From imitation to innovation: the evolution of R&D capabilities and learning processes in the Indian pharmaceutical industry

Journal Item

From imitation to innovation: The evolution of R&D Capabilities and learning processes in the Indian Pharmaceutical Industry

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Abstract

Over the last decade the Indian pharmaceutical industry has emerged as a leading supplier of generic drugs to both developing and developed countries. The movement of the Indian pharmaceutical industry along the R&D value chain represents a remarkable shift from an importer to an innovator of drugs. The Indian government's industrial and technology policies along with changes in Intellectual Property Rights regulation played a crucial role in shaping this development of R&D capability. Using the 'capability creation model' this paper discusses the learning processes and stages involved in this dramatic accumulation of technological capability.

This analysis shows that the Indian pharmaceutical industry has followed a trajectory from duplicative imitation to creative imitation to move up the value chain of pharmaceutical R&D. Finally as a result of changes in patent law the industry is learning to develop capabilities in innovative R&D. The basic and intermediate technological capabilities gained from imitative learning gave these firms a solid base for development of competence in advanced innovative R&D. These finding have implications for government policies as well as firm strategies in other developing countries albeit with some limitations due to global harmonisation of patent laws being promoted by the World Trade Organisation.

1 Introduction

For many years Indian economic and industrial policy was dominated by an import substitution ideology. State interventions and regulations played a key role in directing firm and national level indigenous technology capability development. The existing pharmaceutical industry in India is in many ways a product of a micro economic environment shaped by state regulations and interventions. The industry has come a long way from importing bulk drugs to exporting formulations to highly regulated markets in the developed world. This movement involved different learning processes and stages which are illustrated by the 'capability creation model' in Figure 2 which maps these processes and stages involved in technological capability accumulation onto a pharmaceutical value chain. This paper presents the responses of the Indian pharmaceutical industry to changes in government industrial and regulatory policies. It also tracks the influence of different policy regimes on the development of capabilities and the underlying learning processes in the Indian pharmaceutical industry.

This analysis shows that the Indian pharmaceutical industry's journey from being an import dependent industry to becoming an inventor of original pharmaceuticals has been long and eventful. It shows that the industry has followed a trajectory which started with duplicative imitation followed by creative imitation, rising up the value chain of pharmaceutical R&D and finally as a result of change in patent law industry achieving the learning required to develop capabilities in innovative research and development (R&D). The analysis reveals that the strengthening of patent laws as a result of the TRIPS agreement had a positive impact on large Indian pharmaceutical firms and catalysed their movement from imitators to innovators. It played an important role in creating a 'crisis for their existence' that triggered their movement towards innovative R&D competencies. However it also emerged that imitative R&D in these firms created essential basic capabilities which underpinned innovative R&D. These basic and intermediate technological capabilities acquired through imitative learning certainly gave these firms a solid base for development of competence in advanced innovative R&D. These findings show that the industrial and regulatory policies applied by the Indian government resulted in the development of a self sufficient pharmaceutical industry. These policy measures have implications for other developing countries although with some limitations due to TRIPS agreement. Similarly strategies adopted by Indian firms to move up the value chain have implications for generic firms in other developing countries and advance countries.

Section 2 discusses the changing contours of Indian industrial and technology policy and its role shaping the Indian pharmaceutical industry. Section 3 presents the capability creation model in the Indian pharmaceutical industry and discusses the learning processes involved in technological capability accumulation at the industry level. Section 4 concludes the paper and discusses the implications of the findings.

2 The changing contours of Indian industrial and technology policy

After independence India's industrial growth was shaped by policies based on the import-substitution model and which to a larger extent focused on indigenisation. This indigenisation activity forced the occurrence of much technical effort in firms and this resulted in the development of a wide ranging production base. Some firms used the protection policies to build useful technological capabilities, however, much of the Indian industry was characterised by widespread inefficiency and product obsolescence. Lall (1984) summarises the technological capability development in the pre 1991 era by pointing out that India's industrial performance signifies that it had developed the "broadest and best developed technological capabilities in the third world", whereas on other hand, India had performed poorly in terms of "industrial growth, the expansion of manufacturing exports, the absorption of industrial labour and introduction of innovative products in foreign or domestic markets".

In the post independence era Indian policy makers viewed scientific research as an imperative activity for technological progress, putting an extensive effort into creating a scientific workforce and institutions. Since the 1950s the Indian government has set up a vast and diversified network of R&D institutions under the umbrella of the Council of Scientific and Industrial Research (CSIR). CSIR consists of 43 national laboratories employing around 10,000 highly qualified scientific and technical personnel. However, in India complementary linkages between industry and institutes never evolved due to their different research focus. The major objective of the work done in the Indian R&D institutes was indigenisation; so if some thing is imported, then find the process or mechanism to develop it locally. The restricted competition within the protected environment reduced incentives for innovation and thus prevented an industry-academia collaborative link.

Even a science based industry like pharmaceuticals characterised globally by strong industry-academia linkage, lacked a web of such linkages. Thus a crucial element of technological progress; industry–academia linkages didn't evolve in India. As a result investment by Indian government in R&D did not help these institutes to emerge as a source of technology.

These industrial and technologies policies directed the growth of the pharmaceutical industry in India. To the greater extent the Indian drug policy, R&D institutions and IPR regulation influenced the capability development process in Indian pharmaceutical firms and shaped the evolution of industrial and market structure.

The pharmaceutical industry in India has mainly evolved through three phases, each characterised by different policy regimes and industry's response to those policies.

The first period was prior to 1970, when the industry was relatively small in terms of its production capabilities. The second period is the decade and a half spanning from the 1970s to the beginning of the 1990s, a period during which the output of the industry grew remarkably. In the third phase of expansion, from 1990s onwards, the pharmaceutical industry grew more than three times faster than it did during the 1980s. However the third phase also witnessed major regulatory policy change for the Indian industry. In 1992 the Indian government signed the TRIPS agreement, which led to the introduction of strong patent laws from 1995 which restricted reverse engineering R&D by Indian firms. Abrol (2004), criticising the introduction of strong IPRs, points out that it has neither led to transfer of technology to Indian firms nor has it benefited the Indian population, since firms are not investing in medicines for local needs. However Smith (2000) provides a different point of view suggesting that, if successful, India will be one of the first emerging economies to produce cutting edge technology in pharmaceuticals. Similarly Madanmohan and Krishnan, (2003) show that the Indian industry responded to changes in patent law by building capacity to achieve scale economics. The other preferred strategy is to stabilise and control the environment through developing alternative technology paths. Building on these studies this paper focuses on the capability development processes adopted by the Indian pharmaceutical industry to transform imitative R&D into innovative R&D as a response to changes in patent law. The gradual movement of the Indian pharmaceutical industry from the acquisition of a basic minimum knowledge-base towards the creation of new competences for innovation involved different learning processes and stages. These are explained by developing a capability creation model, which shares the trajectory shown by Kim's (1997) model of technological growth in South Korea; however, the capability creation model also describes the learning processes involved in achieving that growth.

3. Research Methodology

Data collection for this research was carried out in two phases. In the first phase, interviews were conducted with academics, consultants and patent experts associated with Indian pharmaceutical industry. The interview questions used for the first phase was mainly focused on industry level issues such as the effect of changes in patent law on industry structure, market structure and emerging challenges.

In the second phase research focussed on firm level analysis as micro level analysis can provide better understanding of the processes involved in the transformation of existing capabilities and the development of new competencies. Therefore in the second phase a case study methodology (Yin, 1994) was chosen to explore capability development processes in

six innovative Indian firms. Indian pharmaceutical firms which have moved from imitative R&D to innovative R&D were selected for study. A multiple case study design was used and the cases were chosen on the basis of degree of innovativeness and strategies to transform themselves. Only those firms which has filed patents for new chemical entities in both India and the US were selected for the study. The second phase involved interviews with R&D presidents and pharmaceutical scientists from six innovative firms. A total of 33 interviews were conducted, 10 in the first phase, and 23 in the second phase.

The interviews were transcribed and analysed by using techniques like pattern matching (Yin, 1994) and systematic building of analytical tables (Miles and Huberman, 1984). The different patterns were identified and categorised using Atlas.Ti data analysis software. The interview transcripts were analysed by locating series of narratives around the capability development issues in each firm and from these, replicating patterns of learning processes were identified. These patterns were supplemented by secondary data which was collected from industry journals, industry association publications and annual reports of firms. The observed patterns in Indian pharmaceutical firms were then compared with the theoretical patterns identified from the framework to find the similarities and differences between them. The results of analysis were sent to key members of each firm researched and their feedback was included in the final results.

In regard to case studies the main limitations were the depth of analysis possible due to reliance on a few key individuals and the difficulties in accessing historical firm records Triangulation of the responses from the case studies came from comparison between interview responses, firm's annual reports, analyst presentations, other published matter on the firm and coverage in national and business press. This helped to avoid problems of bias in interpreting data and guide towards robust research findings.

4. The capability creation model

The growth of the Indian pharmaceutical industry reflects the rise of the industry up the value chain in terms of activities involved in the pharmaceutical R&D. The vice president of one Indian firm comments,

"if you see historically, from marketing to manufacturing, from R&D of API to generics and now we will be into drug discovery phase. It's a gradual up-gradation through which Indian pharmaceutical industry has gone through".

The growth of Indian pharmaceutical firms on the pharmaceutical value chain is closely aligned with various R&D learning processes such as reverse engineering R&D followed by

creative adaptations and finally collaborative R&D. Although weak patent laws and availability of large supply of chemists played a key role in rise of Indian firms.

The pharmaceutical R&D value chain (Fig 1) characterises pharmaceutical R&D capabilities on the criterion of technological and marketing complexity against the margin of profit in the market associated with a respective category. Basic capability is characterised by the production of intermediate bulk drugs. These are drugs in powder form and involve the lowest level of technological and marketing complexity and correspondingly have low levels of profitability. New chemical entities (NCEs) result from highly technological complex research and represent the most advanced capability. They require a strong marketing infrastructure and due to strong patent protection, the profitability associated with NCEs is very high with the drugs enjoying a monopolist presence in markets for the duration of the patent protection.

{Fig. 1 here}

In the value chain, technological complexities increase at each level with a corresponding increase in profit margin. The increasing technological complexity requires an increased input of original knowledge as well as stronger marketing and distribution infrastructure.

4.1 Processes involved in capability accumulation in Indian pharmaceutical industry

In the capability creation model (fig 2) a basic level of capability is taken as the ability to make minor adaptations to production and to assimilate technology into a firm's environment. Intermediate innovative capability is the ability to generate incremental technical change in product design, quality and production processes, it also includes ability to search and evaluate external sources of technology. Advanced innovative capabilities refer to the ability to generate new products and process innovations. A knowledge-base is categorised as simple and complex, based on the technological challenges involved in developing particular products and underlying capabilities. This classification of level of capabilities is based on Bell and Pavitt (1993) and Lall (1992).

In the pharmaceutical industry, reverse engineering R&D capability; the ability to develop products by copying the process, is categorised as a basic capability. Generics R&D involves incremental change representing intermediate capability while new chemical entity research involves creating new drugs and innovative therapies representing advanced capabilities.

{Fig. 2 here}

The 1970s saw the turning point in the development of the Indian pharmaceutical industry. In the pre 1970 era foreign firms had a disproportionately high share in total Indian domestic pharmaceutical production. These firms together produced 42% of bulk drugs and formulations and produced about 38 % of all bulk drugs produced by the Indian industry (Indian Drug Policy, 1978). To encourage the growth of the domestic industry and reduce dependence on foreign pharmaceutical firms, the Indian government took forward three key policy initiatives in the 1970's. The first policy initiative was the Drug Price Control Order (DPCO) by which the Indian government sought to control the prices of drugs. The second was the adoption of a new weak patent act passed by the Indian parliament in 1970 but becoming effective from 1972. The Indian Patent Act, 1970 was the most conscious attempt by Indian policy makers to improve the terms of accessing international intellectual property. The third initiative was the adoption in 1978 of a drug policy which proposed an elaborate use of industrial licensing to organise capacities in keeping with the broad objective of capability creation in domestic pharmaceutical firms. The Foreign Exchange Related Act (FERA) also influenced the working of multi-national pharmaceutical firms in India as these firms had to reduce their foreign holdings to 40%.

Until 1970, most Indian pharmaceutical firms' initial forays into the pharmaceutical business involved marketing and distribution of imported pharmaceuticals. In 1960, close to 90% of market share was with multi-national corporations (MNCs) and 10% with Indian companies. In the pre-independence era and up to World War II, Indian domestic production only accounted for a fraction of the market for medicine. There were fewer than 10 registered producers of Western-type pharmaceutical products in 1915 and 30 in 1947; many of them were producers of non-pharmaceutical chemicals. The Indian population was largely dependent on imports from foreign firms based in the UK, France and Germany for the supply of medicines. The cost of these medicines was largely out of reach for the majority of the Indian population (Felker et al., 1997). Therefore after independence, the Indian government focused on pharmaceuticals as a priority area and both, private and public investments were sought under the industry policy resolution. Several foreign multinational firms invested in India throughout the 1950s and 60s and until the 1970s these firms dominated the Indian market. Some multinational companies only set up marketing and distribution facilities, importing bulk drugs from their manufacturing facilities. When the Indian government increased pressure against the import of finished products, MNCs set up formulation units and restricted imports to bulk drugs.

The Indian government set up research institutes in the form of CSIR laboratories like the Central Drug Research Institutes and invested in public sector enterprises to establish the domestic pharmaceutical industry. The first priority for the government was to become independent of imports as India was importing almost 90% of its bulk drugs requirement.

Therefore in 1954, the Indian government set up a public sector pharmaceutical firm called Hindustan Antibiotics Limited (HAL) for the production of penicillin and sulfa drugs and in 1961 with Russian cooperation the Indian government set up another pharmaceutical firm; Indian Drugs and Pharmaceuticals Limited (IDPL). The public sector units along with the research institutes and MNC firms who started manufacturing in India developed the basic knowledge-base required for the industry and emerged as the main source of industrial entrepreneurs a decade later (Chaudhari, 1999:11).

Gradually Indian pharmaceutical firms moved into the area of manufacturing formulations and followed with backward integration into production of bulk drugs. But the 1970 patent law changed the industry structure and market by reducing entry barriers for entrepreneurs to operate in this science based industry. This law legalised reverse engineering R&D and paved the way for Indian firms to build basic capabilities in pharmaceutical R&D.

As Table 1 shows the second half of the 1980s saw a remarkable increase in the output of the industry in terms of bulk drugs and formulation production performance. This period saw Indian pharmaceutical firms consolidate their position in the domestic market.

{Table 1 here}

4.2 Duplicative imitation and basic R&D capabilities

In the post 1970 era Indian pharmaceutical firms focused on adapting technology to firm and country specificity and efforts in these directions fostered the development of a basic knowledge-base. Indian pharmaceutical firms, taking the benefit of the weak patent law, used reverse engineering or duplicative imitation as the main mechanism of knowledge acquisition and built a basic capability in process R&D. Managers working in public sector units, research institutes and other Indian firms sensed the opportunities that emerged after 1970 and started creating their own firms on the basis of skills in reverse engineering. These firms started developing drugs by copying or using known processes to manufacture the product at lower costs. Indian firms and research institutes simply followed the patent and reverse engineered the process, albeit with some minor modifications (Fig. 3).

The strategic planning director of leading firm comments,

"Earlier there was no R&D as such, it was simply reverse engineering; whatever patent said you would reproduce and optimise it".

{Fig. 3 here}

In reverse engineering (Fig 3), scientists study the different sequential steps involved in the making of the final compound. In some cases, scientists keep all these steps and change the solvent or in some cases scientists change some steps and arrive at some product with a different process. In most Indian pharmaceutical firms, scientists developed skills in reverse engineering R&D through trial and error experimentation or learning by doing. The former R&D president of a top Indian firm explains the early efforts of firms,

"You have to train people; actually quite a bit of training has gone into this. Nothing like training, every body comes from university, and had no experience of reverse engineering. When there is no reverse engineering really per se in the universities as a course or anything so you have to teach them. Then there were few people already available they can train the younger one. So we have trained the people on the job, that itself investment for a year or so when they really start learning or giving results".

Reverse engineering R&D also involves purposive searching of relevant information, effective interactions among technical members within a project team and with marketing and production departments within the firm, effective interactions with suppliers, customers and trial and error in developing a satisfactory result. These activities helped Indian firms to develop basic capabilities in pharmaceutical product development and management.

Kim and Nelson (2000) suggest that the important aspect of imitative learning is the search for technological information, an important component of accumulating basic innovative capabilities. In the case of reverse engineering pharmaceutical R&D the publicly available knowledge in the patent is not always sufficient on its own to produce a reverse engineered product. Some knowledge is not disclosed in patents but importantly firms need to have the tacit knowledge to complement and interpret disclosed knowledge. Hence the non market imitative or reverse engineering based acquisition of knowledge is likely to require the firm to gain the necessary tacit knowledge and unavailable information, for example through trial and error. In the case of Indian pharmaceutical firms where new products were not registered by original patent holders in India, the Indian firms quickly compiled 'product dossiers' based on published data and supplemented them with limited Phase III clinical trials and got products approved by the drug regulatory authority.

The focus of Indian pharmaceutical firms in the context of reverse engineering R&D was not based on the number of patents a firm had filed but on the number of products a firm could reverse engineer and the time required for imitative process development. Indian firms competed in a fiercely competitive domestic market; in which there can be up to 100 brands for any one molecule. Thus profits in the market were directly related to the efficiency of production processes used by firms and so Indian pharmaceutical firms put an intensive in

house effort to develop cheap processes[1]. This resulted in the rapid acquisition and assimilation of reverse engineering expertise across all firms. This also resulted in a lack of collaboration between industry and academia. As profits were totally linked to the superior production process, firms' made an effort to build these capabilities in-house. The lack of trust due to a weak regularity environment further hampered the development of collaborative research networks between industry and academia.

Kim and Nelson, (2000) point out that a reverse engineering strategy also involves activities that sense potential needs in a market, activities that locate knowledge or products, which would meet the market needs, and activities that would infuse these two elements into a new project. As a result Indian pharmaceutical firms built the organisational capabilities required to operate scale intensive manufacturing facilities and created strong marketing and distribution networks domestically.

By the end of 80s, Indian firms were manufacturing practically every new molecule which was commercially viable without access to process details from the innovator company.

One of the indicators of Indian firms' superior imitative capabilities is the shortening of the time lag between the introduction of a drug in the global market by the inventor and the marketing of the same drug in the Indian market. Over the years Indian firms have been able to progressively shorten the lag between the introduction of a drug by inventor and its introduction in the Indian market indicating superior process R&D capabilities (Table 2).

{Table 2 here}

However this era of protected environment, intensive competition among domestic firms and strong emphasis on reverse engineering, also generated some negative characteristics, which

[1] If an original patent holder has developed the product with process A, then other company develops the product with process B, third company tries to developed product with process C. The profitability of a drug in the market place was mostly determined by the cost and timing of entry in the market. A research based pharmaceutical firm operate on 95% production margins; total cost of manufacturing involved in the development of the drug is 5%. So the marginal or significant improvement in process development does not have a significant effect on profit margins. The Indian pharmaceutical firm operates on an 8% production margin; the cost of manufacturing makes up the 92% of total cost of the product. Therefore even if a firm does a .5% improvement in process, then firm can achieve a significant improvement in margins which finally can result in an effective increase in profit. This was the driving force for firms in developing efficient cheap processes as .5% on an 8% margin makes a big difference.

dominated ‘ways of working’ in Indian pharmaceutical firms. The extensive focus on reverse engineering R&D resulted in the development of an insular technical knowledge-base; Indian firms built strong capabilities in organic and synthetic chemistry, but other areas of innovative pharmaceutical R&D like medicinal chemistry and biology remained neglected. This led to the development of an insular knowledge-base in these firms.

The reverse engineering focused R&D also prevented the development of communication channels like publication and conferences, which help in creating links with a larger scientific community.

The weak patent law also affected the Indian pharmaceutical industry’s regulatory management capability, a key capability required to operate in advanced markets. Due to weak patents laws, patents could neither protect information nor create value for Indian pharmaceutical firms. This is reflected in the negligible publication and patenting activity by Indian pharmaceutical firms in this era, preventing the development of basic IPR management capability.

The other major impact of the protective environment was the lack of any innovative activity in Indian pharmaceutical firms. The weakening of the patent act and the drug price control order of the 1970s forced MNC pharmaceutical firms to reduce their operations in India, thus providing a space for Indian domestic firms to expand in the local market. This provided Indian firms with a domestic market which was large in volume but small in value. The lack of enough value in the Indian market proved detrimental to the emergence of innovative R&D in Indian pharmaceutical firms.

4.3 Creative imitation and intermediate R&D capabilities

After the liberalisation of the pharmaceutical market in the mid 1990’s, some Indian pharmaceutical firms moved towards export markets and specifically generic markets in advanced countries. Indian pharmaceutical firms adopted the strategy of ‘creative imitation’ to manufacture products by developing non-infringement processes. These non-infringing processes can be converted into a patent, which creates a value for firms in the market. According to Kim and Nelson (2000) design copies, creative adaptations, technological leapfrogging and adaptation to another industry are different forms of creative imitations. Creative adaptations are innovative in a way that they are inspired by existing products but differed from them. Creative imitations are aimed at generating facsimile products but with new performance features. It involves not only activities like benchmarking but also notable learning through substantial investment in R&D activities to create imitative products, which may have significantly better performance features than the original.

In the post-1990 era, Indian firms started developing processes which contained some patentable novel elements. The Vice President, Corporate Affairs of top Indian pharmaceutical firm argues,

"what happening was more innovative way of producing the drug; if you would look at what Pfizer did, what DRL did and what Ranbaxy did for various products. Example, Prozac which is Fluoxentine used to be sold in particular dosages and strengths. DRL not only developed the new process to make Fluoxentine but also they developed new dosage form and therefore they got exclusivity in the US. So that innovation".

The creative imitation process starts with the top management of a company selecting a molecule to be developed based on criteria like patent expiry date, market value and complexity of the molecule. Then regulatory team scouts use the patent database to search for loopholes in the patents for selected drugs and report to the R&D team all key information about existing patents on the product, for example, different process patents filed by originator. This is a crucial step in designing the non-infringing and novel process. Then R&D team studies all possible patents –for hydrides, polymorphs, isomers, other crystalline forms and metabolites. The main task of the R&D team is to find processes that don't infringe on any of the originator's process patents. The R&D team has to chemically produce a compound in an efficient way with the same level of bioequivalence as the original compound. Once the R&D team develops the non-infringing process, the regulatory and legal team joins the project again. These teams start working on filling the regulatory approval in terms of a drug master file (DMF) in the case of bulk drugs or an abbreviated new drug application (ANDA) in the case of formulation of products for the US and European markets[2]. The product then moves to the firm's pilot plant for validation and production of exhibit batches to be submitted to the FDA with the drug master file or ANDA application.

[2] A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) containing confidential, detailed information about facilities, processes or articles employed in the manufacturing, processing, packaging, and storing of one or more drugs intended for use in humans or animals, while abbreviated new drug application contains data which when submitted to FDA provides for the review and ultimate approval of a generic drug product.
Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug).

The IPR head of a leading firm explains the subtle difficulties involved in imitating the process creatively,

"suppose you have new molecule and you will like to protect this molecule as far as possible and so you would like to surround it with as many patents as possible. Every major pharmaceutical firm is doing it. Now if I have to enter generic phase after the patent expiration, I have to ensure that I do not fall within spaces covered by the patent of those companies to avoid all that litigation and all that things. So I would have to develop the process of formulation or new product which is beyond the boundaries whatever covered by the scope of the patent. So I would not infringe upon rights of others. This was not done 5-6 years ago, but this is done now. All Indian pharmaceutical firms are focusing on generic markets. Firms want to make sure that it is not going to be sued for infringement. That's role of R&D; it ensures whatever product we develop, it does not infringe on patent of others".

The key aspect of imitation in generics R&D is to copy the product using innovative processes. Indian firms acquired their generics R&D capabilities by assimilating and creatively improving on their reverse engineering R&D capabilities. Success in generic R&D involves strong interaction and coordination between IPR, marketing and R&D departments and requires the presence of organisational mechanisms to facilitate these interactions. Thus creative imitation allowed Indian pharmaceutical firms to develop the regulatory capability required to access global markets, build organisational structures able to manage original research and gain entry into the generic markets of advanced countries. The firms moved up the pharmaceutical R&D value chain by developing products for highly regulated generics markets in advanced countries.

Indian pharmaceutical firms initially exported formulation products to the least developed or developing countries but after 1990 they started exporting formulations products to generics markets in advanced countries (Table. 3). An important event in the expansion of a generic market in the US was the enactment of the Waxman-Hatch Act in 1984. This abolished the requirement for fresh clinical trials of generic drugs and replaced them with simpler and less expensive 'bioequivalence' and 'bio-availability tests'. There are two ways to approach the US generics market;

A. Para III – in which case filings are mainly driven by patent expiry and

B. Para IV – it signifies the patent challenge route to create and tap a block buster opportunity by gaining an exclusive marketing right for a limited period of time.

Some firms like DRL are aggressively pursuing the Para IV route of patent challenge, which is a high risk, high return strategy where firms apply for patent challenging validation of existing patents and by that, taking on an original patent holder. Others like Sun

Pharmaceutical and Ranbaxy have followed the conservative approach of Para III filing. Some firms like Cipla are looking at ways to grow in that space through tie ups, alliances, etc. with other generic firms like Watson and Ivax.

{Table 3 here}

Indian pharmaceutical companies have adopted various strategies to enter the US generic markets. Many Indian pharmaceutical firms have set up their marketing infrastructure in the US. Some firms have acquired US based firms to set up an operation while other firms are forming alliances with generic firms operating in the US for the supply of API or formulation generic products

{Table 4 here}

In the post 1990 era Indian pharmaceutical firms invested heavily in improving production facilities and adopted Good Manufacturing Practices (GMP) and now most leading companies have their manufacturing facilities approved by the USFDA and UK's MCA. By 2003 India had the highest number of FDA-approved plants outside the US. India's 61 such plants are closely seconded by Italy's 60 plants (Fig. 4).

{Fig. 4 here}

Indian pharmaceutical firms filed patents for indigenously developed novel and non-fringing processes with the regulatory authorities in the Europe and US. In earlier years filing patents in different regions, which required the same amount of data as regulators from the developed world helped these firms to acquire the minimum regulatory expertise. This proved to be an effective mechanism for gathering the knowledge required for the successful filing of patents in the US and Europe and was further strengthened by the successful filing of patent applications for generics (ANDA) in the US and by 2000 Indian pharmaceutical firms had firmly established generics R&D capabilities and associated regulatory capabilities (Table 5). There has been a spate of DMF fillings since 2000 and now even small firms are getting into the value added ANDA segment. In 2003 Indian pharmaceutical firms filed 73 ANDA applications with US FDA constituting 20% of the total. At the end of 2003 Indian firms had a total of 106 ANDAs approved by the FDA with 108 more ANDAs on file but not yet approved. In 2003 Indian firms submitted 119 DMFs, almost 30% of total DMF submissions to USFDA.

{Table 5 here}

Exposure to global markets, realisation of future regulatory changes and creative orientation to imitative research, all facilitated the development of the 'research tradition' in these firms. Nelson and Winter (1982) reflecting on imitative learning suggest that 'an imitator working with an extremely sparse set of clues about the product might well adopt the more prestigious title of 'innovator', since most of the problem is really being solved independently'. This upward movement of Indian firms represents the intermediate capability stage as the products resulting from generic R&D require input of original knowledge and can give leverage to firms in global markets.

In the case of Indian pharmaceutical firms creative imitation in the form of generics R&D accelerated their movement towards the acquisition of advanced level capabilities further up the value chain in pharmaceutical R&D. Creative imitation in the form of generics R&D has increased Indian pharmaceutical firms' awareness of opportunities in new drug delivery systems (NDDS) and NCE research. Many skills and activities required in generic R&D are applicable in the innovative process R&D. Managerial experience in generics R&D has given Indian firms some understanding of the complexities involved in innovative research and the organisational infrastructure associated with it. Through their generic business, these firms have built information channels with scientific communities in advanced countries.

4.4 Collaborative R&D and advanced R&D capabilities

The movement from intermediate R&D capabilities to advanced R&D capabilities is very challenging due to the difference of knowledge-base and organisational capability. The advanced level of technological capabilities in the case of pharmaceutical R&D involves new chemical entity research either by using research strategies like analogue research or rational drug design and in terms of process R&D, new drug delivery systems.

Analogue research involves working on predetermined targets for specific diseases to develop molecules that alter the target's mechanism in the diseased person while rational or structure based drug design involves the determination of a disease-causing protein's three-dimensional structure. Once the structure is known, novel chemical entities are designed to 'lock-in' to the protein with the aim of reversing or arresting a disease's progression.

The main focus in drug delivery system research is in improving the effectiveness of an existing drug, in terms of dosage, length of treatment and biodegradability. Many Indian pharmaceutical firms with a proven track record in process R&D see new drug delivery systems as a risk free strategy. The drug delivery improvements do not impinge on the

product patents and the cost of stage I and II trials for an improved drug cost almost 1/10 of a new drug. An improved version of an existing drug also assures good market success.
From 1995, large Indian firms started investing heavily in new drug discovery research and new drug delivery system research as a response to the emerging post TRIPs scenario. The Vice President of R&D of one leading Indian firm suggests,

"Firms have decided strategically whether they should go into drug discovery or drug delivery systems. Some companies like DRL clearly gone into drug discovery and then companies like Ranbaxy who first gone into drug delivery and then drug discovery. It is doing both. So you see again over a period of time; innovation being the platform, R&D becomes the key".

In terms of new chemical entity research, Indian pharmaceutical firms do not compete with multinational giants like Pfizer or Glaxo, instead their strategy is to leverage technical skills. These firms have filed patents for innovative products by using analogue research as their main strategy (Table 6). Indian pharmaceutical firms are working with already validated or known targets where the structural activity of the compound is well known and they try to find a compound that possesses better efficacy or fewer side effects.

{Table 6 here}

Initially Indian firms faced major constraints such as financial and infrastructural resources, an insular knowledge-base and lack of scientists trained in innovative R&D. To leverage the financial cost, Indian pharmaceutical firms started investing the revenue generated from generic business into innovative R&D. The alternative strategy to cover these financial costs was to partner with MNC pharmaceutical firms through licensing of molecules or drug delivery system technology. These licensing agreements usually involve milestone payments and limited marketing rights. An Indian pharmaceutical consultant describes the early efforts of these firms,

"These companies saw the writing on the wall and worked towards developing the expertise in new areas of drug discovery and development research, considering the low resources available to them in comparison to those of MNCs, they have adopted a strategy of collaborative research through a licensing route, by gaining up-front milestone and royalty payments for the molecules licensed by them to MNCs for further clinical development".

For example, Torrent pharmaceutical licensed its anti diabetic molecule to Novartis at a preclinical stage. According to the agreement, initially Torrent will receive a payment of USD 0.5 million and it will develop the molecule to a predefined stage. At this stage Novartis will have the option to acquire rights for further development. If Novartis exercises this option then Torrent will receive an initial payment of $3million and subsequent milestone payments depending on progress. If the product is commercialised Torrent will get royalties and will also lead the co-promotion of the product in India.

The low cost of research in India has also helped Indian pharmaceutical firms' to overcome financial constraints associated with new drug discovery. The cost of drug discovery and development in India could be one tenth of the cost involved in the development of a new molecule in advanced countries.

The other major constraint faced by Indian pharmaceutical firms was the knowledge gaps in new chemical entity research, especially in the various disciplinary areas involved in drug discovery. Indian pharmaceutical firms filled the knowledge gaps by hiring Indian scientists experienced in drug discovery R&D and by adopting a strategy of collaborative research with Indian and overseas research institutes. In the post 1995 era R&D scientists became the focus as Indian firms hired scientists from India as well as overseas universities, companies and research institutes. The Vice President, Corporate Affairs of a top Indian firm explains,

"Indian firm did three things; first they recruited people who had that experience. So you have Dr. Venkatswarlu in DRL and you have Dr. Khanna in Ranbaxy and host of other people; it's not just one person. Second it started doing recruitment in university campuses overseas, in areas where educational qualifications were not available in India and lastly it stared sending scientists to symposia, training programmes, conferences to pick up the ideas".

The new drug discovery research requires knowledge about various disciplinary areas and effective knowledge transfer mechanisms to facilitate the flow of knowledge. Indian pharmaceutical firms employed a collaborative R&D approach to tap disciplinary knowledge bases in research institutes. The director of a leading research institutes points out,

"we have strong group in peptide and nucleotide chemistry and you see lot of interest from industry. Although 10 years ago we had same people with same group and nobody was interested, now we have lot of work".

Indian research institutes have built the strong supporting infrastructure required in drug discovery R&D comprising analytical instruments and facilities for research still lacking in

most firms in the industry. For example, the National Chemical Laboratory has a combinatorial chemistry machine while the Central Drug Research Institute owns a high through-put screening machine. Indian pharmaceutical firms collaborate with Indian research institutes to use these supportive infrastructural facilities.

Recognising the imperative to take proactive measures to give a necessary fillip to R&D, the Government had set up various schemes to encourage collaboration between research institutes and industry. In 1995 under the Department of Science and Technology, the Indian government launched a programme called the New Millennium Leadership Technology Initiative (NMLTI) to bring industry and academia together. The basic objective is to synergise the facilities and competencies of publicly funded R&D institutions, academia and private industry for developing technologies for Indian industry. The NMLTI programme caters to all industries and is not restricted to pharmaceutical research. With a financial outlay of Rs. 800 million, DST has sanctioned 49 pharmaceutical industry/institutions collaborations so far. In this programme 50% of funding comes from the government and 50% from industry.

The Indian government also took major initiatives to increase interactions between industry and public R&D institutions in areas of innovative pharmaceutical R&D. In 2000, the Indian government created a Pharmaceutical Research & Development Support Fund (PRDSF) with an initial allocation of Rs.1500 million as a plan fund for promotion of R&D in the pharmaceutical industry. Recently the Department of Science and Technology cleared five industry-institution research proposals to be funded through the PRDSF programme.

Due to these initiatives many research laboratories have taken up industry sponsored research and established strong partnerships with industrial firms on a long term basis for product and process development projects. In the post TRIPs era CSIR had launched many initiatives as a response to the changing needs of the industry and knowledge generation. The research institutes redefined their role for a post TRIPS scenario by investing in the development of expertise in drug discovery research, generics research and building different relationships for each expertise. In the past, academic research meant publishing journal papers, not releasing technologies into the market place. But now CSIR labs are becoming more market oriented and collaborating with industry to bring the inventions into the market place. The vice president R&D of an Indian firm suggests,

"Most academic institutes are trying to collaborate with the industry. Industry is also trying to outsource some work to academia. To get to see what innovation is there, we collaborate together. So there is a lot of cooperation going on between industry and academia and systems, disciplines are in place.".

Thus Indian pharmaceutical firms are developing advanced pharmaceutical R&D capabilities by adopting collaborative research strategies.

4.5 Capability creation model: Summary

The capability creation model provides a broad sketch of activities, depths of knowledge and abilities associated with the Indian pharmaceutical industry's rise up the value chain. The capability creation model reveals that the Indian pharmaceutical industry moved from basic R&D capabilities to advanced level R&D capabilities by undertaking different types of activities involving R&D processes like duplicative imitation, creative imitation and collaborative R&D.

Over the years the Indian pharmaceutical industry has emerged as one of the most technologically advanced knowledge-based industries in a developing country. Indian policy makers used patent law to infuse life into domestic pharmaceutical firms and provided these firms with protection from competition. Indian firms developed capabilities for producing drugs in bulk and formulation form by using duplicative imitation. At the beginning of 1990 the Indian government liberalised the economy and along with that also opened the Indian pharmaceutical market to multinational firms. Indian pharmaceutical firms responded to this challenge by flooding the generics market in advanced countries with drugs developed through creative imitation. The duplicative imitation era gave these firms two advantages that facilitated generics R&D capability creation –

a. cheap and scale-intensive manufacturing facilities and

b. world class organic chemistry skills, honed by years of reverse engineering.

Thus duplicative imitation created absorptive capability for Indian firms to move further along the pharmaceutical value chain. A firm's ability to develop new knowledge through external sources depends upon its learning capacity, that is, on its ability to acquire, create and disseminate new knowledge. Cohen and Levinthal (1990) refer to this organisational capacity to generate new knowledge as *absorptive capacity* and define it as the ability of a firm to identify, assimilate and apply external knowledge. However absorptive capacity tends to be cumulative and path dependent as it builds on a prior knowledge base and on experience which is firm specific. This prior knowledge base is an essential component of a firm's learning ability or absorptive capacity as existing knowledge increases the ability to make sense of, assimilate and apply new knowledge. In the case of Indian firms duplicative imitation crated prior knowledge bases for the development of innovative R&D capabilities.

However with the strengthening of patent laws, Indian firms focused on creating a business around intellectual property (IP) products by conducting drug discovery research. These firms used collaborative R&D approaches to develop advanced capabilities in pharmaceutical R&D and funded these investments through formulations and bulk generics businesses.

5. Conclusion and discussion

The Indian pharmaceutical industry's emergence as a developer of original pharmaceuticals is quite remarkable. The analysis suggests that the industrial policies adopted by the Indian government played a key role in growth of the Indian pharmaceutical industry. The different industrial policy regimes influenced firm level learning processes and shaped the technological capability accumulation in the Indian pharmaceutical industry. The capability creation model showed different learning processes like duplicative imitation, creative imitation and collaborative R&D used by Indian pharmaceutical firms to move from basic capabilities to advanced capabilities, reflecting the impact of different policy regimes. The implementation of the TRIPS agreement represents an important change in the Indian government's pharmaceutical policy in terms of IPR management. The analysis suggests that TRIPS has increased the focus on R&D in Indian pharmaceutical firms and accelerated the movement of Indian pharmaceutical firms towards the development of innovative R&D capabilities.

The weakening of patent laws in 1970 played a crucial role in shaping and building the Indian pharmaceutical industry. It reduced market entry barriers, legalised reverse engineering and created a competitive domestic market.

The evidence presented in this paper strongly suggests that the weak patent system was the dominant influence on the development of basic and intermediate capabilities in the Indian pharmaceutical industry. It legalised reverse engineering, (an important non-market mediated mechanisms of knowledge acquisition) whilst allowing the Indian pharmaceutical industry to learn and improve its process R&D capabilities and expand production and marketing capacities.

The nature of the domestic market and industrial policies adopted by the Indian government also influenced the development of capabilities in the Indian pharmaceutical industry. The intensely competitive domestic market gave rise to different models and strategies which led growth in the Indian industry. These models and strategies fuelled firm based learning and assimilation of basic capabilities bringing about industrial transformation and development. These insights have implications for firms from other developing countries which could apply the 'capability creation model' and strategies to rise up the value chain in the pharmaceutical industry.

The limited resources typical of many firms from developing countries hinder their ability to provide necessary environments in terms of recruitment of talented personnel, extensive knowledge sources, training and organisational mechanisms to facilitate capability development. Hence in the future, the emphasis of technology policy should be on providing mechanisms that will help firms increase their awareness and access to external knowledge.

Technology policy should assist firms in creating linkages between their internal capabilities and external knowledge and help in assimilating these associations into business opportunities.

This research shows that the strengthening of patent law had a positive impact on large Indian pharmaceutical firms and catalysed their movement from imitators to innovators. The strengthening of patent law changed strategic orientation of the Indian pharmaceutical industry and forced firms to pursue alternative innovative technological trajectories.

The imitative R&D in these firms created important essential basic capabilities and that acted as a base for innovative R&D. The stock of past capabilities and routines creates absorptive capacity and that provides the base on which firms develop new capabilities to cope with change in technology or external environment. In the case of Indian firms the basic and intermediate innovative capabilities learnt as a result of imitative learning certainly gave these firms a solid base for the development of competence in advanced innovative R&D.

Studies investigating technology development in Korea (Kim, 1997) and Taiwan (Hobday, 1995) show that firms in these countries began mainly as imitators, although Korean industry experience shows that this does not continue indefinitely. This research points to a similar pattern of capability development in the Indian pharmaceutical industry. The non-formal mode of imitation; reverse engineering, has played a significant role in development of basic capabilities in the Indian pharmaceutical industry.

This finding supports the observation by Kim and Nelson (2000) who suggest that duplicative imitation, if legal, is an astute strategy in the early industrialisation of low-waged, catching-up countries, as the technology involved is generally mature and readily available and duplicative imitation of mature technology is relatively easy to undertake.

However the universal adoption of strong patent protection will affect the application of imitation and reduce the opportunities for firms in developing countries to use this mode of knowledge acquisition. This certainly raises a question about strengthening patent laws globally, irrespective of the capabilities of domestic industry, especially in developing countries where strong patent laws will hinder the development of basic or intermediate capabilities in firms.

Developing countries are not homogenous. Their scientific and technological capabilities differ widely. The research on developing countries suggests that technology development patterns vary within developing countries. Technology capability developments in East Asian countries share similarities with each other in terms of state intervention in some industries designed to protect and accelerate achievement of international competitiveness through attainment of the requisite technological capabilities. Building on these observations the findings of this research along with other examples such as the emergence of Germany's synthetic dye industry in early twentieth century (Murmann, 2003) and rise of the South

Korean semi conductor industry (Kim, 1997) indicate that the interests of developing countries are best served by tailoring their intellectual property regimes to the particular economic and social circumstances prevailing at the time.

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Fig. 1 Pharmaceutical value chain (Source: Bartlett and Ghoshal, 2000)

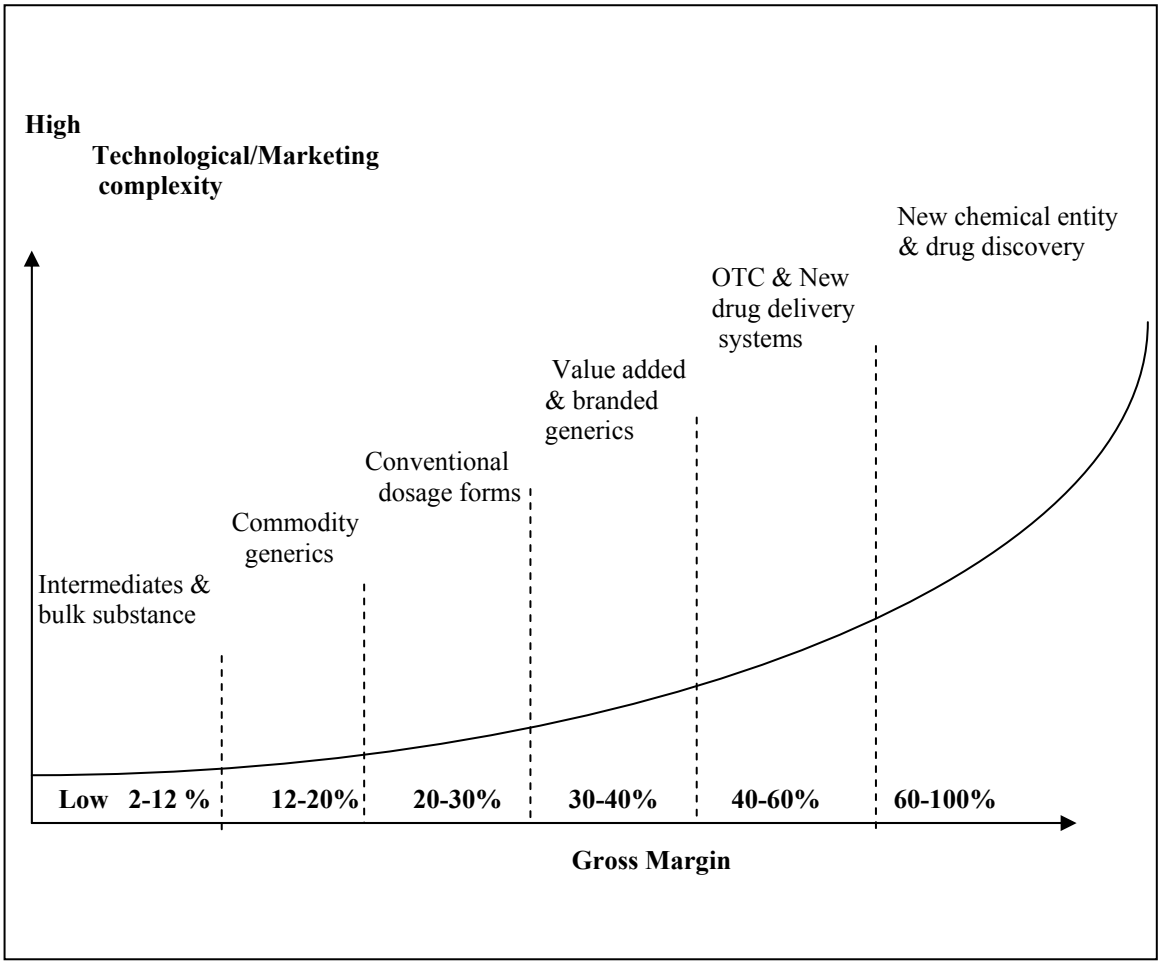

Fig. 2 Capability creation model

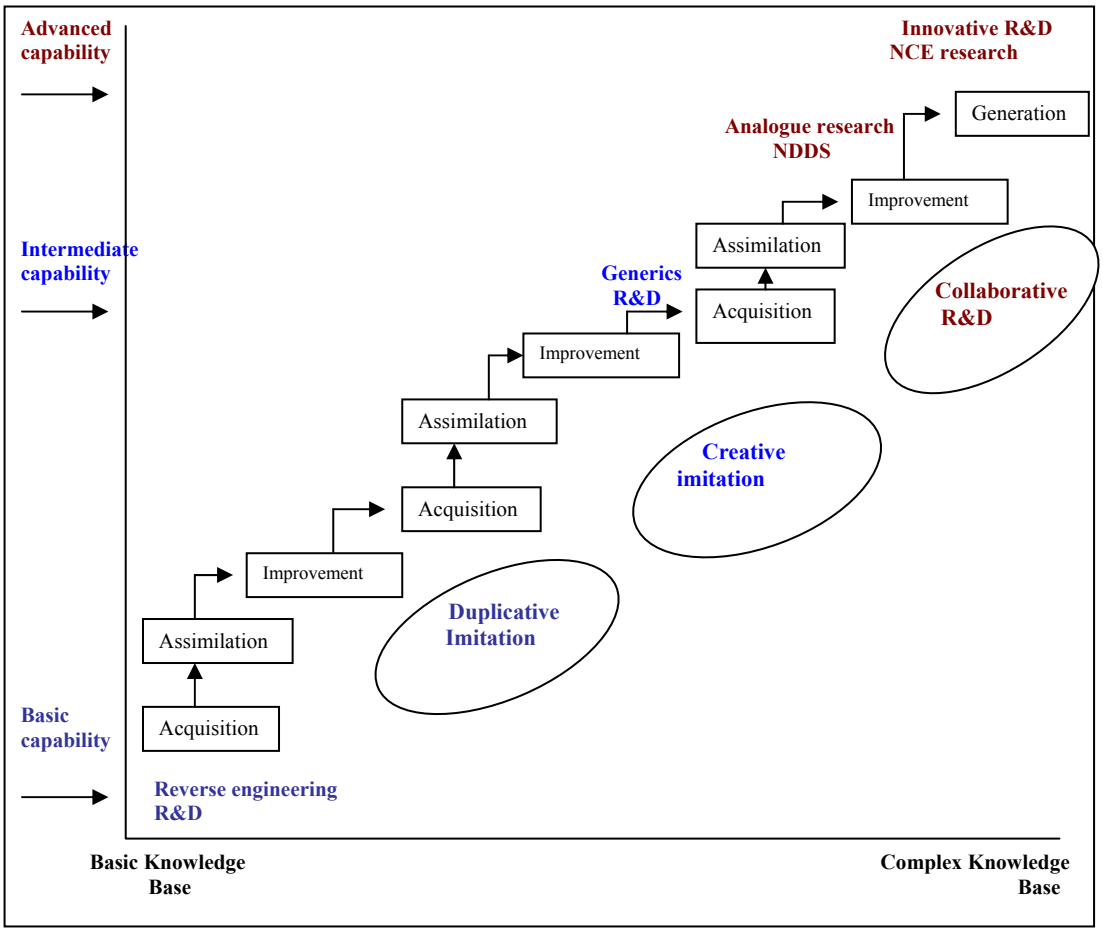

Fig. 3 Reverse engineering product development

Original product

A + B a' + C = original molecule

(Process conditions: temp: X; pressure: Y)

Reverse engineered product

A + b + d = Reverse Engineered Molecule where d = a'+c

(Process conditions: temp: X; pressure: Y)

Fig. 4 USFDA approved plant outside US (Source: US FDA)

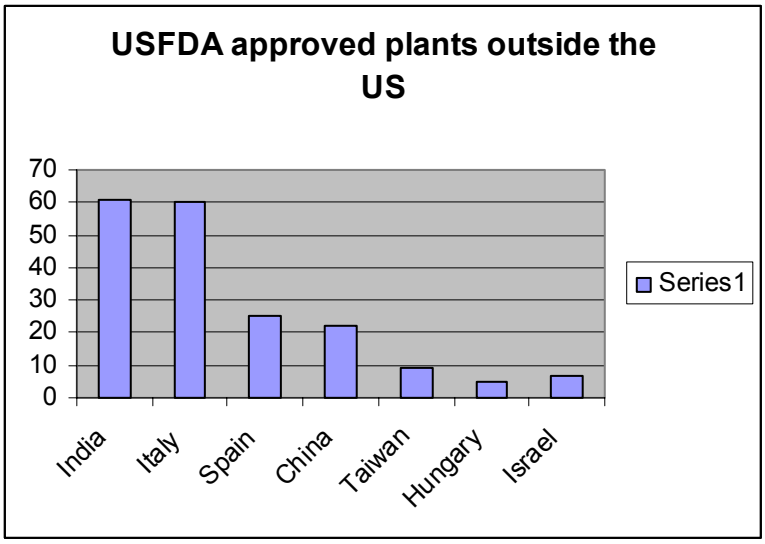

Table 1: Growth in Indian pharmaceutical industry during the 1980s (Source: OPPI, 2001)

	Year	Bulk drugs Rs. Million	Formulations Rs. Million	Total
1	1980-81	2400	12000	14400
2	1981-82	2890	14340	17230
3	1982-83	3450	16600	20050
4	1983-84	3550	17600	21150
5	1984-85	3770	18270	22040
6	1985-86	4160	19450	23610
7	1986-87	4580	21400	25980
8	1987-88	4800	23500	28300
9	1988-89	5500	31500	37000
10	1989-90	6400	34200	40600

Table 2: Time lag between introduction of new drug in the world market and its introduction in India (Source: Keayla, 1996)

No.	Drug	World market introduction by inventor	Indian market introduction by domestic firm	Time lag before introduction in India (years)
1	Ibuprofen	1967	1973	6
2	Salbutamol	1973	1977	4
3	Mebendazole	1974	1978	4
4	Rifampicin	1974	1980	6
5	Cimetidine	1976	1981	5
6	Naproxen	1978	1982	4
7	Bromhexin	1976	1982	6
8	Captopril	1981	1985	4
9	Ranitidine	1981	1985	4
10	Norfloxacin	1984	1988	4
11	Ciprofloxacin	1986	1989	3
12	Acyclovix	1985	1988	3
13	Astemizole	1986	1988	2
14	Larazepam	1977	1978	1

Table 3: Share of bulk drugs and formulations in total exports (Source: OPPI, 2001)

No.	Years	Bulk Drugs (%)	Formulations (%)
1	1990-91	47	53
2	1991-92	44	56
3	1992-93	70	30
4	1993-94	71	29
5	1994-95	66	34
6	1995-96	64	36
7	1996-97	59	41
8	1997-98	57	43
9	1998-99	52	48
10	1999-00	55	45

Table 4: Foreign acquisitions by Indian pharmaceutical companies (Source: Annual Report, 1995-2003)

No.	Year	Indian firm (acquirer)	Name of the firm acquired	Country
1	1995	Ranbaxy	Ohm Labs	USA
2	1997	Sun Pharmaceuticals Ltd	Caraco	USA
3	1998	Wockhardt	Wallis	UK
4	2000	Ranbaxy	Basics	Germany
5	2000	Ranabxy	Veratide	Germany
6	2002	Ranbaxy	Signature	USA
7	2002	Unichem	Niche Generics	UK
8	2002	Dr. Reddy's Laboratories	BMS	UK
9	2002	Dr. Reddy's Laboratories	Meridian	UK
10	2003	Wockhardt	CP Pharma	UK
11	2003	Zydus Cadila	Alpharma	France
12	2004	Ranbaxy	REG Aventis	France
13	2004	Glenmark	Lab Killinger	Brazil
14	2004	Dr. Reddy's Laboratories	Trigenesis	US
15	2004	Jubilant Organosys	PSI group	Belgium

Table 5: Share of Indian firms in ANDA approvals and DMF submissions to USFDA (Source: US FDA)

Year	ANDA			DMF		
	Total	ANDA by Indian firms	Share of Indian approvals	Total	DMF by Indian firms	Share of Indian submissions
1997	572	10	1.7	371	31	9.7
1998	484	9	1.9	944	38	4.0
1999	380	8	2.1	390	44	11.3
2000	583	21	3.6	355	37	10.4
2001	436	18	4.1	344	59	17.2
2002	753	32	4.2	368	79	21.5
2003	627	56	8.9	426	119	28.2

Table 6: Indian pharmaceutical firms' new chemical entity pipeline (Source: Annual Report, 2003)

No.	Companies	Molecules in clinical trials
1	Ranbaxy	6
2	DRL	4
3	NPIL	1
4	Lupin	2
5	Dabur	2
6	Wockhardt	1
7	Torrent	2
8	Glenmark	1
9	Sun Pharma	2
10	Orchid	1