mid-1990s opened the doors for the globalisation of Indian pharma industry. Indian pharma firms have become integral part of the global R&D and production network of MNCs. In other words, they have become partners to the non-equity modes of international production and development.[74] Indian firms could take part in the process because of their strengths which they

have accumulated during the earlier policy regime. With the globalisation process, the focus of Indian pharma firms has shifted away from the domestic market and have got it aligned it with the R&D strategies of MNCs. The orientation of Indian firms has also changed from that of competitors in the earlier policy regime to that of collaborators of a subordinate order in the new regime.

The re-orientation of the R&D focus of Indian pharma industry raises a number of challenges to the public health in the country. With the withdrawal of the private sector from neglected diseases, the public health is facing a serious crisis in the country. The introduction of product patent rights in pharmaceuticals has not been able to attract more investment on diseases more common to India, as the proponents of such a regime had argued when the TRIPS was negotiated in the Uruguay Round. In this context, the following section provides a discussion on the role of the public sector in addressing the market failure of the new patent regime in the country.

The Role of the Public Sector

There are essentially two ways in which the public sector can address the market failure issue. One, the public sector pharma companies are encouraged to undertake R&D on drugs for the neglected diseases. Two, provide additional incentives to the private sector in the form of public private partnerships (PPPs) to conduct R&D on neglected diseases. The first option is not feasible as most of the earlier champions have become sick already. HAL, IDPL, and BCPW have been declared as sick units by the Board of Industrial and Financial Reconstruction. A few other units such as Bengal Immunity, Smith Stainstreet Pharmaceuticals Ltd. and Maharashtra Antibiotics and Pharmaceuticals Ltd. have already been shut down.[75] In spite of the recommendations from various agencies for the revival of pharma PSUs, latest being from the high level panel of the Planning Commission on universal health (Arun Maira panel), nothing has happened in those lines.

The strategy of the Government in addressing the market failure has been the option two – through PPPs. PPPs have been justified as initiatives to synergise the strengths of the public funded R&D institutes such as CSIR

laboratories, universities and academic institutions and the pharma industry. The collaborative research programme under Drugs and the Pharmaceuticals Research Programme (DPRP) of the Department of Science and Technology (DST), initiated in 1994-95, is a PPP specific to the pharma industry. Under the collaborative programme, research is done jointly by the publicly funded R&D institution and the pharma company under the monitoring of DST. The public funded institutions would provide the existing facilities and the service of their R&D personnel and the firm would fund 30 per cent of the recurring expenses of the public funded institution in addition to financing 100 per cent of both capital and recurring expenses of the research undertaken by it. The DST would fund 70 per cent of the recurring costs and 100 per cent capital expenses of the research for the project at the public funded institution. As of 2010, 101 collaborative projects have been sanctioned in the area of tuberculosis, malaria, diarrhoea, diabetes, psychosomatic disorders, kala azar, cataract, dementia, HIV/AIDS, anti-fungal, anti-virals, anti-cancer, anti-bacteria, anti-rabies, anti-obesity, anti-asthma, arthritis, vaccine for dengue, Japanese Encephalitis and Hepatitis-B.[76] Despite a large number of projects being granted, no NCE has been developed out of this programme (Chaudhuri 2010). These projects are piecemeal projects and deal with only particular aspects of drug development. These studies have generated insights that may be useful for future research (Chaudhuri 2005). Perhaps, this is what is expected of this programme as it employs two pronged approach involving "exploratory drug design and drug development on candidate molecules already identified on the one hand and providing cutting edge to Indian industry through innovative process for known/generic drug as well as crucial intermediates on the other."[77]

There may be other factors also involved in no new products coming out of the PPP under DPRP. CSIR laboratories like CDRI do not have much interaction with pharmaceutical industry in the new drug development. In India since 1947, 17 new drugs have been developed of which 15 come from the public sector like CDRI, HAL, etc.[78] These institutes developed drugs, conducted clinical trials in India, obtained marketing approval in India and licensed to Indian firms for marketing. But none of the drugs has been commercially successful (Chaudhuri 2010). A major constraint has been the lack of commercial orientation of these institutes. Domestic firms

find it difficult to promote the product primarily because of the "Indian" tag, as in the case of Cipla (Chaudhuri 2005). Cipla's experience with Deferiprone (brand name Kelfar), drug used for the removal of iron from blood, would perhaps give the answer. Cipla introduced Kelfar in India in 1995. The company faced huge problems in promoting the product in India. Deferiprone was originally developed by Robert Hilder and Geroge Kontoghiorghes of UK in 1983 and phase I and phase II trials were done in Switzerland and England. Cipla got the license for the development of the drug and phase II and phase III trials were conducted in India. When it came to obtaining marketing approval and promoting the product, Cipla faced problems essentially because of the "Indian" tag. It is reported that Cipla faced the question "where else has it been approved?" not only from the Drug Controller but also from the doctors. Finally, Cipla had to bring Geroge Kontoghiorghes to India to impress upon the Drug Controller.[79] Perhaps, the quest of Indian firms to engage in out-licensing has to be seen not merely from their lack of skills and resources point of view but also from the wider context of the drug innovation environment in the country.

Other PPPs from which the pharma firms benefit are the New Millennium Indian Technology Leadership Initiative (NMITLY) of the CSIR and Small Business Innovation Research Initiative (SBIRI) of the Department of Biotechnology. Under NMITLY 42 pharmaceutical R&D projects have been sanctioned in the last six years involving 287 partners, 222 in public sector and 65 in private sector (Abrol *et al*., 2011). Similarly, SBIRI has sanctioned 32 R&D projects in pharmaceuticals till May 2008. Abrol *et al.* (2011) analysed these R&D projects (under NMITLY and SBIRI) and observes that there is not much focus on neglected diseases. The focus has been on global chronic disease conditions.

The PPPs have been able to make the linkages between the public sector laboratories and research institutions and the industry. These partnerships, however, have been catering to the need of the industry to effectively participate in global R&D networks of pharma MNCs than to the need of the country to address the problem of the failure of the market in incentivizing the firms to bring out new therapies for neglected diseases. So, PPP are not an effective alternative to address the market failure. Ablaquin,

the anti-malarial drug developed by the CDRI and licenced to Nicholas Piramal still has not made entry in the $800 million anti-malarial market. So, Government's efforts at development of technologies on neglected diseases will be of no use if the manufacturing industry is averse to them. Revival of the public sector manufacturing industry in pharmaceutical sector is the viable solution to address the problem of lack of innovation in the area of neglected diseases. The Open Source Drug Discovery (OSDD)[80] project, an innovative initiative by the government to promote R&D efforts on neglected diseases, is aimed at a noble cause but at the end there should be someone to take the technology to the needy people.

The proposed Bill "The Protection and Utilization of Publicly Funded Intellectual Property Bill, 2008" needs to be analysed in this context. This Bill was presented in Parliament by the Ministry of Science & Technology, Government of India, and is currently being reviewed by the parliamentary Standing Committee on Science, Technology, Environment and Forests. This Bill is modeled after the Bayh-Dole Act of US and hence better known as Indian Bayh-Dole. The objectives of the Bill include, among others: (a) commercialisation of intellectual property created out of publicly funded R&D; (b) promotion of a culture of innovation in the country; and (c) minimising the dependence of universities, academic and research institutions on government funding.

The objectives of the Bill are laudable but imposing strictures on public funded R&D projects alone will not serve the purpose. First and foremost, the innovation environment has to be ripe enough to promote indigenous innovation. In India in pharmaceuticals at least, the environment has to be made conducive to overcome the stigma of "Indian" tag, which we discussed in earlier sections. Further, a move in the lines outlined in the Bill will only exacerbate what is popularly known as the "90/10 gap". It has already been shown that the focus of R&D in India is heavily tilted towards global diseases and that private industry is moving away from investing in R&D on tropical diseases. A study (Lanjouw and MacLeod 2005) found that Indian companies are investing only 10 per cent of their R&D for diseases more prevalent in developing countries.[81] In most cases of drug development the basic research has been done in the research institutions and laboratories

and then those molecules are licensed to the industry. If commercialisation of the research is over emphasised, the focus of public funded research will also be narrowed to very selective therapeutic areas where the industry has an interest. Researchers will be inclined to concentrate their efforts only on issues of interest to industry, and which can have immediate benefit. Further the exclusive focus on intellectual property and commercialisation would force our pillars of learning and research to become like businesses. Some universities in the US, like the Columbia University and Duke University, in the course of time, have become spending more on patent litigation than spending on research.[82]

Apart from the PPPs there are other incentives also available for the R&D in the pharmaceutical sector. The Drug Policy provides incentives in the form of exemption from price control. The Drug Policy (Drug Policy 1986, as modified in 1994) provides:

a. A manufacturer producing a new drug patented under the Indian Patents Act, 1970, if developed through indigenous R&D, would be eligible for exemption from price control for a period of 15 years from the date of the commencement of its commercial production in the country.
b. A manufacturer producing a drug in the country by a process developed through indigenous R&D and patented under the Indian Patents Act, 1970 would be eligible for exemption from price control until the expiry of the patent from the date of the commencement of its commercial production in the country.
c. A formulation involving a new delivery system developed through indigenous R&D and patented under the Indian Patents Act, 1970, for process patent, would be eligible for exemption from price control in favour of the patent holder formulator from the date of the commencement of its commercial production in the country until the expiry of the patent.

The DPRP also has soft loan schemes for pharma industry R&D projects and grant in aid for clinical trials to pharma industry projects on developing drugs for neglected diseases. The loan scheme became part of the DPRP in 2006, when the Government of India decided to dissolve Pharmaceutical Research and Development Support Fund (PRDSF). The

Pharmaceutical Research and Development Committee (PRDC), under the Chairmanship of Dr. R.A. Mashelkar, mandated to suggest mechanisms for establishing organic linkages between private sector and public sector research institutions and laboratories with a view to synchronising and synergising national R&D efforts in pharmaceuticals recommended the creation of an autonomous Drug Development Promotion Foundation (DDPF) to execute R&D strategy with a one-time contribution of Rs 500 million from the government and an annual outlay of Rs 1000 million which was to be generated by imposing surcharge of 1 per cent on the maximum retail price of formulations. The Government of India did not accept the recommendation of the creation of DDPF and instead established a one-time Pharmaceutical R&D Support Fund (PRDSF) with an initial corpus of Rs1500 million in 2004. The interest accruing on it was to be utilised for supporting collaborative research projects and extending soft loans. Since the interest accrued in not sufficient to support R&D initiatives of the pharma industry, the Government of India dissolved the PRDSF corpus in January 2006 and replaced it with annual budgetary allocation of Rs 1500 million. As DPRP and PRDSF were serving the same cause, PRDSF was merged with DPRP. Under the soft loan programme, loans are extended (up to 70 per cent) to firms engaged in R&D of drugs and pharmaceuticals at consessional rates (simple rate of interest of 3 per cent, repayment in 10 annual equal installments, etc.). Ownership of intellectual property generated out of these projects is on agreed terms. Some of the projects under this programme are in advanced stages of clinical trials.[83] Ranbaxy's RBx 11160 (anti malaria combination drug) is in phase III clinical trials in India and Thailand. Lupin's LL 2011 (anti migraine drug) is in phase III trials and LL 4218 (anti psoriasis drug) is in phase II clinical trials. Dr Reddy's 7295 (for the treatment of advanced and metastatic cancers (colon, pancreas and stomach) and lung has entered clinical trials phase.[84]

The grant in aid programme was constituted specifically to incentivise R&D on neglected diseases, when it was found that the collaborative programme and the loan scheme of DPRP were not attracting investment on neglected diseases. As compared to other schemes of the DPRP, there are only very few takers for the grant in aid scheme. Despite grants been made available to conduct clinical trials, which is the most expensive phase in

the process of new drug development, only two companies - Ranbaxy and Bharat Serum and Vaccines, in the last six years, starting from 2004-05 - have availed this scheme (in 2008-09).[85]

R&D firms in India also benefit from tax and duty exemptions under various provisions. Firms having in house R&D facilities in India and recognised by the Department for Scientific and Industrial Research (DSIR) are eligible for 150 per cent weighted exemption on R&D expenditure under Section 35 (2AB) of Incomes Tax Act. This section is extended to depreciation on investment made in land and building for dedicated research facilities, expenditure incurred for obtaining regulatory approvals and filling of patents abroad and expenditure incurred on clinical trials in India. As of now, this facility is available till 2015.[86] The R&D intensive companies (Gold Standard Companies) are eligible for the benefit of 200 per cent weighted tax exemption. Gold Standard Companies identified on the basis of certain criteria including investing at least 3 per cent of sales turnover in R&D, employing at least 200 scientist in India, have filed at least 10 patent applications in India based on research done in India, etc. Similarly, the reference standard (sample under test) and reference books imported for R&D are exempt from import duty.

The creation of an incentive based system for pharma R&D has not been able to attract Indian pharma firms to conduct R&D on tropical neglected diseases. Being part of the global production and development networks, they find better opportunities in selected chronic disease conditions. With PPPs also failing in attracting firms into neglected diseases, the only way out is the revival of PSUs. The other aspect of the reforms has been the emphasis placed on foreign investment. Now 100 per cent foreign investment is permitted through automatic route in pharmaceuticals in the country. Did it have any impact on the R&D? Following section analyses the impact of liberalisation of foreign investment on R&D.

Foreign Investment in R&D

A major limitation in the study on the impact of liberalisation of foreign investment on R&D is the availability of data. Most of the foreign R&D companies in India are not listed companies and as a result the information on

the R&D focus of these firms is not available publicly. In a first of the kind of the study in India, the DSIR and the Indian Institute of Foreign Trade (IIFT) jointly conducted a study in 2005 based on questionnaire on the foreign R&D centres in India. Of the 119 foreign R&D centers, which responded to the questionnaire, 46 firms belonged to the category of biotechnology and pharmaceuticals. Out of these 46 firms, those firms working exclusively on pharmaceuticals and their R&D activities are given in Table 6.

Table 6: Foreign R&D Centres in India and Technologies Developed

Name of the company	Technologies Developed
Astra Zeneca R&D	1. Cardiovascular 2. Infection 3. Neuro Science 4. Obstetrics & Gynecology 5. Oncology 6. Respiratory
Merck Development Centre Private Limited	1. Antibiotics 2. Antimalarials 3. Cardiologicals 4. Cough and cold formulations 5. Dermatologicals 6. Haematinics 7. Neurologicals 8. ORS 9. Non-steroidal anti inflammatory drugs.
Novartis India Limited	1. Arthritis and bone metabolism 2. Cardiovascular and metabolic diseases 3. Dermatology/Immuno pathology 4. Infectious disease 5. Nervous system disorders 6. Oncology 7. Ophthalmics 8. Transplantation
Novo Nordisk India Private Limited	1. Insulin analogues – Novomix 30 and Novo Rapid (in 2003) 2. Insulin Delivery device – Novolet 3. A third generation durable insulin delivery device – Novopen
Pharma Net India Clinical Services Private Limited	1. Drug-eluting stents 2. Implantable drug/device delivery systems 3. Catheter-based drug-delivery technologies 4. Co-packaged combination products

Table 6 continued...

Table 6 continued...

Pliva Research India Private Limited	1. Anti-infectives 2. Cytostatics 3. Diuretics 4. Various Api 5. Nutraceuticals
Roche Scientific Company India Limited	1. Transplantation 2. Oncology 3. Hepatitis 4. HIV
Gangagen Biotechnologies Limited	Library of over 400 bacteriophages which kill a variety of bacteria present in over 1100 clinical isolates.
Indus Bio Sciences Private Limited	1. CarboHydrate Derivatives 2. Heterocyclic Building Blocks 3. Reagents and Building Blocks 4. Chiral Agents and Building Blocks 5. Nitriles, Acids and Amidines 6. Pyridines, Piperidines, Pyrimidines & Indazoles
John F Welch Technology Centre (GE)	Improved Diagnostic and Treatment Protocols

Source: DSIR-IIFT (2005).

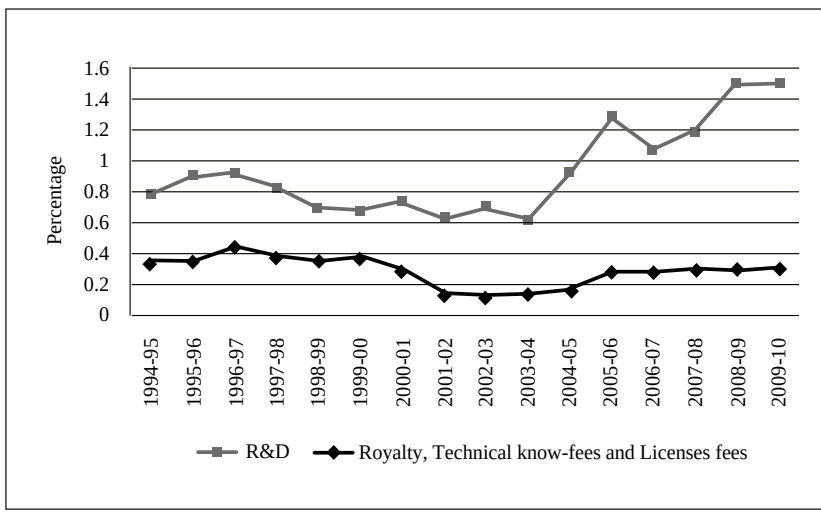
The foreign R&D centres in India claim to do R&D in various therapeutic segments. But it is not clear in which stage of the drug development, their R&D is concentrated. A few of them like Indus Bio Sciences and Pharma Net India Clinical Services seem to be engaged in the development of processes, delivery systems and derivatives. However, we do not have clarity on the R&D activities of the affiliates of MNCs such as AstraZeneca and Novartis.

Using the data from FDI Market Intelligence, Abrol *et al*. (2011) attempted to figure out the R&D focus of foreign firms in India. R&D activities accounted for the highest number of projects carried out among a range of business activities (such as manufacturing, business services, design, etc.), registering 36 out of 83. After examining the purposes of FDI transactions of the R&D projects the study concludes that "a large number of R&D investment projects are focused on developing facilities for phase III clinical trials and other such modules that only integrate Indian talent and facilities into foreign pharmaceutical firms' global objectives" (page 342).

Thus, it comes out that liberalisation of foreign investment has opened the door for outsourcing of clinical trials to India than to new investment on R&D from basic stages for the development of new drugs.

Data available for the listed subsidiaries of MNCs[87] shows that their R&D intensity is very low (Figure 4). It is even lower than the R&D intensity of the public sector pharmaceutical firms in India, which do not have any R&D on new drug development. It may be argued that MNC subsidiaries in India need not make R&D investments for new drug development as their parent firms are already doing the same. In such cases, one would expect that the subsidiaries would be paying royalty and licensee fees to the parent firms for using their technologies. But, the data again shows that their expenditure on royalty, technical know-how fees and license fees is even lower and has declined in the last decade as compared to the second half of the 1990s.

Figure 4: Expenditure on R&D, Royalty, Technical Know-how Fees and License Fees % Sales of MNC Subsidiaries in India



***Source*:** Prowess.

With the product patent regime in place, the expenditure of MNC subsidiaries on royalty, technical know-how fees and license fees should

have gone up as they would be the exclusive suppliers of patented drugs in the country. They might be finding it difficult to get patents for many of their drugs in India because of the conditions laid down in section 3(d) of the Patents Act. The Section 3 of the Indian Patents Act lists inventions that are not patentable and this section contains a clause (d) which states "the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant. Explanation – for the purpose of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy". This provision was incorporated to prevent bad patents and the phenomenon called evergreening.[88] This provision (section 3(d)) brought the ire of the pharma MNCs and United States Trade Representative (USTR) on India.

Available evidence indicates that liberalisation of foreign investment has not resulted in competence building. Global pharma players are opening their centres in India primarily to take advantage of India's endowment in clinical trials and also to reap from the innovative capabilities of Indian firms. It has completely left untouched the need of the country to develop new therapies for neglected tropical diseases.

Summary and Conclusion

The policy reforms aimed at boosting the pharmaceutical R&D include liberalisation of foreign investment and foreign technology collaborations, exemptions from tax obligations, exemptions from drug price regulation and product patent rights to pharmaceutical innovations. Among these reform measures, modification to the intellectual property legislation was the most debated one. The analysis of R&D expenditure of pharmaceutical firms shows that there had been a growth in the R&D intensity since 2000-01, but this began to decline or stagnate after 2005-06. This decline has been

on account of the review of R&D strategy of two leading firms – Ranbaxy and Dr. Reddy's. With their initial success in developing a few molecules in-house, they hiked R&D spending considerably reaching up to 18 per cent of sales turn over. But when they realised that failure rate is quite high and that MNCs are not interested in developing the molecules (out-licensed ones) unless they fit into their business model, the direct outcome was pruning of R&D expenditure. Now, the pharma industry spends 5 per cent of its sales turn over on R&D as compared against 1 per cent in 1994-95.

The R&D profile of Indian pharmaceutical industry includes development of generics, new drug delivery systems and new drug development. The data on patents granted to leading Indian pharma firms by PTO shows that patents on new products account for only 5 per cent and the rest has been on new processes, new dosage forms and drug delivery systems. It appears that the growth in R&D intensity of Indian pharma firms has been the outcome of the fear of shrinking market opportunities, as they will no longer be able to reverse engineer and produce new drugs, rather than induced by the incentives of the new patent regime. In the R&D for new drugs, the analysis of new drug pipeline of leading Indian pharma firms shows that the new patent regime has not been able to become the driving force; the R&D activities of Indian firms are increasingly getting concentrated on life style diseases of global nature and they don't find any opportunity in local diseases such as TB and malaria.

The policy reforms, however, paved the way for the "globalisation" of Indian pharmaceutical industry – it has now become part of the global production and development network of MNCs. Participation of Indian firms in the global network has come more of an income generation opportunity than a means for competence building. The liberalization measures indeed had the objective that foreign investment and technology collaborations increasingly become important channels for competence building. In contract research, collaborative research projects, out-licensing and in-licensing partnerships Indian firms have been partners of subordinate status who perform piecemeal projects in drug research and they are not exposed to the whole process of new drug development. In these collaborations, the scope for transfer of technology and joint ownership of technology is also

very limited. The subordinate status of the Indian firms in the long run may result in a dependency relationship of Indian firms with the MNCs. This can have deleterious consequences to the country in many ways. Being trusted allies in the global strategy of MNCs, Indian companies may lose interest in those therapeutic areas which do not have global presence (for example, tropical country diseases). These allies might also withhold themselves from: exercising compulsory licensing provisions, the TRIPS instrument to counter abuse of patent monopoly rights as well as to address national health emergencies.

The lack of capacity of Indian firms in developing new drugs, both in terms of S&T skills and financial resources, leave them with no other option but to collaborate with MNCs. In the earlier policy regime, the public sector companies and public sector laboratories had played a major role in augmenting the S&T skills of the private sector industry. Under the new policy regime, the public sector companies have been relegated and a few of them have already been closed down. The aversion to indigenous innovations at the regulatory approval stages and at promotional stages further encourages Indian firms to develop new drugs in collaboration with MNCs.

Under the new policy regime R&D for neglected diseases has become a major challenge. Despite public-private partnerships, soft loans, grants and other incentives for pharmaceutical R&D, firms are not forthcoming to invest in developing new drugs for neglected diseases. The success of the Open Source Drug Development Programme of the Council for Scientific and Industrial Research would also depend on the willingness of the industry in taking the product to the market. As the private sector industry is staying away from the neglected diseases market, the only way out is the revival of the public sector companies which in the earlier policy regime played the leading role.

The liberalisation measures, on the other hand, have attracted foreign investment in pharmaceutical R&D in India. A number of foreign R&D centres have been opened up in the country. But it has come out that bulk of foreign investment in R&D in pharma sector has been in the clinical phase, especially in phase III trials and not in the biology and chemistry

research for new drug development. Phase III requires a large number of human subjects in the trials. MNCs are attracted because India provides a large size of population which is ethnically diverse and suffering from various ailments. The English speaking human power and a well developed communication network with information technology capabilities are also advantages in favour of India in clinical trials. Amendment of the Schedule Y of the Drugs and Cosmetics Rules, 1945 removed the restrictions imposed on foreign players in conducting clinical trials in India. The amended rules require that the clinical studies should be conducted in accordance with the principles of the Declaration of Helsinki, Indian Good Clinical Practice Guidelines, and the Ethical Guidelines for Biomedical Research on Humans of Indian Council of Medical Research. Despite all these requirements and the establishment of clinical trial registry of India, unauthorised trials, involving large number of human subjects are rampant in many parts of the country. There have been recent instances of trials being conducted on women without informing them and not obtaining their informed consent. In many instances, the vulnerable and disadvantaged like the poor women have been misused for trials in India, though the Declaration of Helsinki restricts trials on the vulnerable.[89]

Endnotes

1 The other three companies are Bengal Chemical and Pharmaceutical Works Ltd. (BCPW); Rajasthan Drugs and Pharmaceuticals Ltd. (RDPL); and Karnataka Antibiotics and Pharmaceuticals Ltd. (KAPL). BCPW was founded in 1901. RDPL is a subsidiary of IDPL. KAPL is a joint venture of HAL and Karnataka State Industrial and Investment Development Corporation. These are all Central Public Sector Units (PSUs). There are also a number of State pharma PSUs.

2 Bioequivalence tests aim to show that the concerned drug produces similar concentrations in the blood as would the drug approved for marketing elsewhere would do.

3 'Self-reliance displayed by the production of 70% of bulk drugs and almost the entire requirement of formulations within the country', accessed at http://chemicals.nic.in/pharma1.htm on November 16, 2011.

4 The United States' Senate Committee on Drug Prices (1962) – the 'Kefauver Committee' reported that "in drugs, generally, India ranks amongst the highest priced nations of the world" (quoted in Lanjouw 1998). In the late 1990s, studies have found that drugs prices in India is lowest in the world. For example, study by Ghosh and Keayla (1998).

5 Based on Keayla (1994).

6 India's trade balance in pharmaceuticals is positive since 1988-89, Joseph (2002)

7 Based on the data provided in *The 2010 EU Industrial R&D Investment Scoreboard* (http://iri.jrc.ec.europa.eu/research/scoreboard_2010.htm). Of the top 1000 R&D investing global companies from different industries, 10 pharmaceuticals firms were selected on the basis of

their R&D intensity. Daiichi Sankyo of Japan, the top ranking firm among the 10, spent 22% of its turnover in R&D whereas Johnson and Johnson of US, the least ranking firm, spent 9% on R&D.

[8] R&D investment by the public sector pharmaceutical companies does not account for even 0.5% of the total R&D investment made by public as well as private sector pharmaceutical companies. This estimate is based on Prowess data.

[9] These are discussed in section 6 of this paper.

[10] These figures are collected from company websites and media reports.

[11] Annual Report 2004-05.

[12] Annual Report 2008-09.

[13] 'Death of a Dream', *Businessworld*, January 30, 2010.

[14] 'Research and Development', accessed at www.phrma.org on November 16, 2011.

[15] Ibid.

[16] 'Drug Discovery and Development', accessed at www.phrma.org on November 16, 2011.

[17] PhRMA data for US in 1998 and quoted in Chaudhuri (2005).

[18] 'India learns how to discover drugs', Business World, accessed at http://www.businessworld.in/index.php/India-Learns-How-to-Discover-Drugs.html on November 16, 2011.

[19] PDE4 is a protein that triggers off inflammation in various organs of the body.

[20] The 771 version is an injectable and the 2349 is orally taken.

[21] PhRMA estimate given in Chaudhuri (2005).

[22] This figure is based on an unrepresentative sample and excludes the majority of the new drugs which are extensions of existing ones and which have benefited from public funding. These estimates are also adjusted upwards to provide for opportunity cost of capital. The actual out of pocket expenditure per drug estimated by DiMasi, Hansen and Grawobski (2003) was only $403 million and when adjusted for opportunity costs, the estimate rose to $803 million. Other components involved in the R&D estimates are: (i) executive costs in finding and negotiating with other firms for new products, (ii) costs for medical writers and public relations to develop stories and market demand for products in trials as they progress, (iii) support for scientific journals and supplementary issues in which the results of industry-supported research get published, (iv) lectures and courses to inform physicians about current research, (v) legal fees devoted largely to patents and research-related issues, and (vi) land and costs for buildings in which some research is done. Surely, these are not the kind of "investments" that should be considered for the kind of statutory protection that the pharmaceutical industry is seeking. For a detailed discussion, see Dhar and Gopakumar (2008) and Chaudhuri (2005).

[23] These figures are total R&D investment made the firms during the last 12 years.

[24] 'Piramal may reabsorb R&D spin-off", *Live Mint*, October 4, 2010.

[25] 2009 estimate as given in ICRA (2011).

[26] Estimate of Frost and Sulliven, given in *Indian Pharma-CRAMS*, SSKI India Research, September 2007.

[27] More than 160 in 2009. Italy which falls immediately after India has about 50 Plants. For details see ICRA (2011).

[28] Estimate given in ICRA (2011).

[29] 'GSK announces a strategic alliance with Dr. Reddy's to further accelerate sales growth in emerging markets', Press Release of GSK dated June 15, 2009, accessed at http://www.gsk.com/media/pressreleases/2009/2009_pressrelease_10064.htm as on September 22, 2011.

[30] Glenmark-Napo collaboration is discussed in detail in section 4.4 of this paper.

[31] Estimate given in ICRA (2011).

[32] Frost and Sullivan study on 'Contract Research and Manufacturing (CRAM)', 2006.

[33] Estimate given in ICRA (2011).

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[36] Press Release, Jubilant Organosis, December 1, 2009.

[37] Press Release, Jubilant Organosis, December 10, 2009.

[38] Press Release, Jubilant Organosis, November 25, 2006.

[39] Rajya Sabha unstarred question no 874 answered on November 16, 2010.

[40] 'Hyderabad: DCGI suspends illegal human trial of anti-cancer drug', India Today available at http://indiatoday.intoday.in/story/hyderabad-illegal-human-trial-of-anti-cancer-drug-suspended/1/142692.html on September 17, 2011.

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[49] 'Glenmark Pharmaceuticals Ltd and Napo Pharmaceuticals Inc Announce Collaboration Agreement on Napo's Novel Anti-Diahhreal Product Crofelemer', Joint release of Glenmark and Napo, accessed at http://www.glenmarkpharma.com/GLN_NWS/pdf/Napo_GlenmarkCollaboration_07Jul05.pdf on September 21, 2011.

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[51] n. 49.

[52] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugApprovals/ucm050527.htm; data for ANDA approvals (not the first time generics) since 2007 is accessed at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.ReportsMenu; The DMF data downloaded in excel file at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm#download on February 21, 2011.

[53] See Chaudhury (2007) and *Business Standard* 'USFDA door wide open for Indian pharma cos', March 6, 2009.

[54] See Department of Commerce (2008).

[55] KPMG (2006), *The Indian Pharmaceutical Industry: Collaboration for Growth*, p 9 in Sampath (2008).

[56] According to US FDA reports, firms from India had 1735 DMF filings as of 2008. The top 10 Indian firms had 831 DMF filings as of March 2009.

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[59] Based on company annual reports for nine years from 2001-02
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[61] Based on company annual reports for three years from 2006-07
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[63] Based on company Annual Reports for three years from 2007
[64] Based on figures given in the website http://www.piramallifesciences.com/research-pipeline/index.html as on 22nd March 2010
[65] Based on company Annual Reports for five years from 2004-05.
[66] Based on company Annual Reports for four years from 2005-06.
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[68] 'Ranbaxy eyes partnership for malaria drug R&D', *Business Standard*, November 5, 2007.
[69] 'Blow to Ranbaxy Drug Research Plans', *Live Mint*, September 21, 2007.
[70] 'Ranbaxy eyes partnership for malaria drug R&D', *Business Standard*, November 5, 2007.
[71] Information accessed on 'NMITLY' at www.csir.res.in/external/Heads/NMITLI-info.doc on September 28, 2011.
[72] 'Death of a dream', *Business World*, January 30, 2010.
[73] *Gatifloxacin* which is in Phase III trials is sponsored by European Commission/OFLOTUB consortium, Institute de Recherche pour le Development, WHO TDR and Lupin. *Moxifloxacin* which is undergoing Phase II/III trials is sponsored by Global Alliance for TB drug development, US Centers for Disease Control and Prevention, University College London, Johns Hopkins University and Bayer. The compound code named *PA-824* which is in Phase I is sponsored by the TB Alliance. For details, see Planning Commission of India (2006).
[74] The theme of the *World Investment Report 2011* is 'non-equity modes of international production and development'.
[75] Rajya Sabha, Unstarred question no 3389, answered on 23 December 2005.
[76] DST, Annual Report 2010-11.
[77] DPRP, Brochure, January 2008.
[78] 12 by CDRI, one each by RRL Hyderabad, HAL Pune, Trop. Med, Calcutta and 2 by Ciba Geigy.
[79] This incident has come out during the discussion of Sudip Chaudhuri with officials in Cipla and is reported in Chaudhuri (2005).
[80] Open Source Drug Discovery (OSDD) is a CSIR-led global initiative started in 2008 with the aim to discover new drugs for neglected tropical diseases. OSDD charts a novel course in drug discovery process by bringing in openness and collaborative spirit enabling scientists, doctors, software professionals, students and others across the globe to work together to solve key challenges in drug discovery. Government of India has committed Rs1500 million for this project. For details visit www.osdd.net
[81] Based on interaction with 31 firms in India.
[82] 'Does India Need its own bay-Dole?', accessed at http://www.cis-india.org/news/does-india-need-its-own-bayh-dole on September 30, 2011.
[83] This conclusion has been arrived at by comparing the projects sanctioned under DPRP and molecules that are in the advanced stages of clinical trials.
[84] The code names of molecules came out of projects under the loan scheme is available from Id 74. This information is compared against the molecule pipeline data provided in the Annual Report of firms.
[85] Based on the statistics on projects granted under DPRP available at www.dst.gov.in
[86] Draft National Pharmaceutical Policy - 2006, Part A.

[87] Taken over Indian firms such as Ranbaxy, Matrix, etc. have not been included in the classification of MNC subsidiaries.

[88] The term 'evergreening' is used in the literature dealing with patents to indicate the strategy of the patent holder to extend the life of patent by making minor modifications to the product. As a result there are a number of patents, obtained at different periods, on the same product. This results in a situation where the product is protected even when the initial patent is expired. Evergreening is a strategy widely adopted by pharmaceutical MNCs to prevent the generic firms from the manufacture and supply of the generic drugs when the patent expires.

[89] "Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research" (Paragraph 17, Current Version (2008 Version) of the Declaration of Helsinki).

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