

Learning and innovation in the indian pharmaceutical industry: the role of IPR and other policy interventions¹

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Abstract

Through the decades of 1970s and 1980s, the Indian pharmaceutical industry (IPR) reached new heights of process capabilities. At the present juncture, however, the industry is at a watershed, trying to cope with the challenges of globalisation and reforms. It is going through a turbulent phase of adjustment driven by the emerging international economic order of the WTO, especially the TRIPS agreement establishing a new IPR environment. The aim of this paper is to explore the trajectory of learning and innovation in the IPR as it evolved through the various phases of government policy environment and IPR regimes. We conclude that although India has reached impressive heights of technological maturity in pharmaceuticals, it is yet to arrive at the global frontiers of cutting edge drug discovery research. This can only be achieved through sustained technological effort and continued R&D.

Keywords

technological learning and innovation; Indian pharmaceutical industry

Introduction

The Indian pharmaceutical industry (IPR) occupies an important position both nationally and internationally. India ranks 13th among the drug producing countries of the world in value terms and 4th in volume terms with an 8% share of the global pharmaceutical production.¹ The size of the IPR has expanded phenomenally from a mere Rs 100 million (value of production) in 1947 to Rs 50 billion in 1990 and to a massive Rs 500 billion at present.³ The origins of the pharmaceutical industry in India

can be traced back to the colonial (pre-independence) era. But right from its origin through the decades of the 1950s and 1960s, the industry remained largely dominated by foreign firms and drug prices were among the highest in the world (Kafeveur Committee Report 1962).

The decade of the 1970s has been of great importance to the IPR, which witnessed a “process revolution” through concerted effort at acquisition of technological capability fostered by a favourable policy environment, especially a weak patent regime. Through the decades

of 1970s and 1980s, the IPR reached new heights of process capabilities to “knock off” any new drug with a non-infringing process and market them at low prices. At the present juncture, however, the industry is again at a watershed, trying to cope with the challenges of globalisation and reforms. It is going through a turbulent phase of adjustment driven by the emerging international economic order of the WTO, especially the TRIPS agreement establishing a new IPR environment.

The aim of this paper is to explore the trajectory of learning and innovation in the IPR as it evolved through the various phases of government policy environment and IPR regimes. We begin, in section 2, with a discussion of the paradigm shift in the structure and performance of Indian pharmaceutical industry in the form of “process revolution” in the post 1970. This sets the stage for a detailed discussion, in section 3, of the new international economic order post 1990 in so far as it impacts the pharmaceutical sector. Section 4 attempts to analyse the challenges posed by the new order and the consequent adjustments in the industry.

Process revolution in Indian pharmaceuticals post 1970

1970 marked the beginning of a new era for the pharmaceutical industry in India. With the introduction of the Patent Act 1970, there was a concerted effort at generating indigenous technological capability (in production as well as in research) in the pharmaceutical sector with the goal of increasing access to drugs at affordable costs. In fact the decade of 1970s witnessed the passage of several government directives directly shaping the growth path of this sector, including the Drug Price Control Orders (DPCO) 1970 and 1979, Foreign Exchange Regulation Act (FERA) of 1973, New Drug Policy 1978 and of course, the Patent Act 1970. A brief discussion of these policies may be in order.

The *Patent Act 1970* was a radical departure from the earlier Patent Law which accorded product as well as process patent protection up to a period of 10 years (extendable by another 6 years) and acted as a major deterrent to the creation of indigenous technological capability especially through reverse engineering. 1970 Patent Act, by contrast granted only process patent for chemical substances including pharmaceuticals, reduced the duration of patents to 7 years from the date of filing or 5 years from the date of sealing whichever is lower, excluded all imported substances from the domain of patent protection (i.e. only new substances manufactured in India were entitled to patent protection), and placed the burden of proof on the plaintiff in case of infringement.

DPCO 1970 was the first concerted and rational effort to check the ever rising drug prices in India. *DPCO 1979* expanded the coverage of drug price control, bringing about 80% of the Indian pharmaceutical industry (in value terms) under price regulation. The price fixing rules were made more rigid and stringent.

FERA 1973 was introduced to restrict and regulate the operations of foreign (multinational) companies in

India to protect and develop indigenous industrial and technological capability. A 40% ceiling was imposed on foreign equity share, with the exception of “Core” sectors (including pharmaceuticals), where up to 74% foreign equity was allowed to high technology bulk and formulation producers provided their 50% of the bulk is supplied to non-associated formulators and the share of own bulk in their formulation should not exceed 1/5.

The spirit of this policy regime of the 1970s was reinforced by *Drug Policy 1978* with its three-fold objective of self reliance in pharmaceutical technology, self sufficiency in drug production and easy and cheap availability of drugs. This in a sense summarises the policy framework adopted in the 1970s with a clear emphasis on import substitution and self-reliance in the production of bulk as well as formulations and on creating indigenous technological capability of process development (bulk).

Against the backdrop of this policy environment, the pharmaceutical industry in India embarked on a new trajectory of *technological learning based on reverse engineering*, which essentially implies decoding an original process for producing a bulk drug. This involves a detailed understanding of the chemical properties of the active molecule, the excipients used and the chemical process of conversion from the active molecular compound to the final bulk drug. A chemical process incorporates a complex set of parameters, e.g., solvent conditions, temperature, time, stirring methods, use of various chemical and physical substances with different levels of purity etc., all of which have to be simultaneously optimised in order to arrive at the optimum process specification. It is possible to decode all of these parametric specifications of a process through reverse engineering.

One can make a distinction between *two types* of reverse engineering activities: *infringing* and *non-infringing* processes. In case of the former, a reverse engineered process exactly matches the specifications and design of the original process and therefore, needless to mention, the use of such processes infringes upon the intellectual property rights of the innovator of the original process. Hence the scope of such activities is limited to off-patent drugs only. The second category of reverse engineering activities is somewhat more complex as it results in the development of non-infringing processes whereby the same bulk drug may be produced through a different route. Non-infringing processes are relevant only in case of patented drugs, which may be free from product patents but continue to enjoy process patent protection.

With the introduction of the Patent Act of 1970, there has been widespread reverse engineering for non-infringing processes. This is not to suggest that infringing process development (simple imitation) did not taken place. In fact many of the firms began with such simple technological activities (perhaps on off-patent drugs) to acquire more complex capabilities at a later stage. Indeed, the industry acquired substantial technological capability of process development through reverse engineering, both infringing processes for off-patented molecules and

non-infringing processes for patented molecules. This phenomenon has been often referred to as the *process revolution in the Indian pharmaceutical sector*. As a result, the bulk drug industry grew at a phenomenally high rate of 21 and 11% p.a. during the decades of 1970s and 1980s respectively.

Along with process revolution, *simple product development in conventional dosage forms* which had already started in the post independence era, continued in the post 1970s. As a result, the formulation industry also registered impressive growth rates of 13 and 10% p.a. respectively during the same periods. The impetus largely came from the massive expansion of bulk drugs due to the process revolution and the policies to deter captive consumption of bulk.

Indeed there was a marked increase in R&D expenditure of the industry during this period: it stood at Rs 500 million in 1986 accounting for nearly 2% of the industry's sales turnover compared to less than 1% prior to 1970.

The policy environment facilitated free entry of a large number of producers of both bulk and formulation, most of them in the small scale and unorganised sector. The resultant *market structure* was characterised by a limited number of large organised sector units enjoying the lion's share of the market on one hand and a very large number (thousands) of small producers each producing a microscopic fraction of the total industry sales. This implied a wide variation in the quality and price of a drug in the market and multiplicity of formulations. Problems of spurious drugs and irrational combinations have been a natural outcome of this phenomenon. While the policy environment favoured small producers, lack of adequate quality regulations and control mechanisms often resulted in the supply of sub-optimal and ineffective drugs. Apart from deviations from the *quality norms*, the norm itself was often kept at a low level by the regulatory authority to encourage small producers who may not be able to afford sophisticated equipments for various tests/ assays. Indeed there has been a noticeable difference in the parameters of acceptable drug quality in India compared to that of the developed world. *But most drugs were now available in India at affordable prices, the quality variations notwithstanding.*

As an outcome of the policy framework, MNCs became reluctant to launch their new drugs in India. But that did not deprive the Indian patients from the *latest drug discoveries without much delay in launching* (Bhaduri & Ray 2006; Ray & Chakraborty 2007). Indian firms introduced these new drugs in the market using non-infringing processes, perhaps with a time lag marginally exceeding the demand lag. Examples are numerous: Ranitidine (Glaxo) and Amlodipine (Pfizer) are two of the glaring examples of this phenomenon.

The new world order post-1990: India's reforms process

In tune with a newly emerging international economic order, India's economic reforms process began in the late 1980s/1990. WTO has been the prime architect of the

broad framework of this new global order, primarily geared towards free trade and removal of "policy distortions" in all dimensions of a country's economic activity. The idea is to pave the way for liberalised and market driven international flows of goods, services, capital and technology in a multilateral framework. Ironically, however, one also finds provisions for bilateral negotiations and unilateral actions built into the WTO framework, especially when it serves the interest of developed countries. Product regulations and standards, anti-dumping and other safeguard measures are examples of WTO provisions which can be misused (mainly by the developed nations) to counter the spirit of multilateral trade liberalisation propagated by the WTO and the proponents of this new world order.

India's reform process began with *trade reforms* which sought to reduce, rationalise and eventually eliminate all forms of trade restrictions, tariffs, export import licenses, quantitative restrictions and other non-tariff barriers. *Reduction and removal of subsidies* have accompanied trade reforms in India. Policies towards *foreign investment and foreign technologies* have been relaxed. FERA 1973 was modified to Foreign Exchange Management Act (FEMA) 1999. The monitoring of payments for imported raw material, and technical know-how was deregulated, but RBI retained the monitoring authority of the dividend payment. FEMA allows the pharmaceutical MNCs to hike their stakes in India up to 74%. Automatic approval can be granted for foreign technology agreements in *high priority industries* up to a lump sum payment of Rs.10 m, or if the royalty is less than 5% of domestic sales or 8% of exports, subject to a maximum ceiling. For other *non-high priority industries* automatic permission will be given according to the same guidelines *if no free foreign exchange is required for any payments.*

The *Patent Act of 2005* has been direct fallout of the WTO agreements. The salient features of the forthcoming patent regime are summarised below.

- Product patents are allowed in all fields of technology with a uniform duration of 20 years in pharmaceuticals, food products and agrochemical from the date of application.
- Compulsory licenses will be given by the government *only* on the merit of each case, and would be granted in case of national emergency. However, the patent holder will be given a hearing and an opportunity to present his case for intellectual protection.
- There will be no discrimination between imported and domestic goods in so far as intellectual property protection is concerned as par the national treatment clause in WTO.
- For process patents, the burden of proof will rest with the party that infringes. This is in contrast with the requirement of the earlier patent regime. In Patent Act of 1970 burden of proof was on the original innovator.

With the enactment of this law, the policy framework encouraging process development through reverse engineering activities disappears. But the strong product regime is "supposed" to encourage basic and frontier research in the industry.

Other elements of the structural adjustments programme followed by India include *industrial reforms* leading to abolition of industrial licensing, virtual elimination of MRTP regulations, divestment of public sector units and de-reservation and reduction of benefits of the small-scale sector.

Among the specific policy initiatives towards the pharmaceutical sector, *DPCO 1987* followed by *DPCO 1995* appeared as major landmarks reinforcing the policy move towards liberalisation. Both of these policies aimed at *progressive decontrol of drug prices*. It is interesting to note the clear policy shift in the stated principle for controlling drug prices. As opposed to the earlier objective of making drugs available at affordable prices, the DPCO 1995 clearly states that the objective is to prevent monopoly in any market segment. Only 40% of the total finished dosage forms remain under price control in 2001 compared to 85-90% in 1979.

The overall philosophy of the new policy regime is well echoed in the *Drug Policy Statements of 1986, 1994 and 2003*. Licensing requirements for all bulk drugs and formulations are abolished with a few noted exceptions. Restrictions on import of bulk are largely removed. The earlier policy to deter captive consumption of bulk is reversed. Major thrust is placed on drug quality, acknowledging the need to monitor and regulate quality and promote rational use of drugs. It stresses the need to implement *Good Manufacturing Practices (GMP)* for all manufacturing units.

Although the IPR has continued to expand both in terms of production and trade during the decade of the 1990s,⁴ the new policy environment has posed major challenges to the sector which is evident from rising drug prices, downsizing of employment and closure of production facilities of many units including that of multinationals. As a result, the IPR is going through a turbulent phase of adjustments. In the following section, we attempt to trace this adjustment process for the organised segment of the industry. This is not to suggest that the challenges to the small scale units are any less severe or less important, but an analysis of the small scale sector would constitute a separate programme of research study.

Challenges and adjustments post 1990: quality and R&D as the Twin Pillars

The challenges

The major challenges posed by the new policy regime of globalisation and reforms to the Indian pharmaceutical industry, especially those in the organised sector can be synthesised as follows.

Limits to growth through process development

With the introduction of the new patent regime, the conventional corporate growth strategy, based on

non-infringing process development for patented molecules to introduce the latest drugs in the Indian market, adopted by the IPR till now, will no longer be a viable option. Reverse engineering on patented drugs will come to complete halt, raising a big question mark as to how far the Indian pharmaceutical can exploit its process development capabilities acquired through conscious R&D effort during the last quarter of the century. Reverse engineering on off-patent drugs can, of course, continue to give them an edge in the *generic market*. In fact a market of about US\$50b of pharmaceutical products will come off-patent in the next few years.

Limits to the generic market

Given that new drugs will now become the exclusive monopoly of the innovating firm, we believe that the *generic market* will become extremely *crowded* both in India and the world since all non-innovating firms will have to rely on the generic market.

A further limit on the scope of business development based on the generic market may be posed by the high rate of new drug discovery in the 1990s. Since most these new drugs are not “new” in the sense of having a pioneering therapeutic use, but are merely replacing existing drugs with better therapeutic efficacy and lower side effects, new drug discovery *might reduce the life span of existing drugs*. This in turn implies a high rate of obsolescence in the generic pharmaceutical market.

The global pharmaceutical market is becoming increasingly competitive both with respect to price as well as quality. Even with trade liberalisation, the WTO allows for imposition of product regulations and standards to create barriers to free flow of trade. This is being fully exploited by the developed countries to protect their large pharmaceutical markets from low cost imports from the developing world. Therefore *new norms of drug quality* are being introduced worldwide which will further limit the scope of access to the world generic market. With a move towards quality harmonisation, drug quality will act as a principal parameter of success even for Indian firms in years to come.

The adjustments

To cope with these serious challenges, the Indian industry (organised sector) is going through a major phase of restructuring and adjustments. We intend to analyse and capture some of these. We restrict our analysis to two of the major dimensions of the adjustment process. The first relates to the response of the Indian industry to a new paradigm of drug quality. The second looks at the changing role of R&D and technology in this new era of globalisation and reforms.

A new paradigm of drug quality

Drug quality is a complex multi-dimensional concept. First and foremost, quality implies *therapeutic efficacy and safety*. A high quality drug must be *effective* and should not produce any *toxicity or side effects*. In this

regard, *bio-availability* acts as an important parameter of drug quality. A second and most commonly stated parameter of quality pertains to the *impurity profile and stability* of chemical ingredients. A related quality parameter affecting product purity is *contamination* during the production process. Not only keeping minimum impurity is important, but also *consistency* in the specified impurity profile over all batches of production must be adhered to. Detailed *documentation* of all the production stages along with the quality control operations constitutes an added dimension of quality specification as it creates *institutional memory* and makes the entire production process transparent to all concerned parties.⁵ The third set of quality parameters stipulates that the production process should be *environment friendly* and should not create any health hazards within and outside the production unit. The intermediates and excipients of the production process must also be non-hazardous and environment-friendly.⁶

The relative importance of each of these diverse parameters in the final quality specification would vary from country to country depending on the composition of their pharmacopoeial committee and socio-economic priorities of the government. This has resulted in divergence of the technical requirements for quality specification and control in different countries, compelling the globalised industry to replicate many test procedures including clinical trials in order to market new products in different countries. To overcome this problem, the governments of the three largest pharmaceutical markets (United States, Europe, and Japan) have jointly initiated a move towards harmonisation of drug quality through the International Conference on Harmonisation (ICH) from the late 1980s. The *US Pharmacopoeia* (USP) has dominated this harmonisation movement with an in-built bias towards increasingly stringent norms for impurity profile through sophisticated instrumentation and analytical methods.

Prior to the 1990s, *drug quality in India* was loosely defined and remained far below international standards. This is not to suggest that there were no high quality producers even during this period. But quality parameters did not receive much attention by the industry and the regulatory authorities in general. But in the new era of globalisation, characterised by a strict IPR regime, a fast moving technology frontier and a move towards international harmonisation of quality standards, firms will have to explore the growing international market for generic drugs, the United States market in particular. Entry into this highly competitive market calls for stringent quality requirements. Indeed with the threat of ICH, not only US but the entire global market may be subjected to stricter quality norms.

In this new era, the Indian manufacturers have to pay intensive attention to the concept of drug quality, which was hitherto largely ignored and adopt the following operational and organisational changes:

- *Quality control* must be much more rigorous with *stricter parameters* and *sophisticated instrumentation*.

- For formulations, the *quality of active pharmaceutical ingredients* (API or bulk) becomes all important.

- High quality standards as per the multidimensional definition given above demand *up-gradation of production and quality control technology*.

- The *environmental dimensions of quality* necessitate increased attention towards effluent treatment and proper waste management using modern methods and equipment.

- *Detailed documentation* is becoming an important facet of production and quality control.

- Finally, quality has added a new dimension to their R&D thrust. Firms are now trying to develop *new improved analytical methods* for quality specification and control. Some Indian firms have already succeeded in developing superior methods, which have been incorporated in the global quality standards like USP and European Pharmacopoeia (EP). In a sense, Indian players have thus contributed to outward shifts in the global frontiers of drug quality.

Most of these elements of higher drug quality entail *increased automation* of the production process. In many cases, it requires *complete overhauling of the plant set-up* to install sophisticated (often imported) machinery and equipment for production and quality control.

From "Business driven R&D" to "R&D driven Business"

Technological capability of the Indian pharmaceutical industry can be classified into three broad groups:

- Process development capabilities (bulk drug) – infringing and non-infringing

- Product development capabilities (formulations) – conventional dosage forms (CDF), novel drug delivery systems (NDDS) of first and second generations (NDDS1, NDDS2 respectively) and analytical methods for quality

- New drug discovery research (NDDR)

The industry began with *simple product development* capabilities in *CDF* and started producing formulation from imported bulk drug. Eventually, as business expanded, the industry started making explicit effort towards acquisition of technological capability of *process development* in the post 1970s with the overriding objective of developing non-infringing cost-minimising processes. By the end of the 1980s, the IPR reached new heights of process technology, which acted as the key driving force behind the Indian pharmaceutical revolution. So far the evolution of technological capability followed the conventional trajectory of technological development outlined in the standard economic literature.⁷

However, in the 1990s we find a *renewed emphasis on product development*, but this time not on *CDF* but on *NDDS1* (controlled/ sustained release dosage forms) and on *NDDS2* (targeted release dosage forms) undertaken by a handful of firms only. This movement is dictated by the new policy environment whereby business expan-

sion through non-infringing process development will be severely limited. NDDS1 and NDDS2, catering to the specialised needs of the fastidious patient, are clear signs of a movement towards R&D driven business – these new technological developments attempt to open up new dimensions of pharmaceutical business in India.

Advanced product development capabilities (NDDS and analytical methods) paved the way for *new drug discovery research (NDDR)* in India. The existing skills in chemistry along with strengthening of biology expertise (molecular and structural biology, in particular) required for NDDS research and experience in handling sophisticated equipment facilitated NDDR in India. However, the nature, process and the steps of NDDR in India typically reflect the evolution of technological capability of a typical LDC with limited risk-taking, financial and research capabilities. The me-too type NDDR in India, predominantly focusing on inventing-around an existing inhibitor for a given target, are far less risky and less expensive than finding a new target itself. It has primarily been driven by existing skills and capabilities rather than venturing into new areas of capability building and R&D investments.

Given that Indian capability is not yet mature enough to compete with the global players in new drug discovery research at a level playing field, the IPR regime in India continues to be somewhat protective to the needs of the Indian players. The Patent Act 2005, within the TRIPS guidelines, has kept the patentability criteria rather stringent, limiting grant of patents for pharmaceutical substances to new chemical entities and new medical entities involving one or more inventive steps. As such, other pharmaceutical innovations (including combination of known drugs, new use claims of existing drugs, etc) are excluding from grant of patents in India. The idea is to prevent ever-greening of patents by the large global players engaged in new drug discovery research and to foster India's capability to invent around and arrive at me-too type drugs. Although India has reached impressive heights of technological maturity in pharmaceuticals, but it is yet to arrive at the global frontiers of cutting edge drug discovery research. This can only be achieved through sustained technological effort and continued R&D. Indeed, in the post reforms scenario, R&D will play the central role in maintaining a successful trajectory of growth and development of the Indian pharmaceutical industry. The industry will now be characterised by R&D driven business rather than business driven R&D.

Notes

1. This paper draws heavily on one of my earlier papers, Ray (2004, 2005).

2. *India in Business* website of the Ministry of External Affairs (Investment and Technology Promotion (ITP) Division), Government of India. <http://www.indiain-business.nic.in/industry-infrastructure/industrial-sectors/drug-pharma.htm>

3. National Pharmaceutical Policy 2006, Ministry of Chemicals and Petrochemicals, Government of India.

4. See Key Statistics, OPPI (www.indiaoppi.com/keystat.htm) for detail.

5. Consequently, there has been a rising tendency towards automation of the production technology to eliminate input variations, human touch, and produce consistent batches with detailed computerised documentation.

6. Increased automation might take care of the problems of “unsafe” contact of labour with hazardous chemical ingredients and processes. Another way to solve the problem is to replace chemical processes by bio-technological processes as being done in developed nations.

7. See Katz (1984, 87), Lall (1987).

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