

**Post-2005 TRIPS scenario in patent protection in the  
pharmaceutical sector:  
The case of the generic pharmaceutical industry in India**

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## **1 Executive Summary**

The impact of a strengthening of the patent regime on access to medicines has remained in focus ever since the Punta del Este Ministerial Declaration decided to include intellectual property rights (IPRs) in the mandate for the Uruguay Round negotiations. This debate was of particular relevance for India where a strong generic industry had taken roots since the 1970s, which was able to provide medicines at prices that were among the lowest in the world.

The trigger for the emergence of the generic pharmaceutical industry in India was the adoption of the Patents Act in 1970 (henceforth Patents Act, 1970) to incorporate the recommendations following from a detailed study by expert groups of the intellectual property regime to alter the existing regime to make it more in line with socio-economic needs. Two key provisions facilitated the materialization of the generic pharmaceutical production: the introduction of a process patent regime for chemicals but not for product patents and second; the cutting of the term of patent protection for pharmaceuticals.

India's accession to the WTO, which brought obligations to implement the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS), changed the conditions that had seen the Indian pharmaceutical industry take roots. For the industry, the critical issue was the (re-) introduction of the product patent regime and the limitations that this change has imposed on its ability to produce technologies through reverse engineering. It was widely held that the future prospects of the industry hinged critically on the ability of the policy makers to exploit the flexibilities that existed in the framework provided by the Agreement on TRIPS. If this was the "Plan I" of the strategy that was required to meet the challenges posed by the TRIPS Agreement, there was a need to have a "Plan II" wherein the pharmaceutical industry adopted measures to protect its longer term interests.

India's commitment to fully implement the Agreement on TRIPS required three sets of amendments to the country's Patents Act. While developing countries, in general, were allowed to make their patent laws TRIPS compliant through an amendment that was to be introduced by January 1, 2000, countries like India which had process patent regime instead of product patent protection covering pharmaceuticals and agricultural chemicals, would enjoy a longer transition period before they were required to introduce product patents from January 1, 2005 as follows from Article 65(4) TRIPS Agreement. The longer transition period, however, came with a set of conditions. In the first place, India was required by the WTO Panel in the India – Patent Protection for Pharmaceutical and Agricultural Chemical Products case to provide "a means" by which product patent applications can be filed from January 1, 1995 (better known as the "mail-box" provision) following from Article 70.8(a) TRIPS Agreement. If the products figuring in these applications were granted a patent in any WTO member country and the products

had obtained marketing approval in any WTO Member country, then exclusive marketing rights (EMRs) for five years had to be granted by India until the patent on the product was either granted or rejected in India. The first amendment of the Patents Act, 1970, notified in 1999, introduced these amendments.

In 2002, a second amendment was introduced for bringing the Patents Act in conformity with all the substantive provisions the TRIPS Agreement, with the exception of product patent protection for pharmaceuticals as an additional transition period of five years was applicable. The key issues included in the Second Amendment were, re-defining patentable subject matter, extension of the term of patent protection to 20 years and amending the compulsory licensing system.

A third amendment was introduced in 2005 to extend product patent protection to areas of technology not so protectable in its territory on the initial getting into effect of the TRIPS Agreement (being 1 January 1996) following the lapse of the transition period under the TRIPS Agreement. Hence, India included product patent protection for pharmaceuticals that were hitherto only covered by process patents. Although the third amendment had a narrow remit, the Government used the opportunity to undertake a review of the Patents Act. Among the major issues included in the third amendment were provisions relating to opposition to the grant of patents.

From the perspective of the generic pharmaceutical industry in India, the TRIPS-consistent patent law addresses three sets of issues that could have immediate impact. First, the adoption of a new definition for “pharmaceutical substance”, which should be a “new entity involving one or more inventive steps”. The second is the exclusion of “mere discovery of a new form of a known substance” and “new use for a known substance” from the ambit of patenting, which could prevent grant of patents on formulations. And, the third, protecting the interests of producers who are already producing the products that may be granted patent protection in the new regime. The last mentioned issue has assumed importance given that India was required to accept “mail-box” applications from January 1, 1995, which are being examined after the product patent regime was introduced in 2005.

Detailed provisions for the grant of compulsory licences are among the features of the Indian Patents Act, as amended. The Act provides that an application for the grant of compulsory licence can be made only after three years from the date of grant of the patent unless exceptional circumstances like national emergency or extreme emergency can be used to justify the grant of a licence on an earlier date. Three broad grounds for the grant of the compulsory licences have been spelt out thus: (a) reasonable requirements of the public with respect to the patented invention have not been satisfied, (b) the patented invention is not available to the public at a reasonably affordable price, and (c) the patented invention is not worked in the territory of India. However, a compulsory licence can be granted only when the patentee is paid adequate remuneration taking into account the economic value of the authorization.

This study provided a detailed analysis of the performance of generic pharmaceutical industry in India, particularly since the mid-1990s. This period is significant for it

coincides with the implementation of the TRIPS Agreement by India. As stated in the foregoing, India was required to provide a “mail-box” for receiving product patent applications from January 1, 1995, which was in keeping with the transitional arrangements of the Agreement. The analysis provided in this study shows that the leading firms of the industry were able to consolidate their position in the Indian industry despite the challenges posed by the emerging patent regime. The performance of these firms was on an upswing since the beginning of the 1990s, but in the current decade, considerable improvement was seen. A major contributor to the process of consolidation of the leading Indian firms was the increase in their R&D spending, with Ranbaxy and Dr Reddy’s leading the way.

The benefits from increase in R&D spending of the leading Indian firms were multifarious. The firms were able to increase their presence in the larger markets, which was evidenced by the increases in market approvals in both the US and the UK. An equally significant development was that Ranbaxy and Dr Reddy’s, the two largest among the Indian firms, were able to produce improved generics and Novel Drug Delivery Systems (NDDS), which have opened the doors for collaboration with the pioneer producers. And, last, but not the least, the emergence of India as the hub for contract research and manufacturing. This development has added significance since a number of global pharmaceutical majors have established joint ventures with the Indian generic producers.

In the past, new drug development has been an area of relative weakness of the Indian firms. And, although Indian firms are yet to make a mark in the area of new drug discovery, the leading firms seem to be on course for major developments even on this front given the sharp increase in their patenting activity of late. This activity could be strengthened by the increased efforts made by the Government to participate in the R&D activities involving the industry.

An attempt was made to develop institutional basis for strengthening government support for the R&D resources available with the industry. In 2000, the government appointed the Pharmaceutical Research and Development Committee (PRDC), which recommended increased funding from publicly available sources. Complementing the focus areas that the PRDC had identified was the increase in the R&D collaboration between the Government-owned research laboratories (mostly under the Council of Scientific and Industrial Research) and the industry.

It is in the market for ARV drugs that the Indian industry has established itself as a major player globally. This development has taken place particularly since the Global Fund to Fight AIDS, Tuberculosis and Malaria (henceforth “Global Fund”), started providing funds for the free treatment programme. During the period June 2003 and January 2006, the Global Fund provided nearly US \$ 34 million for procurement of ARV drugs and the share of the Indian firms was close to 25%. With the global community now focused on obtaining drugs at affordable prices, it does appear increasingly probable that the pharmaceutical industries in the developing world, like the one existing in India, would offer the much-needed solutions.

Finally, the study emphasises the point that these successful forays of the Indian pharmaceutical firms would have to be assessed in the context of its role in accessing medicines at affordable prices. The increasing tendencies shown by the leading Indian firms to seek patents on incrementally modified drugs, does reveal a bleak side of the industry. Besides, the R&D priorities are being increasingly set in tune with the global trends, and this focus has increased since the firms have enhanced their level of collaboration with the foreign firms. Particularly affected in this process would be the “neglected diseases”.

### **List of Abbreviations**

ANDA: Abbreviated New Drug Application  
API: Active Pharmaceutical Ingredient  
ART: Anti-retroviral Therapy  
ARV: Anti-retroviral  
BLA: Biologics License Application  
CCMB: Centre for Cellular and Molecular Biology  
CDRI: Central Drug Research Institute  
CIPR: Commission on Intellectual Property Rights  
CSIR: Council of Scientific and Industrial Research  
DDPB: Drug Development Promotion Board  
DDPF: Drug Development Promotion Foundation  
DMF: Drug Master File  
EMRs: Exclusive Marketing Rights  
FDA: United States Federal Drug Administration  
FDCs: Fixed Dose Combinations  
FTC: Federal Trade Commission  
HHS: US Department of Health and Human Services  
ICMR: Indian Council of Medical Research  
IICT: Indian Institute of Chemical Technology  
IMD: Incrementally Modified Drug  
IND: Investigational New Drug Application  
MHRA: Medicines and Healthcare Products Regulatory Agency  
MSF: Médecins Sans Frontières  
NCE: New Chemical Entity  
NDA: New Drug Application  
NDDS: Novel Drug Delivery Systems  
NME: New Molecular Entity  
NRTI: Nucleoside Reverse Transcriptase Inhibitor  
NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor  
OTC: Over-the-Counter  
PRDC: Pharmaceutical Research and Development Committee  
PRDSF: Pharmaceutical R&D Support Fund  
TDF: Tenofovir Disoproxil Fumarate  
TRIPS: Trade Related Aspects of Intellectual Property Rights  
USPTO: US Patent and Trademark Office

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## **Introduction**

Ever since the Uruguay Round of multilateral trade negotiations were initiated two decades back, India has seen the issue of intellectual property rights being constantly put under the scanner. The accompanying debate has mostly focused on the changes in the patent regime that the proposed Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) would usher in and the implications that these changes would have on the access to medicines.

This debate has a historical basis in India. One of the first laws that the country took up for review after it became a sovereign state in 1947 was the patent law<sup>1</sup>. The patent regime then existing was examined by two expert groups<sup>2</sup> and findings of these expert groups were considered in-depth by the Indian Parliament<sup>3</sup>. The culmination of this process was the Patents Act of 1970, which is widely considered as the basis for the development of a strong pharmaceutical industry in India.

The changes effected by Patents Act, 1970 had at least three major implications for the pharmaceutical industry. In the first place, only process patents were allowed in the area of chemicals, which included pharmaceuticals. Secondly, the term of patent was reduced for process patents in pharmaceuticals. While all other areas the term of patent was fixed at 14 years from the date of application for the patent, for pharmaceuticals the term of patent was seven years from the date of application for a patent or five years from its date of grant, whichever was shorter. And, finally, instead of compulsory licences, a system of licences of right was introduced for the pharmaceutical sector, which provided for the grant of licences in an expeditious manner.

The development of an indigenous pharmaceutical industry in India following the adoption Patents Act of 1970, together with the operation of the Drug Price Control Order, which was also introduced in 1970, resulted in a southward movement in the prices of drugs in the country. In the 1960s, when the Patents and Designs Act of 1911 was in place, prices of drugs were found to be among the highest in the world, but in the 1990s, the drug prices in most therapeutic groups were lower by considerable margins<sup>4</sup>. In a country where a majority of its population do not have access to modern drugs, maintenance of drug prices at low levels held the key to people's access to drugs.

But the TRIPS Agreement has changed the conditions which saw the Indian pharmaceutical industry take roots. For the industry, the critical issue was the (re-) introduction of the product patent regime and the limitations that this change has imposed

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<sup>1</sup> Patents and Designs Act of 1911

<sup>2</sup> The Bakshi Tek Chand Committee set the process in motion 1948 and was followed by the Justice Rajagopala Ayyangar Committee report, which was submitted in 1957. See Govt of India (1950) and Govt of India (1959).

<sup>3</sup> During this period, the concerned Bill was referred to two Committees of the Parliament comprising of members from both Houses. See Lok Sabha (1966) and Lok Sabha (1969).

<sup>4</sup> In 1961, at a time when India had strong intellectual property laws, a U.S. Senate Committee headed by Senator Kefauver reported that "in drugs, generally, India ranks amongst the highest priced nations of the world". See Lanjouw (1998).

on its ability to produce technologies through reverse engineering<sup>5</sup>. It was widely held that the future prospects of the industry hinged critically on the ability of the policy makers to exploit the flexibilities that existed in the framework provided by the Agreement on TRIPS<sup>6</sup>.

If this was the “Plan I” of the strategy that was required to meet the challenges posed by the TRIPS Agreement, there was a need to have a “Plan II” wherein the pharmaceutical industry adopted measures to protect its longer term interests.

This paper explores the above-mentioned “Plans” that were adopted to answer the questions posed by the Agreement on TRIPS. In Section I, the features of the TRIPS-consistent patent law that India has put in place through three amendments introduced between 1999 and 2005 have been analysed. Section II looks at the changes that have been afoot in the Indian pharmaceutical industry while the patents regime was undergoing changes. The focus of this discussion would be the response of Indian pharmaceutical industry to the challenges posed in the realm of technology, now that the process patent regime has ceased to exist. Finally, in Section III, we would focus on the issue of access to HIV/AIDS drugs and the role of the Indian pharmaceutical industry in this critical area.

It needs to be stated here that the paper does not deal with all aspects of the TRIPS Agreement that could possibly have their impacts felt on the pharmaceutical industry. For instance, the issue of protection of test and other data concerning new chemical entities that are submitted to the authorities for obtaining marketing approval for pharmaceutical products<sup>7</sup> has not been included in the discussion. The reason for excluding this issue is that India is currently engaged in the process of developing a legal regime that conforming to the requirements of Article 39.3<sup>8</sup>. At present, data submitted to the Drug Controller General of India for obtaining marketing approval<sup>9</sup> are “deemed” to have been protected under the India’s Official Secrets Act, 1923. A generally accepted view is that the provisions of the Drugs and Cosmetics Act do not provide any remedy to the applicant for marketing approval in case the data submitted are not protected. At the same time, it is contented that the existing legal regime for providing marketing does not strictly conform to the provisions of Article 39.3 of the TRIPS Agreement since it covers

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<sup>5</sup> In addition to the fact that a regime allowing only process patents in the area of pharmaceuticals is TRIPS-inconsistent, the Agreement on TRIPS also includes a deterrent for the process patents owners. Article 34 provides that “if the subject matter of a patent is a process for obtaining a product, the judicial authorities shall have the authority to order the defendant to prove that the process to obtain an identical product is different from the patented process”. In other words, there is a reversal of burden of proof in case of litigations involving process patents.

<sup>6</sup> This issue was extensively discussed in the debate centring on the amendments to the Indian Patents Act for making the legislation TRIPS compliant. Several dimensions of this issue are discussed in a later section

<sup>7</sup> Article 39.3 of the TRIPS Agreement.

<sup>8</sup> An Expert Group has been set up by the Govt. of India to provide advice on the legal regime for the “Protection of Undisclosed information under Article 39.3 of the TRIPS Agreement”.

<sup>9</sup> Marketing approvals for pharmaceutical products are provided under the Drugs and Cosmetics Act, 1940 and the Drugs and Cosmetics Rules, 1945.

“new drug and its formulations”<sup>10</sup> and not “new chemical entities” as is required to be done under Article 39.3.

## **2 Amendments of the Indian Patents Act under the TRIPS Regime**

India’s commitment to fully implement the Agreement on TRIPS required three sets of amendments to the country’s Patents Act. While developing countries, in general, were allowed to make their patent laws TRIPS compliant through an amendment that was to be introduced by January 1, 2000, countries like India which had process patent regime covering pharmaceuticals and agricultural chemicals, would enjoy a longer transition period before they were required to introduce product patents from January 1, 2005<sup>11</sup>. The longer transition period, however, came with a set of conditions elaborated in Articles 70.8 and 70.9 of the TRIPS Agreement.

The above-mentioned Articles are included in the “Transitional Arrangements”, which required India to introduce two provisions in its Patents Act. Article 70.8 of the TRIPS Agreement required India to provide “a means” by which product patent applications can be filed from January 1, 1995 (“mailbox”, see below). If the products figuring in these applications were granted a patent in any of the WTO member countries and the products had obtained marketing approval in any of the WTO Member countries, then, according to Article 70.9, five years exclusive marketing rights (EMRs) had to be granted by India before the patent on the product was either granted or rejected in India. The first amendment of the Patents Act, 1970 introduced the requirements under the “transitional arrangements through Section 5(2), which allowed product patent applications to be filed, while Chapter IVA provided for the grant of EMRs<sup>12</sup>.

On January 1, 2000, a Second Amendment had to be introduced for bringing the Patents Act in conformity with all the substantive provisions the TRIPS Agreement, barring those related to the introduction of product patents. The key issues included in the Second Amendment were, re-defining patentable subject matter, extension of the term of patent protection to 20 years and amending the compulsory licensing system<sup>13</sup>.

A third amendment had to be introduced by January 1, 2005 to introduce product patent regime in areas, including pharmaceuticals that were hitherto covered by process patents. Although the Third Amendment had a narrow remit, the Government used the opportunity to undertake yet another review of the Patents Act. Among the major issues included in the Third Amendment were provisions relating to opposition to the grant of patents<sup>14</sup>.

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<sup>10</sup> Rule 122B of the Drugs and Cosmetics Act.

<sup>11</sup> Articles 65.2 and 65.4 of the TRIPS Agreement.

<sup>12</sup> This amendment was notified in the Gazette of India on 26 March 1999 as the Patents (Amendment) Act, 1999.

<sup>13</sup> This amendment was notified in the Gazette of India on 25 June 2002 as the Patents (Amendment) Act, 2002. See Govt of India (2002)

<sup>14</sup> The third amendment was notified in the Gazette of India on 5 April 2005 as the Patents (Amendment) Act, 2005. See Govt of India (2005a)

## **2.1 A Perspective for India's TRIPS-Compliant Patent Law**

It may be noted that two of the three amendments of its Patents Act that India had undertaken were adopted in the backdrop of significant global developments. Growing concerns in developing countries regarding access to medicines at prices that their citizens could afford led to considerable confabulations amongst the WTO members. The outcome of this process was the Ministerial Declaration adopted at the conclusion of the Doha Ministerial Conference held in 2001 on TRIPS Agreement and Public Health (henceforth, Doha Declaration).

The Doha Declaration unequivocally stated at the outset “that TRIPS Agreement *does not and should not prevent Members from taking measures to protect public health*” (emphasis added). The Ministers further stated “that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members’ right to protect public health and, in particular, to promote access to medicines for all”. It was emphasised that the WTO Members have the right to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose.

Two critical issues were particularly emphasised in the Doha Declaration. The first was that the provisions of the TRIPS Agreement should “be read in the light of the object and purpose of the Agreement as expressed, in particular, in its objectives and principles”. The objectives of the Agreement on TRIPS provided in Article 7 states that the protection and enforcement of intellectual property rights should among other things be “conducive to social and economic welfare, and to a balance of rights and obligations”. Furthermore, Article 8 of the Agreement directs WTO Members to adopt measures necessary to protect public health and nutrition while formulating or amending their laws and regulations relating to intellectual property. Thus, Articles 7 and 8 of the TRIPS Agreement require that WTO Members must ensure that the laws relating to all forms of intellectual property rights covered by the Agreement give due consideration to issues like protection of public health and nutrition and do not merely serve the interests of the owners of intellectual property.

The second area of focus of the Doha Declaration was compulsory licences, the instrument that could have a vital role to play in determining the future prospects of the Indian pharmaceutical industry. It was mentioned in an earlier discussion that over the past few decades, India witnessed the development of a strong pharmaceutical industry largely because of the absence of the product patent regime. However, with the product patent regime establishing itself following the adoption of a TRIPS-consistent patent regime by India, the future of the pharmaceutical industry in India would critically hinge on the ability of the producers to obtain licences from the owners of proprietary technologies. For obtaining the licences, these producers would have to depend on compulsory licences, an instrument that has been embedded in the patent system for preventing abuse of patent monopoly. The grounds for the grant of compulsory licences include the refusal of the patent holder to exploit the patent commercially in the country

granting the rights<sup>15</sup>. At the same time, however, the prospective beneficiaries of the compulsory licensing system would have to demonstrate that they have “made efforts to obtain authorization from the right holder on reasonable commercial terms and conditions and that such efforts have not been successful within a reasonable period of time”<sup>16</sup>.

In some ways, the Doha Declaration goes well beyond the provisions of the Paris Convention. The Declaration states that every WTO Member has “the right to grant compulsory licences and *the freedom to determine the grounds upon which such licences are granted*” (emphasis added). This, in other words, implies that the Doha Declaration allows WTO Member countries to use compulsory licensing system for realising public interest objectives like access to medicines.

The developments centring on the Agreement on TRIPS that have taken place during the past few years, a clear articulation of which was the Doha Declaration, bring home the point that the TRIPS-consistent patent laws have to take into consideration the interests of the public at large, besides of course granting patent rights on inventions that unambiguously represent advances in technology. This later point is particularly important given that the patent offices in some of the more advanced countries like the US, have been granting patents on the so-called incrementally modified drugs (IMDs), which could include new formulations, new combinations of active ingredients or new salts or esters of approved compounds<sup>17</sup>. Recent studies have found that in the United States brand manufacturers have flooded the market with IMDs, which “in 85% of the cases, do not provide significant improvement over currently marketed therapies”<sup>18</sup>. Firms have been more attracted towards IMDs because of the strong economic incentives that they bring with them. According to one of the major pharmaceutical firms, development of an IMD is “safer, faster, and more cost effective for the developer as an incremental improvement rather than an original product”<sup>19</sup>. What is an advantage for the firms is usually a disadvantage for the consumers since these IMDs have contributed substantially to the rising prices of medicines<sup>20</sup>.

These developments taking place in countries like the United States, which provide the most extensive patent rights, should be seen as useful guideposts for the policy makers in

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<sup>15</sup> The Paris Convention, which has set the global standards for patenting since it was adopted in 1883, provides in Article 5A that the signatories to the Convention have the “right to take legislative measures providing for the grant of compulsory licenses to prevent the abuses which might result from the exercise of the exclusive rights conferred by the patent, for example, failure to work”. It may also be mentioned that Article 2 of the TRIPS Agreement requires that WTO Members are required to comply with the substantive provisions of the Paris Convention.

<sup>16</sup> Article 31(b) of the TRIPS Agreement.

<sup>17</sup> National Institute for Health Care Management (2002), p. 5.

<sup>18</sup> National Institute for Health Care Management (2002), p. 19.

<sup>19</sup> Submission by Dr. Nahed Ahmed, Vice President, Productivity, Portfolio & Project Management Drug Innovation & Approval, Aventis Pharmaceuticals Inc. to the United States Federal Trade Commission/Department of Justice Hearings on “Competition and Intellectual Property Law and Policy in the Knowledge-Based Economy”. See United States Federal Trade Commission/Department of Justice (2002).

<sup>20</sup> National Institute for Health Care Management (2002), p. 19.

India while they are in the process of adoption of a TRIPS-consistent patent regime. In a country where access to medicines at affordable prices is a major area of concern, one hardly needs to labour on the point that adequate safeguards need to be provided to ensure that the country does not witness the spectre of high prices medicines caused by the grant of IMD patents. What this implies is that strengthening of the rights of the patent holders, which is the cornerstone of the TRIPS Agreement, must be tempered by the inclusion of provisions that effectively address public interest concerns. The following discussion provides a perspective on India's patent law amendments that were undertaken to introduce a TRIPS-consistent patent regime.

## **2.2 Analysing the amendments**

The above discussion suggests that several issues would need careful consideration as India implements a TRIPS-compliant patent regime. The following is a non-exhaustive list: (i) defining the scope of patentability to address among other issues, patents on IMDs, (ii) provisions for the grant of compulsory licences, (iii) opposition proceedings, (iv) specific exceptions as for example "parallel imports", and (v) provisions relating to providing immunity to generic producers that are already in the market.

### **2.2.1 Scope of Patentability**

It may be argued that it is of critical importance to define scope of patentability since in many jurisdictions, and in particular, those existing in developed countries, the definitions adopted are often so open-ended that they have undesirable consequences, as for instance, the grant on patents on IMDs. And as a later discussion would indicate, the process of examination of the product applications that are currently in the "mailbox" has revealed that patents on IMDs is indeed a real threat which has to be addressed by all relevant stakeholders in a concerted manner. The "mailbox" provisions, introduced through the amendment of the Patents Act in 1999, required India to accept applications for product patents in the area of pharmaceuticals and agro-chemicals even before the product patent regime was put in place. The purpose of the "mailbox", as based on Article 70.8, TRIPS Agreement, was to provide inventors with a means of filing applications for pharmaceutical product patents during the transition period (i.e. until 1 January 2005). Upon termination of the transition period, all applications in the mailbox then have to be examined. The effect of the "mailbox" is a legal fiction: according to Article 70.8 (b), TRIPS Agreement, the patentability criteria of novelty, inventive step and industrial applicability shall be applied after the transition period as if they were being applied on the date of filing/date of priority. In other words, the novelty of an invention is preserved, although the respective product might have been available to the public for some time.

The "mailbox" provision has attracted more than 9,000 product patent applications, a significant proportion of which is in the area of pharmaceuticals that would have to be

examined according to the provisions of the recently amended Act<sup>21</sup>. It has been pointed out that between 1995 and 2003, only 274 new chemical entities have been granted marketing approval by the United States Federal Drug Administration (FDA), and this implies that an overwhelming majority of the applications in the “mailbox” cover IMDs.

Narrowing down the scope of patentability, particularly in respect of pharmaceuticals should be seen as the first step for ensuring that the IMDs do not get patent rights in India. This required that the amended law provide appropriate definitions/clarifications in respect of the three criteria used for assessing whether or not a claimed invention is patentable, viz. novelty, inventive step and industrial application. It needs to be noted here that the TRIPS Agreement does not define any of these three criteria, implying thereby that the WTO Member countries are free to adopt their own definitions.

Two issues are important in this context. These are the elaboration of the criteria for patentability and the issue of patentable subject matter. Four amendments were introduced in the Patents Act, and some of these require close examination.

The first is the elaboration of the definition of “inventive step”, which was accepted as being coterminous with non-obviousness in the earlier version of the Patents Act 1970<sup>22</sup>. According to Section 2(ja), “inventive step” means a feature of the invention that involves technical advance as compared to the existing knowledge or having economic significance or both ...” How the Patent Office interprets this definition would be seen with interest on two counts. First, the extent of “technical advance” that would be considered sufficient for the grant of the rights could depend largely on the subjective judgement of a patent examiner. In other words, a patent examiner would require a clear set of guidelines further to ensure that incremental innovations of the kind that the IMDs represent are not granted patent rights. Secondly, assessment of the inventive step based on the “economic significance” of an invention could lead to erroneous outcomes. This problem could arise from the exaggerated claims regarding the economic value of the invention that the patent applicant would be tempted to make to take advantage of this provision.

The second amendment of this genre that requires a re-look is the introduction of a new definition for “pharmaceutical substance”. Section 2(ta) of the Patents Act, as amended, defines a pharmaceutical substance as “any new entity involving one or more inventive steps”. If the real objective of the definition was to narrow the scope of patenting of pharmaceutical products, it falls far short of meeting this objective. In fact, the existing definition opens the door for frivolous claims aplenty in this area. It has been argued for instance that the term ‘chemical’ should have been inserted so that the definition would be ‘any new chemical entity’<sup>23</sup>. That this suggestion has considerable merit can be seen from the manner in which the FDA deals with this issue. According to the FDA, new chemical entity (NCE) or a new molecular entity (NME) means a drug that contains no

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<sup>21</sup> This figure has been quoted by Access to Medicine and Treatment Campaign (AMTC). See Narrain (2005).

<sup>22</sup> An invention is considered as having an “inventive step” if it is non-obvious to anyone skilled in the art.

<sup>23</sup> Gopakumar and Amin (2005)..

active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. An active moiety means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance<sup>24</sup>.

A third amendment tries to exclude discoveries or new use of a known substance from the ambit of patenting. Here again, the language used leaves far too much of an ambiguity. A good example of this is the exclusion of “the mere discovery of a new form of a known substance *which does not result in the enhancement of the known efficacy of that substance*” (emphasis added) from patentable inventions.

While answers to several of these issues may eventually be settled through the disputes including those that would be in the nature of opposition to the grant of patents, there is obviously a need to get legal certainty on this contentious issue.<sup>25</sup> Reflecting this need, the Government of India had set up a five-member “Technical Expert Group on Patent Law Issues” in April 2005 headed by Dr. R.A. Mashelkar, Director General, Council of Scientific and Industrial Research (CSIR). The Group was given the following terms of reference<sup>26</sup>:

- (a) whether it would be TRIPS (Trade-Related Intellectual Property Rights) compatible to limit the grant of patents for pharmaceutical substance to new chemical entity or to new medical entity involving one or more inventive steps; and,
- (b) whether it would be TRIPS compatible to exclude micro-organisms from patenting<sup>27</sup>.

The Report of the Group is still awaited.

As regards the patentable subject matter, the key change introduced was the mandatory requirement for removing the “process-patent-alone” regime in case of chemicals. This involved removal of Section 5(1) of Patents Act, 1970 which provides for process patents in this field. This has meant that from January 1, 2005 product patent applications are being accepted and examined. Included in these product patent applications would be those applications that were made since 1995 using the “mailbox” provisions. The “mailbox” provisions were introduced in the Patents Act through the first amendment undertaken in 1999 in order to fulfil the condition imposed in Article 70 of the TRIPS Agreement (the so-called “Transitional Arrangements”). As was mentioned earlier, the

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<sup>24</sup> Wikipedia, the free encyclopaedia ([http://en.wikipedia.org/wiki/New\\_chemical\\_entity](http://en.wikipedia.org/wiki/New_chemical_entity))

<sup>25</sup> See a later discussion for some of the law suits that have been filed opposing patents on drugs on some critical diseases.

<sup>26</sup> Govt of India (2005b).

<sup>27</sup> There is a view that micro-organisms should not be patented given that the review of Article 27.3(b) has been pending since 1999. Several public interest groups have supported the view that has been held by the African Group that patenting of life forms should not be allowed in the TRIPS-consistent patent regime. For the views of the African Group see WTO (1999) and WTO (2003).

“Transitional Arrangements” were in the nature of a trade-off for the longer period that India could enjoy for making its Patents Law compatible with the TRIPS Agreement<sup>28</sup>.

It is vitally important that the scope of patentability, definition of pharmaceutical entity, is laid down in clear and unambiguous manner. This step would go a long way in reducing the number of patent litigations, which are threatening to increase. The obvious targets are patents that are being sought for drugs can be used for treating diseases like HIV/AIDS, cancer and TB. In recent months, two significant developments have taken place. The first involved the Novartis patent on a drug used for the treatment of cancer, Gleevec. Product patent application for Gleevec was made using the “mailbox” provisions, which meant that Novartis could enjoy five-years of EMRs on the basis of the application made. The EMRs were granted in November 2004, but the grant of the patent was opposed and the opposition was finally upheld in January 2006 (see Box 1 for details).

The second case involves GlaxoSmithKline’s Combivir, a fixed-dose combination of two AIDS drugs (zidovudine/lamivudine, or AZT/3TC). Opposition to the grant of this patent was submitted on March 31, 2006 by a two civil society groups, the Indian Network of People Living with HIV/AIDS and the Manipur Network of Positive People. The opposition was based both on technical and health grounds<sup>29</sup>. The Indian groups opposing the patent are arguing that Glaxo's Combivir (AZT/3TC) is not a new invention but simply the combination of two existing drugs.

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<sup>28</sup>Article 65 of the TRIPS Agreement gave developing countries a period of five years from the establishment of the WTO to amend their patent laws. However, developing countries having a process patent regime were given a further period of five years to introduce product patents in the areas that were covered by process patents in the pre-TRIPS phase.

<sup>29</sup> See MSF (2006a).

### **Box 1: The Gleevec Case**

Imatinib Mesylate is regarded as the most effective drug for Chronic Myeloid Leukaemia, a form of leukaemia. In India, annually around 25,000 people become the victims of Chronic Myeloid Leukaemia.

Novartis holds the patent for the drug and markets it under the brand name of Gleevec. Imatinib Mesylate was granted marketing approval in the US in 2001. Subsequently, the USFDA also approved Imatinib Mesylate for the treatment of gastrointestinal stromal tumours.

The Drug Controller General of India (DCGI) gave the marketing approval for Gleevec in 2001. Novartis started the marketing of the drug through importation. In 2003, an Indian company, Natco Pharma, launched generic version of Imatinib Mesylate. Besides Natco, five other firms Camlin, Cipla, Sun Pharma, Ranbaxy and Intas are also in the market with their generic versions of Imatinib Mesylate.

In November 2004 Novartis obtained an Exclusive Marketing Right (EMR) for Gleevec having applied for it in 1998. In its application, Novartis indicated that Gleevec qualified for the grant of EMRs since it had been granted marketing approval in Australia. Even though Novartis got the patent and marketing approval from the US but did not rely on US approval and patents for EMR in India. The decision to grant EMR was challenged by one of the generic manufacturers in the Delhi High Court. Meanwhile, Novartis obtained stay from the Chennai High Court and prevented all other generic firms from producing and marketing generic versions of Imatinib Mesylate.

After the third amendment of Patents Act, the affected pharmaceutical firms and public interest groups used the provisions relating to pre-grant opposition to challenge the product patent application on Gleevec. Patent application was challenged on the following grounds: (i) prior publication, (ii) lack of inventive step, (iii) insufficient description, (iv) last priority date and (v) subsequent patenting of known substance.

According to petitioners, Novartis had disclosed the substance in an application filed in the US in 1994 taking priority from a Swiss patent application filed in 1992. The USPTO granted patent on this application in 1996. The US application stated that owing to the close relationship between the novel compounds in free form and in the form of their salts, including those that could be used as intermediaries, any reference to the free compounds should be understood as including the corresponding salts where appropriate and expedient. Hence, Novartis' claim for beta crystal salt format of Imatinib Mesylate has been anticipated through publication. Further, petitioners also pointed out that the steps stated in the patent application for creating the beta crystal form of Imatinib Mesylate is an obvious step and lacks inventive step. It was pointed out that the patent application failed to describe the steps involved for the manufacture of beta crystal form of Imatinib Mesylate. Patent application was also opposed on the ground of loss of priority date. The application in question was filed in 1998 taking priority from a Swiss application of 1997. However, on the date of filing in India, Switzerland was not recognized as Convention Country in India and therefore the date of application in Switzerland could not be considered as the "priority date". And, finally, under the Indian Patents Act, salts are not patentable unless the applicant the patent claim is not based on the enhanced efficacy. Novartis failed to provide any evidence on the enhanced efficacy of the beta crystal form of Imatinib Mesylate. Considering these objections, Indian Patent Office rejected Novartis' patent application on 27th January 2006. In response, Novartis in May 2006 took the case to the High Court in Chennai, challenging the validity of Section 3(d) of the Indian Patents Act (which makes the patentability of new forms of known substances dependent on the proof of enhanced efficacy of the known substance). In particular, Novartis claims inconsistency of this provision with the TRIPS Agreement, as it allegedly introduces additional patentability requirements beyond the minimum standards of novelty, inventive step and industrial applicability (see IP Watch (2006))

### **2.2.2 Future of the Generic Producers**

One of the more contentious issues that the third amendment of the Patents Act had to address was the future of the generic producers in India who are currently producing the products and whose product patent applications are in the “mailbox”. These producers would have to cease operations in India should patent rights be granted to such products under the new dispensation<sup>30</sup>.

Section 11A of the Patents Act, 1970, as amended, protects the interests of such generic producers whose business interests may be affected in the product patent regime. This section states that “the patent holder shall only be entitled to receive *reasonable royalty* from such enterprises *which have made significant investment* and were producing and marketing the concerned product” before January 1, 2005, and “which continue to manufacture the product covered by the patent on the date of grant of the patent ...” (emphasis added). In addition to this, it is provided that “no infringement proceedings shall be instituted against these enterprises”.

Although this provision is expected to provide succour to the generic producers, it would have to face a number of imponderables. First, the threshold for assessing whether or not a given level of investment can be considered “significant” is not clear. This lacuna regarding the definition of “significant” poses threat of infringement suits as the patent holder may challenge any definition of “significant investment” that may be proposed to extract high royalty payments.

A further problem may be encountered while defining the term “reasonable royalty”. This issue would be discussed in greater detail in the following section

### **2.2.3 Compulsory Licensing**

In the context of the on-going debate on the patent law reforms, a key issue, which is often glossed over, is that the compulsory licensing system is one of the essential pillars of the patent system. It has been well recognised that compulsory licences are expected to play an important role in preventing abuse of patent rights that may arise when the patent holder tries to pre-empt entry of competitors using his statutory rights.

The context for this issue has been provided by the Paris Convention. Article 5A of the Stockholm Act of the Paris Convention clarifies that “failure to work<sup>31</sup>” or “insufficient working” of a patent constitutes an “abuse” of patent rights. In the event of an abuse of the patent rights arising from non-working or insufficient working, the patent granting authority was given the powers to issue a licence to anyone who was willing to “work” the patent.

Viewing from it a more functional perspective, the instrument of compulsory licence provides an opportunity to the prospective users of technology, in particular the

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<sup>30</sup> This stems from the fact that the patent rights can be used to prevent anyone from making, using, offering for sale, selling or importing the product covered by the patent.

<sup>31</sup> Read “Commercial exploitation”.

developing countries, to gain access to proprietary technologies. The compulsory licensing system could be immensely useful for the firms in the Indian pharmaceutical industry for they can no longer meet their technology-requirements by taking recourse to reverse engineering.

Attempts to implement the compulsory licensing system may end up in widely differing outcomes, primarily because patent owners and potential users of patented technologies, the developing countries, have given widely contradicting interpretations of how a TRIPS-consistent compulsory licensing system should function. The patent-community has given a narrow interpretation of the provisions, arguing that compulsory licences should be used only under exceptional circumstances<sup>32</sup>. On the other hand, Governments of several developing countries have tried to use the compulsory licensing system in a manner that would allow their domestic enterprises to engage in production, since this has been seen as a critical aspect of promoting access to medicines<sup>33</sup>.

Developments over the past few years indicate that the point of view of developing countries has been getting better support from the global community. In 2001, legal uncertainties in respect of the use of compulsory licensing provisions for public health concerns were effectively removed by the Doha Declaration on TRIPS Agreement and Public Health. The Declaration stated unequivocally that “[E]ach Member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted”.

The Commission on Intellectual Property Rights (CIPR), which was instituted by UK Department for International Development, was equally supportive of the compulsory licensing system. In its report, “Integrating Intellectual Property Rights and Development Policy”, the Commission emphasised that “developing countries should establish workable laws and procedures to give effect to compulsory licensing and provide appropriate provisions for government use”<sup>34</sup>. The CIPR recommended that developing countries should adopt effective compulsory licensing mechanisms which include straightforward, transparent and fast procedures that do not suspend the execution of the licence. Moreover, the CIPR emphasised that developing countries should fully exploit the flexibilities within TRIPS for determining compulsory licensing, as well as for non-commercial use by the government, including production for export.

Despite the above-mentioned developments, the compulsory licence system provided by India in its amended Patents Act may not fully meet the requirements of the domestic pharmaceutical industry. We maintain this view for the reasons explained below.

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<sup>32</sup> According to the Pharmaceutical Research and Manufacturers of America (PhRMA), the association of the global pharmaceutical majors, “Compulsory licenses, are an exceptional remedy for use only in the case of market failure or significant abuse of a patent (e.g. a demonstrated antitrust violation linked to use of a specific patent, or a state of national emergency under which normal rules of commerce are suspended)”. For details see Coalition for Intellectual Property Rights (2002),

<sup>33</sup> South Africa and Brazil are among the more prominent countries that have included compulsory licensing provisions in their patent laws.

<sup>34</sup> Commission on Intellectual Property Rights (2002), , p. 44.

The Indian Patents Act provides that an application for the grant of compulsory licence can be made only after three years from the date of grant of the patent unless exceptional circumstances like national emergency or extreme emergency can be used to justify the grant of a licence on an earlier date. Three broad grounds for the grant of the compulsory licences have been spelt out thus: (a) reasonable requirements of the public with respect to the patented invention have not been satisfied, (b) the patented invention is not available to the public at a reasonably affordable price, and (c) the patented invention is not worked in the territory of India. The Patents Act sets out the circumstances under which “reasonable requirements of the public” would not have been met. Such circumstances would arise if the patent holder refuses to grant a licence on reasonable terms, and which, in turn, affects: (i) development of new trade or industry in the country, and (ii) establishment or development of commercial activities in India, and (iii) development of the export market for a patented article manufactured in India. The last mentioned provision is aimed at ensuring that India has the option to export the products that have been produced using the licences from the patent holders. The major impact of this provision could be felt in the pharmaceutical sector, where India could well emerge as a major supplier of pharmaceuticals to the developing countries that do not have sufficient domestic manufacturing facilities.

But while the above-mentioned conditions for the grant of compulsory licences can be seen to be facilitating the grant of the licences, the Act also stipulates that the relevant authority have to take into consideration four additional factors before the licences can be granted. These include: (a) the nature of the invention, the time which has elapsed since the sealing of the patent and the measures already taken by the patentee or any licensees to make full use of the invention; (b) the ability of the applicant to work the invention to the public advantage; (c) the capacity of the applicant to undertake the risk in providing capital and working the invention, and (d) the efforts made by the applicant to obtain a licence from patentee on reasonable terms and conditions and that such efforts were not successful within a reasonable period<sup>35</sup>.

Consideration of these factors for granting compulsory licences gives rise to several problems. First, the procedural requirements are too onerous and could consequently result in delays. Secondly, it is not clear whether the grant of a compulsory licence would automatically follow the refusal of a patentee to issue a voluntary licence on reasonable commercial terms. Thirdly, the grounds for the determination of anti-competitive practices have not been spelt out either the Patents Act or Competition Act<sup>36</sup>. And, finally, there is no ceiling on the remuneration payable to the patent holder, which will inevitably lead to demand for excessive royalty and unnecessary litigations. As would be

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<sup>35</sup> The third amendment provided some crucial clarifications pertaining to this condition. The designated authority has been allowed to interpret the term “reasonable period” to mean a period not ordinarily exceeding six months (Section 84(6)).

<sup>36</sup> In fact, India’s Competition Act (enacted in 2002) does not address abuses of patent rights. Section 3(5) of the Competition Act, states: “Nothing contained in this section shall restrict ... the right of any person to restrain any infringement of, or to impose reasonable conditions, as may be necessary for protecting any of his rights which have been or may be conferred upon him under ... the Patents Act, 1970. See Govt of India (2003)

discussed below, the last mentioned problem has the potential of blocking the way for the use of compulsory licensing system.

The remuneration that a patent holder could demand following the decision to grant compulsory licence for the “working” of patents in the country of grant act may become a serious constraint for the smooth functioning of the compulsory licensing system. This situation arises because the Agreement on TRIPS provides the rights holder a distinctly superior bargaining position. Article 31(h) of the TRIPS Agreement, which provides the guideposts in this regard, states that “the right holder shall be paid adequate remuneration ... taking into account the economic value of the authorization” (emphasis added). This Article has the potential of rendering the cost of the licence prohibitive for the drug majors have claimed that the average cost of bringing one new medicine to market is at least a billion US dollars<sup>37</sup>.

Royalty payments would be a critical issue in the implementation of the compulsory licensing system as is provided in the Indian Patents Act. Besides the problems alluded to above, there are evidences galore of developing countries being unable to afford proprietary technologies because the high cost of acquiring such technologies. This situation has occurred primarily because the owners of technology have been able to use their superior bargaining position to seek terms that have suited their interests<sup>38</sup>. In an age when a web of patents covering a single product (better known as patent thickets<sup>39</sup>) have become commonplace, multiple licences are often required to be negotiated before any enterprise can commence production. Patent thickets have also given rise to another problem, viz. royalty stacking. According to an OECD study, firms have reported that in some cases royalty payments can exceed 20% of their net sales<sup>40</sup>. And, in South Africa, GlaxoSmithKline demanded a royalty of 25% before the courts intervened. A higher royalty will increase the price of generic drugs and this, in the ultimate analysis would militate against the existence of the generic producers whose *raison d’etre* is to supply medicines at affordable prices.

India’s own experience with technology licensing agreements makes interesting reading. Past trends show that the licensors were able to secure payments for their technologies

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<sup>37</sup> The Pharmaceutical Research and Manufacturers of America (PhRMA) states that it takes as long as 15 years and cost nearly 1 billion dollars to bring a new medicine from the laboratory to a pharmacy shelf. This figure has, however, been challenged by several public interest groups. See PhRMA (2006).

<sup>38</sup> A well-documented Indian case from the pre-1970 phase, when the country had a product patent regime cogently illustrates this issue. In response to an application for compulsory licence by a government – owned research institute, Haffkine Institute, the patentee indicated that it was willing to grant a voluntary licence. At the end of the negotiations, however, the patentee demanded a royalty of 25%. Further negotiations followed, and after more than four years, the patentee agreed to reduce the royalty to 10 per cent, which was still higher than 5% limit fixed by the government. This protracted process of negotiations for obtaining a licence was found too costly by the prospective licensee and it was forced to abandon the project. For details see, Lok Sabha (1969).

<sup>39</sup> A more formal definition of patent thicket is the following: it is a “dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology”, see Shapiro (2001) quoted in Federal Trade Commission (2003).

<sup>40</sup> OECD (2002), p. 15.

even when they were not transferring proprietary technologies. Surveys of foreign collaboration agreements conducted over a three decade period by the Reserve Bank of India revealed that proprietary technologies were transferred in only about 50% of the cases<sup>41</sup>.

The provisions in the Indian Patents Act relating to the payment of royalty and other remuneration for obtaining a licence do not address the above-mentioned problems. In fact, Section 90 provides that the remuneration would take into consideration the perspective of the patentee, which includes the expenditure incurred by the patentee for making and developing the invention and for obtaining and keeping the patent in force. It may be argued that these considerations for determining the royalty and other remuneration would enhance the already superior bargaining position of the patentee and that these would need to be tempered with public interest considerations as well<sup>42</sup>.

These were some of the considerations that were highlighted by the Doha Declaration on TRIPS Agreement and Public Health, which, as stated earlier, provides the flexibilities to the Member countries to adopt an effective compulsory licensing system. However, in light of the above-discussion it can be concluded that India has not ensured that its compulsory licensing system can function in a manner that public interest concerns can be addressed. While the procedural complexities would delay the grant of licences, ambiguities on the methodology for determining remuneration to the patentee, can be a serious roadblock. The latter issue, in our view, requires focused attention.

It may be suggested in this context that two alternative frameworks for calculating the value of licences granted by invoking the provisions relating to compulsory licences may be considered. These formed parts of two bills that were part of bills that were presented to the 107<sup>th</sup> Congress of the United States in 2001. The Affordable Prescription Drugs and Medical Inventions Act (HR 1708) seeks to amend the US Patent Law (Title 35, United States Code) to provide for compulsory licensing of certain patented inventions relating to health. The Public Health Emergency Medicines Act (HR 3235) aims at providing for compulsory licensing of certain patented inventions relating to health care emergencies, through an amendment of the US Patent Law.

Boxes 2 and 3 provide the details of methodologies that have been suggested in the proposed Acts for determining the remuneration that the patentee should be paid in case compulsory licences are issued for “working” patented medicines.

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<sup>41</sup> Reserve Bank of India (1974); Reserve Bank of India (1985), p. 36.

<sup>42</sup> Dhar and Rao (2004).

**Box 3: Considerations for Determining Remuneration for use of a Patent**

In determining the reasonableness of licensing terms and the remuneration for the use of a patent under subsection (c), the Secretary of Health and Human Services or the Federal Trade Commission (as the case may be) shall consider—

1. the risks and costs associated with the invention claimed in the patent and the commercial development of products that use the invention;
2. the efficacy and innovative nature and importance to the public health of the invention or products using the invention;
3. the degree to which the invention benefited from publicly funded research;
4. the need for adequate incentives for the creation and commercialization of new inventions;
5. the interests of the public as patients and payers for health care services; and
6. the public health benefits of expanded access to the invention.

Source: House of Representatives, Affordable Prescription Drugs and Medical Inventions Act (H. R. 1708): To amend Title 35, United States Code, to provide for Compulsory Licensing of certain patented inventions relating to health, 107th Congress, 1st Session, May 3, 2001.

**Box 2: Compensation for Use of a Patent**

In exercising the right under subsection (a) to authorize other use of the subject matter of a patent, the right holder shall be paid reasonable remuneration for the use of the patent. In determining the reasonableness of remuneration for the use of a patent, the Secretary of Health and Human Services may consider—

1. evidence of the risks and costs associated with the invention claimed in the patent and the commercial development of products that use the invention;
2. evidence of the efficacy and innovative nature and importance to the public health of the invention or products using the invention;
3. the degree to which the invention benefited from publicly funded research;
4. the need for adequate incentives for the creation and commercialisation of new inventions;
5. the interests of the public as patients and payers for health care services;
6. the public health benefits of expanded access to the invention;
7. the benefits of making the invention available to working families and retired persons;
8. the need to correct anti-competitive practices; or
9. other public interest considerations.

Source: House of Representatives, Public Health Emergency Medicines Act (H. R. 3235): To amend title 35, United States Code, to provide for compulsory licensing of certain patented inventions relating to health care emergencies, 107th Congress, 1st Session, November 6, 2001

The limitations of the compulsory licensing system that we have alluded to above would necessitate, in our view, a review in light of the experience gained from the implementation of the newly amended Patents Act. This experience would be of crucial value since India does not have much to show in terms of a viable compulsory licensing system<sup>43</sup>. In the product patent regime, i.e. in the pre-1970 phase, only five applications were made for the grant of compulsory licenses. Of these, licences were granted in only two cases and refused in one case. In the two remaining cases, the applications were eventually withdrawn<sup>44</sup>.

The post-1970 phase saw India introduce a process patent regime covering all forms of chemicals, including pharmaceuticals. Furthermore, the term of process patent protection covering pharmaceuticals was set at five to seven years<sup>45</sup>. While the process patent regime allowed the Indian pharmaceutical firms to generate alternative processes for manufacturing products that were under product patent in other jurisdictions, the shortening of the term of pharmaceutical (process) patent proved to be a damper for foreign firms to seek patents in India.

#### **2.2.4 Opposition Proceedings**

Another issue of considerable significance to India that the third amendment of the Patents Act has dealt with is the issue of opposition to the grant of patents. While the Ordinance that was brought in December 2004 watered-down the provisions relating to pre-grant opposition while introducing post-grant opposition, the amended legislation restores the ground on which pre-grant opposition can be made. Although the grounds for opposition available in the pre-grant stage have been restored, the right of appeal is available only for post-grant opposition. India has thus become the only country among the major patent granting ones, which provides for both pre- and post-grant opposition in its patent legislation. It may well be argued that by so doing India has put the patent applicant in a disadvantageous position, an argument that can bring the entire procedure for opposition to the grant of patents before the courts.

An issue of immediate relevance in this context is the manner in which the opposition proceedings are conducted in case of applications that are in the “mailbox”. Following “Gleevec” case, discussed earlier, pre-grant opposition proceedings have been initiated in more than 100 cases. Besides, the domestic industry, public interest groups have also initiated opposition proceedings<sup>46</sup>. However, effectiveness of the opposition proceedings depends upon the access to information on the mailbox applications. The Patent Office in 2005 has issued a notification in its official journal that inventions either filed or claiming

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<sup>43</sup> Although India had introduced the Patents and Designs Act in 1911, provisions specifically dealing with compulsory licenses for pharmaceutical patents were introduced only in 1953. See, Rao (2002)

<sup>44</sup> Chaudhuri (1984).

<sup>45</sup> The term was five years from the date of grant of a patent, or seven years from the date of its application, whichever was shorter.

<sup>46</sup> In May 2006, the Indian Network for People Living with HIV/AIDS (INP+) and the Delhi Network of Positive People filed an opposition to the grant of patent on tenofovir disoproxil fumarate (TDF), a key AIDS drug that is marketed under the brand name Gilead, see MSF (2006b)

priority on July 30, 2003 have been deemed to be published. However, no physical publications have been available to date. This lack of publication takes away the possibility of accessing information relating to the patent application and the ability to oppose the same. Lastly the Act refers to the publication of an application, but fails make the publication of the complete specification available to the public. This will greatly hamper opposition proceedings

### **2.2.5 The Two Exemptions**

Section 107A of the Patents Act, 1970, as amended contains two notable exemptions. The first relates to what is better known as the “Bolar Exemptions” and the second exemption seeks to define the contours of parallel imports.

#### **2.2.5.1 “Bolar Exemption”**

One of the less focused areas of the Indian Patents Act, as amended, is the provision providing for the so-called “Bolar exemption”<sup>47</sup>. The basic idea behind the “Bolar exemption” is to create conditions so that the generic drug manufacturers can introduce their products immediately after the patent on a drug lapses. With the leading firms in the Indian pharmaceutical showing considerable degree of dynamism in recent years, which we shall discuss in the following section, the “Bolar exemption” assumes considerable importance for the future of the generic producers in India.

The “Bolar exemption” became a feature of the US patent statute in 1984, following the ruling of the Court of Appeals for the Federal Circuit in *Roche Products Inc. v. Bolar Pharmaceuticals Co. Inc.* This case involved a generic manufacturer (Bolar Pharmaceuticals) who had used a patented invention to test and apply for marketing authorisation of its version of a patented medicine. The Court had determined that the common law “experimental use” defence only covered experimentation for scientific, not commercial, purposes, and that the generic manufacturer’s activities therefore amounted to an infringement of the relevant patents<sup>48</sup>.

Section 271(e)(1) of the US patent law (35 USC), which provided the “Bolar” or “experimental use exception” allowed the generic firms to conduct research on patented drugs prior to the expiration of the patent, so long as the experiments were “reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products”. The effectiveness of the “experimental use exception” was however dependent on the interpretation of the term ““reasonably related”, and not unexpectedly, this term was the subject matter of a litigation between Merck KGaA and Integra Lifesciences, which was adjudicated upon by the US Supreme Court<sup>49</sup>.

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<sup>47</sup> Also called “Experimental Use Exception”.

<sup>48</sup> WTO (2000), p 37.

<sup>49</sup> Supreme Court of the United States (2005)

In a significant ruling, the US Supreme Court clarified that “Section 271(e)(1)’s exemption from infringement extends to all uses of patented inventions that are reasonably related to the development and submission of any information under the FDCA<sup>50</sup>,” (emphasis in original) and that “[t]his necessarily includes preclinical studies of patented compounds that are appropriate for submission to the FDA in the regulatory process.” The Court held that Section 271(e)(1) applies to preclinical in vitro and in vivo studies intended to obtain information on the “pharmacological, toxicological, pharmacokinetic, and biological qualities of the drug in animals”.

Following from the precedence set in the US, Canada took two significant steps to make carve outs in its Patent Act. Section 55.2(1), or the “regulatory review exception”, of the Canadian Patent Act allowed all activities related to the development and submission of information required to obtain marketing approval for pharmaceutical products carried out by a third party without the consent of the patent holder at any time during the patent term. Further, Sections 55.2(2) and (3), or the “stockpiling” exception, of the Patent Act together with the Manufacturing and Storage of Patented Medicines Regulations allowed manufacturing and stockpiling of pharmaceutical products during the six months immediately prior to the expiration of the 20-year patent term.

The Members of the EC brought a dispute to the WTO maintaining that the above mentioned sections of the Canadian Patent Act violated the rights of the patent holder as provided in Article 28 of the TRIPS Agreement. According to the EC, the “Bolar exemptions” provided by Canada using Section 55.2(1) of its Patents Act took away all the rights a patent granted its owner, i.e. making, constructing, using (this included importing) and selling, and did not stipulate any quantitative limits for these activities. The only limitation set out by the law consisted in the objective of these activities, i.e. they must be “... reasonably related to the development and submission of information” required for obtaining marketing approval anywhere in the world. In addition, the permissible activities under Section 55.2(1) of the Canadian Patent Act were not limited in time. The EC argued that this in other words implies that the activities might be performed without the consent of the right holder at any point in time during the 20-year patent term.

Section 55.2(2) and (3) of the Canadian Patents Act allowed anybody in Canada to perform the acts of making, constructing and using of the invention during the last six months of the patent term without the authorization of the patent holder. EU argued that in order to perform the above-mentioned acts, no particular authorization was needed from the Canadian authorities. Besides, the provisions did not qualify the terms of the extent and volume of the use, and no royalty fees were to be paid to the patent holder. In fact, EU’s view was that the patent holder did not have any right to be informed of such “unauthorized” use of his invention.

The findings of the panel adjudicating this dispute was that while the “regulatory review exception” i.e., Section 55.2(1) of the Canadian Patent Act, was consistent with Canada’s

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obligations under the TRIPS Agreement, Sections 55.2(2) and (3), the stockpiling exception, violated the provisions of the Agreement.

The “Bolar exemption” was included in the Second Amendment of the Indian Patents Act, 1970. Section 107A(a) of the amended law contains the relevant provisions:

Any act of making, constructing, using, selling or importing<sup>51</sup> a patented invention solely for uses reasonably related to the development and submission of information required for the time being in force, in India or in a country other than India, that regulates the manufacture, construction, use, sale or import of any product.

Although in its essentials, Section 107A(a) mirrors the provisions of the Canadian Patent Act, it has one significant difference. Included in the exception to the rights is the act of importation, which the Canadian Patent Act does not provide. The implications of including the act of importation as a part of the “Bolar exemptions” are not immediately obvious. Nor is it clear as to how this exemption may in any way affect the applicability of Section 107A(b) that provides for parallel imports.

#### **2.2.5.2 Parallel imports**

The Agreement on TRIPS allows for the parallel imports, although the specific circumstances under which such imports can take place have not been defined. The Indian Patents Act, 1970 has taken the initiative to include the provision of parallel imports. The relevant provision, provided under Section 107A(b) reads as follows:

“Importation of patented products by any person from a person who is duly authorised under the law to produce and sell or distribute the product”

As has been explained by the Government, this provision of parallel import of patented product was introduced for “ensuring availability of patented products at cheaper price to the consumers”<sup>52</sup>. In particular, reference to a person “duly authorised under the law” to produce and sell or distribute the product seems to indicate that parallel imports may include products produced under compulsory license. OECD countries have traditionally excluded such possibility, limiting parallel imports to products marketed abroad with the consent of the patent holder. The TRIPS Agreement is silent on this issue.

The three amendments to the Indian Patents Act, which have introduced a TRIPS-consistent patent regime in the country, were brought about in the backdrop of intense debates that were focused on the need to establish a balance between the rights of the patent holders and the interests of the public at large. These debates have emphasised the point that with the rights of the patent holders getting strengthened through Agreement on TRIPS there is an urgent need to ensure a balance through the introduction of more effective instruments so that the public interest concerns, as for example, access to medicines at affordable prices are addressed. Holding the key to the realisation of the objective of access to medicines was the existence of a viable pharmaceutical industry in

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<sup>51</sup> As amended by the Patents (Amendment) Act, 2005.

<sup>52</sup> Lok Sabha Secretariat (2005).

the country. It was therefore imperative that all available flexibilities in the framework provided by the Agreement on TRIPS were exploited fully so as to provide the space for the Indian pharmaceutical industry to expand.

Although the TRIPS-consistent Patents Act has been in operation for about a year now, there is growing evidence that its implementation would be “litigation-ridden”. This portends to the uncertain times that await pharmaceutical firms.

It may be argued however, while the flexibilities are in the nature of necessary conditions for the future prospects of the pharmaceutical industry in the post-TRIPS patent regime, they are not sufficient conditions. The determining factor, in our view, would be the manner in which domestic firms would be able to evolve strategies for meeting the challenges posed by the introduction of the TRIPS-consistent patent regime. The following Section analyses the performance of the Indian pharmaceutical industry for making an assessment of how the domestic firms are meet the post-TRIPS challenges.

### **3 Recent Performance of the Indian Pharmaceutical Industry**

The Indian pharmaceutical industry has evolved over three phases. The first was the period prior to 1970, when the industry was dominated by a small set of foreign owned and controlled firms<sup>53</sup>. The second phase, spanning the second half of 1970s to the early 1990s, was a period during which the industry experienced structural transformation through the growth of the Indian generic industry. Much of the credit for this development should be taken by the Patents Act of 1970. As mentioned in an earlier discussion, introduced two changes in the country’s patent regime viz. introduction of a process patent regime and shortening the term of pharmaceutical patents, both of which had considerable impact on the development of the pharmaceutical industry. In its third phase, i.e. since the beginning of the 1990s, the pharmaceutical industry has seen the rapid consolidation of the position of generic producers<sup>54</sup>.

The decade of the 1990s saw the strongest performance of the Indian pharmaceutical industry on several fronts. Not only did the industry improve its production performance seen in the previous decades, and that too by a significant margin, the industry turned into a net foreign exchange earner during the decade in question. The important feature of this performance was that it followed the change in the policy orientation of the Indian economy that took place in 1991. From the relatively inward looking policies in place till the end of the 1980s, the policy regime adopted in 1991 brought down the walls of protection behind which Indian industry had developed in the past. The biggest challenge

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<sup>53</sup>In India, a distinction was made between “foreign owned” and “foreign controlled” firms. “Foreign owned” firms were those in which non-residents had majority in the equity (voting) shares. The “foreign controlled” firms were identified by the Reserve Bank of India as those firms in which the equity (voting) shares were 26% or more.

<sup>54</sup> For a discussion on the evolution of the Indian pharmaceutical industry see Dhar and Rao (2002)

for Indian industry posed by the new regime arose from the need to adopt measures that would improve its competitive strength.

As regards its structure, the Indian pharmaceutical industry consists of a large private sector, which can be further divided into the large Indian private sector, affiliates of foreign firms in India<sup>55</sup>, and small scale units. The market structure of the Indian pharmaceutical industry can be characterized as “long tailed”, i.e. there are a small number of large firms and a large number of small firms<sup>56</sup>.

The decade of the 1990s was singularly important for it saw the Indian pharmaceutical industry perform strongly on all fronts. Total production of the industry expanded more than four-fold in value terms (in domestic currency). The dollar value of exports too had a similar increase. There was strong evidence that the Indian industry was getting increasingly outward oriented – the share of exports in total production almost doubled during the decade<sup>57</sup>.

The strong performance of the industry resulted from significant contributions made by the leading generic producers, particularly during the post-1995 phase. The most obvious of these is that the operations of the generic producers in India (which we shall henceforth refer to as the “Indian pharmaceutical firms”) have expanded far more strongly as compared to those that are the affiliates of foreign firms. This is evidenced by the fact that while in 1995, five of the top ten pharmaceutical firms (in terms of sales turnover) were foreign affiliates, in 2004 GlaxoSmithKline was the only foreign affiliate in the top ten list. What appears most striking is that this robust performance by the Indian pharmaceutical firms has come during a phase when they were facing an uncertain future, with the process patent regime being dismantled following India’s accession to the WTO.

The period between 1995 and 2004 has seen an all round consolidation of the leading firms in the Indian industry. The first indicator for analysing the performance of the pharmaceutical industry that we shall use is the net worth of the firms, which is a reflection of their respective market values. Table 1 below provides the details.

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<sup>55</sup> The foreign owned and controlled firms were forced to “Indianise” by diluting their foreign equity holding in the beginning of the 1970s. As a result, most of these firms became “foreign-controlled”, which, according to the Reserve Bank of India (India’s Central Bank), were firms having more than 25% foreign equity holding.

<sup>56</sup> “There are about 250 large units and about 8,000 small scale units in operation...” in the pharmaceutical industry, Government of India (2000)

<sup>57</sup> Dhar and Rao (2002)

**Table 1: Net Worth of Leading Indian Pharmaceutical Firms (US \$ million)**

| Firm Name                               | Dec-95 | Dec-97 | Dec-99 | Dec-00 | Dec-01 | Dec-02 | Dec-03 | Dec-04 |
|---|--------|--------|--------|--------|--------|--------|--------|--------|
| Ranbaxy Laboratories Ltd.               | 204.8  | 320.8  | 334.6  | 335.9  | 315.6  | 392.8  | 479.3  | 545.5  |
| Dr. Reddy's Laboratories Ltd.           | 75.7   | 77.0   | 81.0   | 88.0   | 100.4  | 303.3  | 373.4  | 445.5  |
| Cipla Ltd.                              | 26.6   | 74.0   | 107.2  | 130.2  | 156.2  | 184.4  | 219.0  | 272.9  |
| Sun Pharmaceutical Inds. Ltd.           | 29.6   | 47.7   | 73.5   | 84.2   | 101.9  | 112.3  | 143.9  | 187.1  |
| Aurobindo Pharma Ltd.                   | 9.8    | 13.4   | 29.6   | 50.7   | 60.6   | 75.6   | 110.2  | 164.6  |
| Wockhardt Ltd.                          | 0.0    | 152.5  | 151.8  | 60.3   | 72.4   | 77.4   | 97.8   | 135.1  |
| Cadila Healthcare Ltd.                  | 0.0    | 13.2   | 20.2   | 113.7  | 118.9  | 115.6  | 90.7   | 114.2  |
| Lupin Ltd.                              | 10.7   | 13.3   | 15.7   | 15.0   | 79.0   | 71.2   | 79.0   | 97.5   |
| Nicholas Piramal India Ltd.             | 63.2   | 82.2   | 73.4   | 85.5   | 89.8   | 52.5   | 78.3   | 96.7   |
| Orchid Chemicals & Pharmaceuticals Ltd. | 13.9   | 32.2   | 39.4   | 83.5   | 82.8   | 62.8   | 83.1   | 91.1   |

Source: CMIE, Prowess database

The Table indicates that most of the top ten firms of the industry saw steep increases in their net worth. Some of the larger firms, Dr Reddy's and Cipla, in particular, experienced very high rates of growth of net worth during the nine years for which data have been presented in the Table. In the mid-1990s, Ranbaxy was the largest Indian pharmaceutical producing firm by a considerable distance, but in 2004, while Dr Reddy's had grown to a comparable size, firms like Cipla were fast catching with the leaders.

Further evidence that the years 1995-2004 was a period of consolidation for the leading pharmaceutical firms can be had from the figures for total sales for the ten top firms (Table 2)

**Table 2: Total Sales Net Worth of Leading Indian Pharmaceutical Firms(US \$ million)**

| Firms                                   | Dec-95 | Dec-97 | Dec-99 | Dec-00 | Dec-01 | Dec-02 | Dec-03 | Dec-04 |
|---|--------|--------|--------|--------|--------|--------|--------|--------|
| Ranbaxy Laboratories Ltd.               | 252.7  | 326.3  | 448.6  | 457.8  | 517.1  | 725.6  | 876.7  | 930.4  |
| Cipla Ltd.                              | 95.1   | 127.5  | 148.7  | 178.2  | 233.0  | 293.7  | 325.0  | 447.3  |
| Dr. Reddy's Laboratories Ltd.           | 63.2   | 70.4   | 101.2  | 113.8  | 217.0  | 358.9  | 352.3  | 400.2  |
| Nicholas Piramal India Ltd.             | 49.6   | 137.6  | 105.0  | 113.1  | 125.8  | 200.3  | 237.2  | 313.5  |
| Aurobindo Pharma Ltd.                   | 27.5   | 62.5   | 130.8  | 172.1  | 219.0  | 217.7  | 246.5  | 291.9  |
| Lupin Ltd.                              | 18.8   | 25.8   | 26.2   | 15.3   | 199.0  | 202.0  | 225.6  | 260.6  |
| Cadila Healthcare Ltd.                  | N.A.   | 63.6   | 85.9   | 110.3  | 111.4  | 123.5  | 212.5  | 255.1  |
| Sun Pharmaceutical Inds. Ltd.           | 26.8   | 49.4   | 85.3   | 110.5  | 134.1  | 156.8  | 177.5  | 206.0  |
| Wockhardt Ltd.                          | N.A.   | 88.4   | 206.9  | 128.9  | 142.2  | 155.5  | 158.5  | 191.8  |
| Orchid Chemicals & Pharmaceuticals Ltd. | 14.3   | 54.6   | 79.5   | 83.0   | 81.3   | 89.2   | 112.2  | 155.2  |

Source: CMIE, Prowess database

The largest firm in the Indian pharmaceutical industry, viz. Ranbaxy, was fast approaching a billion US dollars in terms of sales turnover in 2004, after registering a four-fold increase for the period since 1995. It should be noted is that in 1995, Ranbaxy was the only firm that has sales turnover exceeding US \$ 100 million, but in 2004, no less than 16 Indian firms figured in this list.

Table 3 captures the profitability ratios of the leading firms in the Indian pharmaceutical industry. Most of the top ten firms, in terms of sales turnover, recorded double-digit profitability ratios for the past few years. Dr. Reddy's has been a consistent performer; the firm had consistently recorded double-digit profitability ratios for the entire period 1995-2004.

**Table 3: Profitability Ratios of Leading Indian Pharmaceutical Firms (Figs. in %)**

| Firm Name                               | Dec-95 | Dec-97 | Dec-99 | Dec-00 | Dec-01 | Dec-02 | Dec-03 | Dec-04 |
|---|--------|--------|--------|--------|--------|--------|--------|--------|
| Ranbaxy Laboratories Ltd.               | 11.4   | 13.1   | 8.3    | 6.7    | 8.3    | 18.7   | 19.0   | 12.9   |
| Cipla Ltd.                              | 11.1   | 19.6   | 22.0   | 20.2   | 20.5   | 20.3   | 18.4   | 18.5   |
| Dr. Reddy's Laboratories Ltd.           | 18.0   | 15.2   | 13.3   | 14.0   | 21.3   | 32.6   | 23.5   | 15.4   |
| Nicholas Piramal India Ltd.             | 12.0   | 6.1    | 9.6    | 8.3    | 11.7   | 10.3   | 13.7   | 13.3   |
| Aurobindo Pharma Ltd.                   | 7.0    | 8.1    | 11.4   | 14.3   | 11.4   | 9.9    | 13.8   | 14.5   |
| Lupin Ltd.                              | 13.5   | 17.8   | 18.4   | 4.6    | 13.7   | 16.7   | 13.7   | 18.9   |
| Cadila Healthcare Ltd.                  | N.A.   | 6.2    | 9.5    | 9.7    | 11.0   | 11.3   | 11.2   | 9.1    |
| Sun Pharmaceutical Inds. Ltd.           | 16.5   | 16.6   | 16.9   | 17.4   | 21.7   | 23.4   | 27.8   | 18.4   |
| Wockhardt Ltd.                          | N.A.   | 16.9   | 15.1   | 12.8   | 16.9   | 16.1   | 17.4   | 22.2   |
| Orchid Chemicals & Pharmaceuticals Ltd. | 12.3   | 18.1   | 13.1   | 9.5    | 13.4   | 7.0    | 8.1    | 8.2    |
| Ipcalaboratories Ltd.                   | 10.2   | 8.4    | 10.0   | 7.3    | 7.7    | 11.8   | 14.7   | 14.3   |

Source: CMIE, Prowess database

A noteworthy feature of the pharmaceutical industry is that the industry was the most profitable among all the leading sectors of the Indian industry. Interestingly, the profitability ratio of the pharmaceutical industry increased almost consistently through the period for which data are presented in Table 4. It needs to be mentioned here that the pharmaceutical industry had out-performed other sectors of the industry despite facing an additional dose of uncertainty arising from the changes in the patent regime, a point that was made in an earlier discussion.

**Table 4: Profitability of some of the major sectors in Indian Industry**

| Sectors                 | Dec-95 | Dec-97 | Dec-99 | Dec-00 | Dec-01 | Dec-02 | Dec-03 | Dec-04 |
|-------------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| Chemicals               | 5.8    | 4.8    | 4.8    | 4.2    | 3.5    | 4.4    | 5.8    | 6.3    |
| Food & beverages        | 4.8    | 4.1    | 4.9    | 4.8    | 5.1    | 4.2    | 3.6    | 5.2    |
| Machinery               | 5.5    | 3.7    | 3.5    | 2.6    | 1.5    | 2.7    | 1.7    | 3.1    |
| Textiles                | 5.6    | 0.6    | -1.9   | -1.0   | -2.4   | -2.9   | 0.9    | -0.4   |
| Transport equipment     | 5.8    | 7.3    | 3.1    | 3.3    | 1.0    | 3.3    | 5.0    | 6.3    |
| Drugs & pharmaceuticals | 8.8    | 7.5    | 6.6    | 7.5    | 10.0   | 12.4   | 11.3   | 13.4   |

Source: CMIE, Prowess database

The integration with the global economy, which for many sectors of the Indian economy appeared as a threat, was for the pharmaceutical industry, a wide window of opportunities. This was essentially because the leading firms of the industry were considerably more outward oriented as compared to those belonging to other industries. The trend towards enhancing the outward orientation of the industry had begun in the early 1990s, which went through a rapid consolidation in the subsequent years. This was particularly noticeable in case of the large firms in the industry. Table 5 shows that for the two largest firms, viz. Ranbaxy and Dr. Reddy's, exports in terms of value were more than one-half of their sales turnovers. For these firms, therefore, foreign markets were relatively more important than the domestic market and this gave them the impetus to improve their operating efficiencies

**Table 5: Ratio of Exports to Total Sales Turnover of the Leading Firms (Figs. in %)**

| Firm Name                               | Dec-95 | Dec-97 | Dec-99 | Dec-00 | Dec-01 | Dec-02 | Dec-03 | Dec-04 |
|---|--------|--------|--------|--------|--------|--------|--------|--------|
| Ranbaxy Laboratories Ltd.               | 37.4   | 43.9   | 42.3   | 38.0   | 44.2   | 55.0   | 57.7   | 56.2   |
| Cipla Ltd.                              | 10.4   | 13.8   | 19.1   | 18.6   | 25.0   | 35.5   | 36.4   | 42.2   |
| Dr. Reddy's Laboratories Ltd.           | 32.1   | 28.0   | 27.8   | 26.5   | 43.3   | 54.5   | 53.9   | 53.4   |
| Nicholas Piramal India Ltd.             | 5.9    | 8.6    | 1.3    | 0.9    | 0.5    | 1.0    | 3.7    | 6.8    |
| Aurobindo Pharma Ltd.                   | 29.2   | 40.8   | 39.2   | 49.3   | 54.5   | 46.9   | 47.3   | 47.9   |
| Lupin Ltd.                              | 0.0    | 0.2    | 0.0    | 18.2   | 25.5   | 32.2   | 37.8   | 47.5   |
| Cadila Healthcare Ltd.                  |        | 8.8    | 8.5    | 8.0    | 11.8   | 14.4   | 10.0   | 15.1   |
| Sun Pharmaceutical Inds. Ltd.           | 5.0    | 5.0    | 17.3   | 11.5   | 18.5   | 17.9   | 16.3   | 21.6   |
| Wockhardt Ltd.                          |        | 21.5   | 15.8   | 21.0   | 25.3   | 31.1   | 36.7   | 36.5   |
| Orchid Chemicals & Pharmaceuticals Ltd. | 95.9   | 94.3   | 87.7   | 80.9   | 85.7   | 83.2   | 83.2   | 74.9   |

Source: CMIE, Prowess database

This strong performance of the Indian pharmaceutical industry resulted from a number of its inherent advantages. It has been argued that Indian firms have lower costs – estimated to be one-eighth in R&D activities and one-fifth in manufacturing - as compared to the

Western firms<sup>58</sup>. The cost advantages are most pronounced in respect of lower fixed asset costs and labour costs, where the costs in India can be one-eighth of the cost in the US.

#### **4 The Technology Dimension**

A major factor driving the progress of the leading firms in the Indian pharmaceutical industry was their emphases on the technology. This section explores this dimension of the industry in detail.

The pharmaceutical industry can be divided into three product groupings, viz., bulk drugs, intermediates and formulations. While bulk drug production can be sustained over a long period only through sustained involvement in research and development (R&D) activities, formulations production can be carried out relatively low level technological sophistication.

A typology of the world's pharmaceutical industries was provided by Ballance et al<sup>59</sup>. They identified ten countries, all of which were developed, as countries having sophisticated pharmaceutical industry and a significant research base. Another group of seventeen countries were identified as countries having innovative capabilities. India was identified as once of the countries belonging to this group. The authors noted that while this group of countries were not active in discovering new chemical entities, they had the necessary technological capabilities to reverse engineer existing drugs. However, as we shall see in subsequent discussion, the Indian pharmaceutical industry has come a long way since the above-mentioned characterisation was made. The industry has taken definite strides towards development of innovative processes and discovery of new drugs.

During the past decade, however, the R&D profile of the Indian pharmaceutical industry has undergone major changes. The most obvious of these is the manifold increase in the spending on R&D that was witnessed, particularly since the beginning of the current decade. In 2004, R&D spending of the organised pharmaceutical industry as a whole was nearly US \$ 340 million, which was an increase of more than 300% from the level existing in 2000 (Table 6).

**Table 6: R&D Expenditures in Major Sectors Indian Industry (Figs. in US \$ million)**

| Sectors  | Dec-95 | Dec-97 | Dec-99 | Dec-00 | Dec-01 | Dec-02 | Dec-03 | Dec-04 |
|--|--------|--------|--------|--------|--------|--------|--------|--------|
| Chemicals:                                     | 110.6  | 168.9  | 184.4  | 187.6  | 222.4  | 278.8  | 306.1  | 447.9  |
| <i>Of which:</i><br>Drugs &<br>pharmaceuticals | 51.7   | 73.6   | 78.0   | 85.9   | 117.7  | 171.9  | 204.6  | 339.7  |
| Food & beverages                               | 9.1    | 9.1    | 11.4   | 8.9    | 11.0   | 12.6   | 15.2   | 22.4   |
| Machinery                                      | 85.8   | 122.6  | 98.5   | 102.9  | 108.0  | 109.8  | 111.4  | 153.8  |
| Textiles                                       | 8.1    | 85.0   | 7.8    | 8.1    | 5.8    | 7.6    | 8.0    | 6.9    |

Source: CMIE, Prowess database

<sup>58</sup> Grace (2004)

<sup>59</sup> Ballance et al (1992)

Table 6 shows that the R&D spending undertaken by the pharmaceutical industry during 1995-2004, has two key features, One, the level of spending was significantly higher than that recorded by other industry groups. And, two, the pharmaceutical industry was the only one among the leading industries to have consistently improved its R&D spending.

The increase in R&D intensity of the Indian pharmaceutical industry since 2000 is the other significant aspect. This is an indication that the pharmaceutical industry in India was allocating increasing amounts of its sales turnover towards R&D spending. Table 7 shows that R&D intensity of the industry went up by more than 150% since the beginning of the decade.

**Table 7: Ratio of R&D to Sales of Major Sectors of Indian Industry**

(Figs. in %)

| Sectors                 | Dec-95 | Dec-98 | Dec-99 | Dec-00 | Dec-01 | Dec-02 | Dec-03 | Dec-04 |
|-------------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| Chemicals               | 0.2    | 0.3    | 0.3    | 0.2    | 0.2    | 0.3    | 0.3    | 0.4    |
| Drugs & pharmaceuticals | 1.4    | 1.3    | 1.5    | 1.6    | 2.1    | 2.7    | 2.9    | 4.1    |
| Food & beverages        | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    |
| Machinery               | 0.6    | 0.7    | 0.6    | 0.6    | 0.6    | 0.6    | 0.7    | 0.8    |
| Textiles                | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    |

Source: CMIE, Prowess database

The average R&D intensity for the pharmaceutical industry understates the progress that is being made by the leading firms (Table 8). Since the year 2000, most of the major pharmaceutical firms in India started expending increasing shares of their sales turnover on their R&D budgets. The two largest among the Indian pharmaceutical firms, viz. Ranbaxy and Dr. Reddy's Laboratories showed the most impressive increase in their R&D intensities, with the latter spending more than 12% of their sales on R&D. In fact, R&D intensity of Dr. Reddy's Laboratories registered the sharpest increase among the leading firms in the Indian industry. Perhaps the more important dimension here is that some of the medium sized enterprises, like Glenmark Pharmaceutical and Torrent Pharmaceuticals are among the highest spenders on R&D. This indicates that the increase in R&D propensity of the Indian pharmaceutical industry is having a spread-effect.

**Table 8: Firms with highest R&D intensities (Figs. in %)**

| Company Name                  | Dec-95 | Dec-97 | Dec-99 | Dec-00 | Dec-01 | Dec-02 | Dec-03 | Dec-04 |
|-------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| Dr. Reddy's Laboratories Ltd. | 2.0    | 3.1    | 2.2    | 2.7    | 4.2    | 5.9    | 9.6    | 12.3   |
| Sun Pharmaceutical Inds. Ltd. | 4.0    | 4.0    | 2.7    | 3.9    | 4.0    | 4.5    | 7.7    | 11.4   |
| Glenmark Pharmaceuticals Ltd. |        | 0.3    | 3.6    | 3.6    | 12.0   | 4.6    | 9.1    | 9.7    |
| Ranbaxy Laboratories Ltd.     | 4.6    | 4.3    | 2.9    | 3.7    | 3.3    | 5.6    | 6.5    | 9.3    |
| Wockhardt Ltd.                |        | 8.5    | 4.2    | 7.2    | 6.2    | 6.2    | 7.9    | 7.9    |
| Torrent Pharmaceuticals Ltd.  | 2.7    | 8.2    | 9.6    | 0.0    | 5.3    | 5.1    | 7.4    | 7.8    |
| Cadila Healthcare Ltd.        |        | 1.0    | 3.5    | 4.5    | 7.9    | 7.1    | 3.7    | 7.5    |

Source: CMIE, Prowess database

The R&D intensities of the major firms in India look considerably better in 2004 when the figures are compared with those of the global pharmaceutical majors. Table 9 gives the R&D intensities of top ten pharmaceutical firms (in terms of sales) as recorded in 2004-05

**Table 9: R&D Intensities of Global Pharmaceutical Majors in 2004-05**

| Rank<br>(in terms of sales turnover) | Firm                       | R&D to Sales (%) |
|--------------------------------------|----------------------------|------------------|
| 1                                    | Pfizer Inc, USA            | 14.6             |
| 2                                    | GlaxoSmithKline, UK        | 13.9             |
| 3                                    | Sanofi-Aventis, France     | 15.6             |
| 4                                    | Johnson & Johnson, USA     | 11.0             |
| 5                                    | Roche, Switzerland         | 16.3             |
| 6                                    | Novartis AG, Switzerland   | 14.9             |
| 7                                    | Merck Inc, USA             | 17.5             |
| 8                                    | AstraZeneca, UK            | 17.7             |
| 9                                    | Eli Lilly and Company, USA | 19.4             |
| 10                                   | Bristol-Myers Squibb, USA  | 12.9             |

Source: UK Department of Trade and Industry, R&D Scoreboard 2005 ([http://www.innovation.gov.uk/rd\\_scoreboard/index.asp](http://www.innovation.gov.uk/rd_scoreboard/index.asp))

Tables 8 and 9 show that in 2004-05, R&D intensities of the largest firms in the global industry and the largest Indian firms are yet very divergent - the Indian firms are considerably behind the global firms having highest R&D intensities. But with leading firms in the Indian industry increasing their R&D activities in a consistent manner, the next few years could witness these firms close the existing gap in R&D intensities with the global firms.

## **4.1 R&D Activities of the Indian Pharmaceutical Industry**

Analysis of the R&D activities of Indian pharmaceutical firms requires examination of two dimensions. These are: (i) the organisation of R&D activities, and (ii) specific areas of involvement.

It is pertinent to note in this context that in recent years, R&D efforts of the industry have received support from the Government, which has initiated measures for supporting pharmaceutical R&D. This includes exploration of collaboration between the pharmaceutical firms and the large network of public sector research institutions. This dimension would be explored in the concluding part of this section.

### **4.1.1 Organisation of R&D Activities**

The leading firms in the Indian pharmaceutical industry have adopted a three-pronged strategy to strengthen its technological sinews. First, their in-house R&D activities have been beefed-up, which is evident not only from their increased R&D spending indicated above, as also the range of activities that the firms have been engaged in. Second, Indian firms have started entering into alliances with foreign firms. Although these alliances are focused essentially on product development, which would help the Indian firms expand their presence in the global market, there have also been R&D-based alliances, including contract research being undertaken by the firms in India.

### **4.1.2 Areas of R&D Spending**

The R&D structure built by the leading firms in the Indian pharmaceutical industry has four dimensions. These are: (i) development of generics, (ii) novel drug delivery systems (iii) development of new processes and (iv) new drug discovery and research. The following discussion provides the main features of R&D activities undertaken by the domestic firms.

#### **4.1.2.1 Development of Generics**

During the past few years, the global market for generics has been expanding at a substantially higher rate than the proprietary medicines. In 2005, for instance, the global pharmaceutical industry grew by almost 7%, with the ten major markets<sup>60</sup>, registering a growth of 5.7%, compared with 7.2% the previous year<sup>61</sup>. In contrast, 2005 sales of generics in the top eight markets (US, Canada, France, Germany, Italy, Spain, U.K. and Japan, and are expected to experience double-digit growth over the next five years. The expansion registered by the generic industry in 2005 was substantially higher than the projections made in 2004, which showed that the sales of generic medicines in the seven

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<sup>60</sup> Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, the UK and the US (Source: IMS Health)

<sup>61</sup> IMS Health Reports Global Pharmaceutical Market grew 7 percent in 2005, to \$602 billion, Mar 21, 2006.

largest markets (the US, Canada, Germany, France, Italy, Spain and the U.K.) would reach \$59.9 billion by 2008.

Perhaps the most significant driver for the expansion of the generic industry was the acceptance of its low priced products by the consumers. According to estimates provided by the Congressional Budget Office, US consumers saved \$ 8-10 billion on retail prescription drug purchases in 1994 by purchasing generic equivalents. It was further noted that “with patents set to expire within the next four years on brand-name drugs that have combined retail sales of almost \$20 billion, the already substantial savings are likely to increase dramatically”<sup>62</sup>. And, it is in this lucrative market for generic medicines that the leading Indian firms have established their presence.

The trigger for the development of the generics market in the US came in the form of legislative action initiated in the first half of the 1980s. The Drug Price Competition and Patent Restoration Act of 1984 (better known as “the Hatch-Waxman Act”) created opportunities for marketing of generics or the so-called abbreviated new drug applications (ANDAs)<sup>63</sup>. The Hatch-Waxman Act established the ANDA approval process, which allows lower-priced generic versions of previously approved innovator drugs to be brought into the market. The details of the approval processes provided under the “Hatch-Waxman Act” are provided in the Appendix.

Data obtained from the FDA show that the leading Indian firms have taken measured steps towards establishing themselves as important players in the ever-expanding market for generics in the US. It appears that these moves taken in the world’s largest market for drugs have enabled the Indian firms to extend their presence in markets in Europe, most notably in the UK.

Two sets of data indicate the extent to which Indian pharmaceutical firms have been seeking opportunities to market their products in the US. The first set of data pertains to the market approvals that the leading Indian pharmaceutical firms have received for their products in the US. The second set of data relates to the “Drug Master Files”. A Drug Master File (DMF) is a package of proprietary information that is voluntarily filed by a company with the FDA. The information contained in a DMF is kept confidential until such time as an FDA reviewer requests a review of the DMF. This is done only by FDA reviewers in conjunction with their review of a specific Investigational New Drug Application (IND), New Drug Application (NDA), Abbreviated New Drug Application (ANDA), Biologics License Application (BLA) or for an Active Pharmaceutical

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<sup>62</sup> Federal Trade Commission (2002).

<sup>63</sup> 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). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy, volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.

Ingredient (API). The DMFs can therefore be seen as an expression of interest that firms that have filed them have in obtaining marketing approval in the US.

Data on market approvals in the US provided by the FDA show that seven Indian firms have obtained approvals for their product thus far. Year-wise approvals obtained by the top 5 firms are provided in Table 10<sup>64</sup>.

**Table 10: Market Approvals obtained by the Leading Indian Firms in the US**

| <b>Firms</b>                 | <b>Before 2000</b> | <b>2000</b> | <b>2001</b> | <b>2002</b> | <b>2003</b> | <b>2004</b> | <b>2005</b> | <b>Total</b> |
|------------------------------|--------------------|-------------|-------------|-------------|-------------|-------------|-------------|--------------|
| Ranbaxy Laboratories Ltd*    | 24                 | 17          | 7           | 27          | 39          | 34          | 26          | 174          |
| Dr Reddy's Laboratories Ltd* | 1                  | 3           | 11          | 5           | 5           | 11          | 8           | 44           |
| Lupin Ltd                    | 0                  | 0           | 0           | 0           | 9           | 1           | 14          | 24           |
| Aurobindo Pharma Ltd         | 0                  | 0           | 0           | 0           | 0           | 13          | 7           | 20           |
| Wockhardt Ltd*               | 7                  | 4           | 2           | 0           | 4           | 0           | 5           | 22           |

\* Includes approvals taken by the firms that are its subsidiaries

Source: US FDA Orange Book

As can be seen from the Table 10 an overwhelming proportion of the approvals obtained by the Indian firms were in the post-2000 period. For instance, Ranbaxy, which has the largest number of approvals among the Indian firms, had only 24 approvals prior to 2000. But in the following six years, the firm had obtained approvals for another 150 drugs.

An interesting aspect of the FDA approvals obtained by Ranbaxy and Dr. Reddy's Laboratories, the two largest firms in terms of number of approvals, is that most of their approved drugs are prescription drugs<sup>65</sup>. In case of Ranbaxy, only 6 of the 174 approved drugs are OTC (over-the-counter) drugs, while for Dr. Reddy's, 4 of their 44 FDA approved drugs belong to the OTC category.

Since 2002, both Ranbaxy and Dr. Reddy's have taken steps towards registering themselves as the first movers in the generics' for a number of drugs. Data obtained from the FDA shows that while Ranbaxy has been able to obtain approvals for 22 drugs as the "first-time generics" between 2002 and 2005, Dr. Reddy's has been able to obtain similar approvals for 8 drugs.

A significant recent development for the Indian firms is their entry in the market for anti-retroviral (ARV) drugs in the US. Two firms, viz. Ranbaxy and Aurobindo Pharma, have been able to obtain tentative or full approval from the US Department of Health and Human Services (HHS) and the FDA for five ARV drugs during 2004-05. These drugs were approved as a part of the Emergency Plan for AIDS Relief<sup>66</sup> that President George

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<sup>64</sup> The two remaining firms are Sun Pharmaceuticals and Glenmark Pharmaceuticals.

<sup>65</sup> Approvals granted by the FDA are for either prescription or the OTC (over-the-counter) drugs.

<sup>66</sup> Better known as "President's Emergency Plan for AIDS Relief", or PEPFAR.

Bush had announced in 2003 for bringing low-cost, high-quality anti-retroviral therapy (ART) to the patients. The Indian firms had also marked their significant presence in the implementation of the Global Fund to Fight AIDS, Tuberculosis and Malaria that was established in 2002. The details in this regard are given in the following section

The second indicator of the increased interest of the Indian pharmaceutical industry in the US market was sharp increase in the filings of Drug Master Files (DMFs) in recent years. The database maintained by the FDA provides an “active list” of “Type II DMFs” by pharmaceutical firms that supply drug substances, drug products, intermediates, and material used in their manufacture<sup>67</sup>. While in the overall list of “active Type II DMFs”, Indian pharmaceutical firms have a share of almost 13%, during a more recent period viz., 2000-05, their share had increased to 22%. Table 11 provides a list of firms from the Indian pharmaceutical industry that were most active in “active Type II DMFs” filings.

**Table 11: DMF Filings by the top 10 firms in the Indian Pharmaceutical industry**

| Firms                                    | No of DMF Filings |
|--|-------------------|
| Dr Reddy's Laboratories Ltd              | 63                |
| Cipla Ltd                                | 59                |
| Matrix Laboratories Ltd.                 | 53                |
| Aurobindo Pharma Ltd                     | 48                |
| Ranbaxy Laboratories Ltd                 | 41                |
| Cadila Healthcare Limited                | 37                |
| Sun Pharmaceuticals Inds Ltd             | 34                |
| Lupin Ltd                                | 25                |
| Orchid Chemicals and Pharmaceuticals Ltd | 22                |
| Wockhardt Ltd                            | 18                |

Source: US FDA

The above discussion indicates quite cogently that the firms from the Indian pharmaceutical industry have been improving their presence in the market for generics in the US. The number of approvals, including approvals as “first time generics”, that some of the leading firms in the industry have obtained particularly since the beginning of the current decade is a testimony of this fact. There has, however, been yet another dimension of the dynamism that the Indian firms have shown in the US markets lately and this relates to the challenges they have mounted on the patent holders while seeking approval for their generic products.

In an earlier discussion, we had indicated the market for generics in the US was given the initial boost by the Hatch-Waxman Act of 1984. The Act requires that an abbreviated new drug application (ANDA) must include a patent certification (better known as

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<sup>67</sup> DMFs can be of four types: Type I pertains to manufacturing site, facilities, operating procedures, and personnel (this was discontinued in the year 2000); Type II relate to drug substances, drug substance intermediates, and material used in their preparation, or drug product; Type III concern packaging material; Type IV relate to excipient, colorant, flavour, essence, or material used in their preparation; and Type V relate to FDA accepted reference information.

paragraph I-IV certification)<sup>68</sup>. While paragraphs I-III applications can be made only after the patent has expired or with the consent of the patent holder, Paragraph IV allows the generic manufacturer to either challenge the validity of applicable patents or certify that the generic equivalent product will not infringe any patent held by the pioneer drug company. If the generic producer is able to obtain approval from the FDA on a “paragraph IV” application, it can get 180-day market exclusivity for its product. The implication of this “market exclusivity” is that during the “exclusivity” period, other generic manufacturers are denied entry into the market. However, if the producer of the patented drug files an objection against the move by the generic manufacturer to obtain a “paragraph IV” approval, the former can obtain a 30-month stay on the decision allowing the latter to operate in the market. In a study conducted by the Federal Trade Commission (FTC), it was pointed out that the “paragraph IV” provisions are biased against the interests of the generic producers and that changes need to be brought about. Based on the recommendations of the FTC, some amendments to the “paragraph IV” provisions have been introduced.

There is no doubt that “paragraph IV” route for obtaining market approvals for their products is quite attractive for the generic manufacturers because the 180-day market exclusivity provides them an opportunity to leap-frog over the competing firms in what is an extremely competitive market. But then, there is a risk of losing out on the entry into the market altogether since the owner of the patent which has been challenged, can obtain a 30-month stay. From the available evidence, it seems that the two leading Indian firms, viz. Ranbaxy and Dr. Reddy’s have decided to take the risks of using the “paragraph IV” option.

The impetus for Ranbaxy’s paragraph IV challenges was provided by the success that it had registered while contesting the patent infringement suit brought by GlaxoSmithKline against Ranbaxy’s Cefuroxime Axetil, a generic version of GlaxoSmithKline’s antibiotic Ceftin. GlaxoSmithKline filed the suit in the US District Court of New Jersey in October 2000, and the court issued a preliminary injunction which prevented Ranbaxy from marketing its generic version. In 2001, however, Ranbaxy commercially launched its product after the United States Court of Appeals for the Federal Circuit vacated the preliminary injunction. After a full trial, the district court ruled that Ranbaxy’s product did not infringe GlaxoSmithKline’s patent and that Ranbaxy was not required to pay any damages.

More recently, Ranbaxy has had yet another success as it could enter into an agreement with Cephalon, Inc. to settle their pending patent infringement dispute in the US related to Provigil (Modafinil) Tablets. According to the terms of the agreement, Cephalon granted Ranbaxy a non-exclusive royalty-bearing licence to market and sell a generic version of Provigil in the US, which would become effective in October 2011 but no later than 2012. An earlier entry by Ranbaxy could occur based upon the entry of another generic version of Provigil. In addition, the two firms also agreed to a series of business arrangements related to Modafinil. Cephalon also agreed to enter into certain

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<sup>68</sup> For details see Appendix

arrangements with Ranbaxy related to the supply of active pharmaceutical ingredient of Modafinil.

Alongside the above-mentioned successes, Ranbaxy has had to face a number of failures. The most recent case was the one involving Pfizer's blockbuster blood pressure drug, Accupril. In response to the suit brought by the patent owner viz. Pfizer and Warner Lambert Co., the Court of Appeals for the Federal Circuit ruled that Ranbaxy's generic version of the drug violated the patent. What implications this case would have on the pending paragraph IV challenges of Ranbaxy would be seen with interest<sup>69</sup>.

Although the paragraph IV challenges made by Dr Reddy's make up for a longer list as compared to that of Ranbaxy's, the former has not yet been successful in defending its generics against suits brought by the patent owners. Some of the major firms against which Dr. Reddy's had made paragraph IV challenges include Pfizer, Novartis, GlaxoSmithKline and Eli Lilly.

The generic drug manufactures from India have also started establishing their presence in Europe, and in particular the UK. Data obtained from the Medicines and Healthcare Products Regulatory Agency (MHRA) for the period 2001-2005 confirms this fact. Here again, the two leading firms, Ranbaxy and Dr Reddy's, have led the way and they have been joined by three other firms, viz. Aurobindo Pharma, Nicholas Primal and Orchid Healthcare. Ranbaxy obtained the largest number of approvals (204), followed by Dr. Reddy's Laboratories (57). Table 12 gives the year-wise approvals obtained by the top three Indian firms to have obtained approvals from MHRA.

**Table 12: Year-wise Approvals Obtained from MHRA by the top-3 Firms (2001-2005)**

| <b>Firms</b>                | <b>2001</b> | <b>2002</b> | <b>2003</b> | <b>2004</b> | <b>2005</b> | <b>Total</b> |
|-----------------------------|-------------|-------------|-------------|-------------|-------------|--------------|
| Ranbaxy Laboratories Ltd    | 62          | 24          | 32          | 65          | 21          | 204          |
| Dr Reddy's Laboratories Ltd | ...         | 7           | 13          | 20          | 17          | 57           |
| Aurobindo Pharma Ltd        | ...         | ...         | ...         | 2           | 17          | 19           |

Source: UK, Department of Health, Medicine and Healthcare Products Regulatory Agency

The above discussion points to the increasing presence of the leading firms from the Indian pharmaceutical industry in some of the larger markets for drugs in the world. Interestingly, the increase in the market penetration by these firms has taken place since the beginning of the current decade. This implies that the consolidation of the operations of the leading pharmaceutical firms seen during the past decade had a key role to play in increasing their presence in the global markets.

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<sup>69</sup> The pending paragraph IV challenges of Ranbaxy include: (i) AstraZeneca patents on the ulcer treatment drug Nixium (Esomeprazole Magnesium), (ii) GlaxoSmithKline patents on the antiviral drug Valtrex (Valacyclovir HCl), (iii) Takeda Chemical Industry patents on anti-diabetic drug, Actos (Pioglitazone HCl) and (iv) Wyeth and Scherer and Cardinal Health patents on cold and sinus drug Advil (Ibuprofen and pseudo-ephedrine).

It would appear that seeking global markets is only one aspect of the strategy adopted by the leading Indian firms. The other aspect of the strategy is to deepen the R&D activities in order that the firms can benefit from dynamic efficiencies. The R&D activities were focused on two areas. The first is the area of Novel Drug Delivery Systems, an activity in which the leading Indian pharmaceutical firm, viz., Ranbaxy, has experienced landmark successes. The second area is the production of innovative drugs, i.e., drugs on which the firms have sought patent protection, especially in some of the developed countries.

#### **4.1.2.2 Novel Drug Delivery Systems**

Novel drug delivery systems (NDDS) have been the focus of activities of most leading firms in the Indian pharmaceutical industry. Developing a new drug delivery system is far simpler in terms of the costs incurred and the time expended, besides, of course the degree of expertise required. NDDS of an existing drug could be developed in 3-4 years with an investment of \$20-50 million<sup>70</sup>.

Regulatory requirements in case of a drug with NDDS would involve establishing its bioequivalence with the 'normal' brand. This, in simple terms, means that the drug in its new mode of delivery should provide similar concentrations in the blood, as would the conventional drug. Several Indian firms are working towards this end – JB Chemicals, Cadila Healthcare, Zydus Cadila, Morepen Laboratories, Neuland Laboratories and Aurobindo.

In the area of NDDS, Ranbaxy recorded the most noteworthy success. The firm was able to develop an improved version of one the new generation antibiotics, viz. ciprofloxacin, which was developed by Bayer AG and was under patent protection until 2003. Ranbaxy Laboratories was able to produce a once-a-day formulation instead of the multiple-dose a day therapy promised by the Bayer formulation. The Ranbaxy formulation assured better patient-compliance and was hence, considered to be a major step forward. Bayer recognised the improvement and entered into a licensing agreement with Ranbaxy for its version of ciprofloxacin. Under the agreement, Ranbaxy Laboratories received US\$ 65 million from Bayer over a four-year period, with an initial payment of US \$ 10 million. The agreement allowed Bayer AG to have the worldwide marketing rights over ciprofloxacin, except in India and the CIS countries where Ranbaxy Laboratories had the marketing rights.

In 2001, significant progress was made by the company towards developing platform technologies and products in the area of Oral-Controlled Release system. Ranbaxy initiated the process of clinical development of its once-a-day formulations of Ofloxacin by filing an IND application with the US FDA in late 2001.

The current global market for products with NDDS is estimated to be about \$ 20-22 billion. Some estimates have indicated that by 2009, the market for NDDS in the US will be worth \$91 billion. The US drug delivery industry is transforming ordinary drugs into better drugs optimised for a broad range of applications. Drug delivery is helping to

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<sup>70</sup> Quoted by industry sources.

expand other pharmaceutical industry sub-sectors such as biotechnology drugs, generic drugs, specialty pharmaceuticals and more. Major pharmaceutical firms are using the technology to extend their drug product life cycles. That the Indian firms have shown considerable promise in this rapidly expanding segment of the industry augurs well for their future prospects.

#### 4.1.2.3 Development of Innovative Drugs

The propensity of the leading firms in the Indian pharmaceutical industry to increase their R&D intensity is possibly best reflected in their drive to obtain patents not only in India, but in several developed countries as well. As with other activities described in the foregoing, patenting activities of top 10 spenders on R&D have improved consistently since 1999-2000. The best among the performers is the top spender on R&D, viz. Ranbaxy. Global patent filings of the firm increased from a mere 14 during 1999 to more than 250 during 2005. Besides Ranbaxy, Cipla and Dr. Reddy's have also contributed to the increase in the patent applications filed by the leading Indian firms, which in 2005 had increased to nearly 500. Table 13 gives the details

**Table 13: Worldwide Patent Filings of leading Indian pharmaceutical firms**

(Number of applications)

| <b>Firms</b>                            | <b>1999</b> | <b>2000</b> | <b>2001</b> | <b>2002</b> | <b>2003</b> | <b>2004</b> | <b>2005</b> |
|---|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Ranbaxy Laboratories Ltd.               | 14          | 31          | 53          | 69          | 127         | 208         | 259         |
| Cipla Ltd.                              | 0           | 5           | 15          | 12          | 21          | 38          | 56          |
| Dr. Reddy's Laboratories Ltd.           | 3           | 5           | 5           | 25          | 69          | 77          | 49          |
| Lupin Ltd.                              | 12          | 9           | 8           | 8           | 12          | 25          | 32          |
| Cadila Healthcare Ltd.                  | 1           | 2           | 3           | 9           | 14          | 19          | 29          |
| Wockhardt Ltd.                          | 2           | 0           | 3           | 14          | 14          | 18          | 25          |
| Orchid Chemicals & Pharmaceuticals Ltd. | 0           | 1           | 1           | 7           | 31          | 48          | 25          |
| Nicholas Piramal India Ltd.             | 0           | 0           | 1           | 7           | 4           | 8           | 11          |
| Sun Pharmaceutical Inds. Ltd.           | 1           | 0           | 2           | 0           | 2           | 8           | 4           |
| Aurobindo Pharma Ltd.                   | 0           | 0           | 0           | 5           | 6           | 9           | 2           |
| <b>Total</b>                            | <b>33</b>   | <b>53</b>   | <b>91</b>   | <b>156</b>  | <b>300</b>  | <b>458</b>  | <b>492</b>  |

Source: EPO

The top three firms in terms of the patent applications made have increasing tendency to seek international patents. This is evidenced by the fact that almost 50% of the applications made by both Ranbaxy and Cipla have been made through the PCT route<sup>71</sup>.

<sup>71</sup> The PCT, or Patent Cooperation Treaty, which operates under the aegis of the World Intellectual Property Organization (WIPO), allows patent applicants to use a single application to seek patents in a number of countries. In her/his application for a patent submitted in a designated PCT Office, which exists in every PCT Member State, the applicant can indicate the countries in which she/he is seeking patent rights. Within a period of 18 months, the PCT process informs the applicant if the invention she/he is seeking protection for, is patentable in the countries listed in the application.

Dr Reddy's, however, shows a different tendency, with the share of PCT applications in the total patent applications falling during 2004 and 2005.

**Table 14: PCT applications made by the top three firms in terms of patent applications**

(Number of applications)

| <b>Firms</b>                  | <b>1999</b> | <b>2000</b> | <b>2001</b> | <b>2002</b> | <b>2003</b> | <b>2004</b> | <b>2005</b> |
|-------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Ranbaxy Laboratories Ltd.     | 2           | 15          | 21          | 27          | 47          | 105         | 129         |
| Cipla Ltd.                    | 0           | 3           | 6           | 4           | 8           | 22          | 25          |
| Dr. Reddy's Laboratories Ltd. | 6           | 8           | 4           | 20          | 38          | 15          | 17          |

Source: EPO

As regards their preferred destinations for seeking patent rights the three top firms have shown a marked variation. For Ranbaxy, member states of the EPO<sup>72</sup> seem to be the preferred destination with the firm having applied for 73 patents during 2005. For Dr. Reddy's on the other hand, the US has been the major area of interest with the firm having made patent 31 applications during 2005, which is far in excess of the applications it has made using the PCT route. In contrast, Cipla has applied for patents in countries other than in the US or EPO member states.

It may however be argued that the penchant for obtaining patent rights that the leading Indian firms have shown during the past few years could have longer term implications for access to medicines at affordable prices in India. Many observers are of the view that these firms have benefited from the lax patenting standards that been used by the patent offices in several developed countries, most notably the US Patent and Trademark Office (USPTO). It is a well-documented fact that the patenting standards adopted by the USPTO have their basis the severe constraint it faces in terms of resources to examine the increasing number of patent applications that it receives annually in a proper manner. Consequently, "questionable patents" or patents of "poor quality" have been granted by the USPTO<sup>73</sup>. Examples of patents of "questionable quality" granted in the area of pharmaceuticals would be those that are granted for formulations or for new use of a known substance, which may be treated as incrementally modified drugs (IMDs)<sup>74</sup>. The

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<sup>72</sup> The EPO has membership of 31 states, which includes all EU Member States except Malta. Other members of the EPO are Bulgaria, Iceland, Liechtenstein, Romania, Switzerland and Turkey.

<sup>73</sup> It has been argued that if the USPTO had more examiners, made a greater effort to keep experienced examiners, and gave patent examiners more time to spend on their initial examination, the PTO would issue fewer questionable patents. This comment on the working of the USPTO has been made by the Federal Trade Commission in its Report. See Federal Trade Commission (2003). See also Blumenthal (2006).

<sup>74</sup> This characterisation of formulations and new-use patents are patents of "questionable quality" has been made in the amendment to India's Patents Act, 1970. The Indian policy makers have accepted the argument that patents are granted for inventions and that patents on formulations and new-use of known substances do not merit a 20-year patent protection since these products do not represent substantial effort on the part of the innovator. But while mere formulations or new-use of known substances have been excluded from

quality of patent on IMDs can be best judged from the comment made by FDA that in a vast majority of cases IMDs “do not provide significant improvement over currently marketed therapies”<sup>75</sup>.

The increasing evidence relating to the grant of patents in the US, which are in the nature of incremental innovation, have arisen because the strong economic incentives that they bring with them have driven the firms towards IMDs. The lawmakers in the country, mindful of the above-mentioned adverse implications of the functioning of the patent system in the area of pharmaceuticals, tried to provide an alternative route for accessing drugs at affordable prices by promoting the generic industry. In an earlier discussion, we had indicated that the Hatch-Waxman Act was adopted in 1984, which allowed the space to the generic drug manufacturers to challenge the patent holders by seeking market approval using the paragraph IV route, which would have given them 180-day market exclusivity. In other words, no other generic drug manufacturer would be allowed to operate in the market once approval under paragraph IV was obtained.

But the experience of the Indian pharmaceutical firms has shown that the paragraph IV option has not proved very profitable since the patent holders have been able to block the entry of the generic producers by obtaining a 30-month stay that they are allowed under the Hatch-Waxman Act<sup>76</sup>. For the generic drug manufacturers seeking market exclusivity for their product, which may well be an IMD, the option could then be to obtain a patent. That generic manufacturers are inclined to take patents for their NDDS and this evidenced by the fact that Ranbaxy has obtained two patents on its most successful NDDS involving ciprofloxacin<sup>77</sup>. As stated earlier, Ranbaxy had licensed the ciprofloxacin NDDS to Bayer AG, the owner of the patent on the product, even before the expiry of the patent.

With several of the leading Indian firms having acquired significant expertise in developing the generics, which are essentially in the nature of IMDs, it is not surprising that alliance building efforts involving some of the major pharmaceutical firms in the global market are being witnessed in India. Two forms of alliances are being witnessed in India. The first involves collaboration between the foreign and the domestic firm in India. The second, and a more recent, but perhaps strategically more significant in the longer term, is the increasing evidence of Indian firms making acquisitions in the foreign markets. The following section elaborates this phenomenon.

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the ambit of patenting, there remains a grey area in respect of patenting of pharmaceuticals in India that could be influenced by the patenting standards set by the patent offices in the developed countries in general and the USPTO in particular.

<sup>75</sup> This point was made in detail an earlier discussion.

<sup>76</sup> Some amendments have been introduced in the provisions governing paragraph IV, which essentially limits the application of the 30-month stay. For details see Annex.

<sup>77</sup> The first of these patents (Pat No. 6261601) was obtained in 2001 and the second (Pat No. 6960356) in 2005.

### **4.1.3 Alliance Building Efforts**

The first significant of these alliances between Indian and foreign firms in the area of pharmaceuticals was the one involving Ranbaxy. This was an interest case for it involved the first commercially viable process that came out of the Ranbaxy R&D stable involving Cefaclor, a cephalosporin antibiotic.

Although the initial forays of Ranbaxy Laboratories into research and development (R&D) activities began in the late 1970s, it was not until the late 1980s that the firm had made some progress in this area through the development of a novel process for Cefaclor. Patent for Cefaclor, was owned by Eli Lilly obtained in 1979. This antibiotic was one of the best selling drugs in 1980s. Ranbaxy started work on developing a new seven-stage process for the production of Cefaclor in 1989. After spending nearly Rs. 20 million on a three-year project, Ranbaxy had emerged as the only other manufacturer of Cefaclor besides the patent holder, Eli Lilly. Not only did Ranbaxy produce the product successfully; it also managed to obtain high yields from its process. In 1993, Eli Lilly and Ranbaxy Laboratories agreed to set up two joint ventures in India. One was to conduct research in India and the other was to market Eli Lilly's products in the South Asian market.

What started as exceptional collaborative venture more than a decade and a half back has now become the most happening event in the Indian pharmaceutical industry. Not only are the leading firms in the Indian industry involved in R&D collaborations with some of the global pharmaceutical majors, their exertions have prompted smaller enterprises to enter into a variety of collaborative ventures with foreign enterprises. These collaborations have taken two principal forms. The first involves contract research arrangements, the second, contract manufacturing and outsourcing arrangements.

Contract research arrangements have included activities related to product development as well. One of the critical components in this regard is clinical trials. Clinical trials in India are considered to be cheaper and faster than those in developed markets. Available estimates indicate that in India, contract research organisations can hire the required personnel at less than a third of the wages prevailing in most developed countries. Besides, the Indian population provides a vast diversity in terms of ethnicity as well as the disease profile. Because of these advantages, overall clinical development costs in India are estimated to be 40–60% lower than those in most developed countries<sup>78</sup>.

Among the successful cases of product development through contract research that has been recorded thus far, two cases involving Ranbaxy and Dr Reddy's are the most interesting. In March 2003, Ranbaxy successfully challenged GlaxoSmithKline's patent on Cefitin, but, soon afterwards, GlaxoSmithKline hired Ranbaxy to research on molecules that could become the building blocks for drugs. According to the agreement,

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<sup>78</sup> Grace (2004). The objective of preclinical studies is to come up with a molecule that is effective against the disease vector and safe in animal testing. This is the Investigational New Drug (IND) stage. This stage of investigation may take anywhere between 3 to 5 years and cost between \$100-150 million overseas or about Rs.40-60 crore in India.

GlaxoSmithKline assumed exclusive commercialisation responsibilities worldwide, while Ranbaxy would have the rights over Indian markets (although Ranbaxy could co-promote in the US and the EU, with permission from its collaborator). Similarly, Novartis is working with Dr Reddy's in various R&D areas, despite an ongoing lawsuit over a generic version of Novartis' antifungal cream Lamisil. Some of the more recent contract research arrangements are included in Box 4.

Contract manufacturing has emerged as a major growth area in the pharmaceuticals sector. The Boston Consulting Group has estimated that the contract manufacturing market for global firms in India would touch \$900 million by 2010. Industry estimates suggest that the Indian firms bagged manufacturing contracts worth \$75 million in 2004. Although most of the firms active in this area belong to the group of the smaller and emerging firms, there have been several large firms that have also entered into the fray. Thus, the mid-sized firms in the industry, including Dishman Pharma, Divis Laboratories and Matrix Laboratories, have been undertaking contract jobs for global pharmaceutical majors along with their larger counterparts firms like Orchid Pharmaceuticals. Top global firms like Pfizer, Merck, GSK, Sanofi-Aventis, Novartis and Teva etc. are largely depending on Indian firms for many of their Active Pharmaceutical Ingredient (APIs) and intermediates<sup>79</sup>.

The trends observed in the collaborations between the foreign and the India firms in the Indian pharmaceutical industry do portend to a strengthening of the industry in the ensuing years. While the larger firms would be able to effectively compete with the global players, now that they have are establishing partnerships in the area of product development, the smaller firms would be able to improve their bottom lines by becoming dedicated suppliers to the global pharmaceutical majors. This could indeed provide sustenance to the Indian pharmaceutical industry in the long term.

During the past couple of years, yet another dimension has been added to the activities of the Indian pharmaceutical firms. Several of the firms have been involved in the acquisition of firms based in the developed and some of the more advanced among the developing countries. Annex Table 2 provides a non-exhaustive list of acquisitions that have taken place since 2004. It may be noted from Annex 2 foreign acquisitions by the Indian firms have not been restricted to only the top firms. Several of the mid-sized firms like Glenmark Pharma, have been among the firms that have been more active in the acquiring firms.

Coming on back some impressive performance on the export front, this development may be termed as "trade-led investment", which has until now been conceptualised only in the context of the FTAs<sup>80</sup>. And while India is actively engaged in FTA negotiations with a number of its trading partners, including the EU, the ASEAN and the MERCOSUR members, the lead taken by the Indian pharmaceutical firms to enhance trade and investment possibilities in the industry could provide useful guidance for the negotiating process.

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<sup>79</sup> FICCI (2005).

<sup>80</sup> UNCTAD (2003), Annexes,.

**Box 4: Collaborative Ventures Involving Foreign and Indian Pharmaceutical Firms**

1. Matrix Laboratories Ltd. signed a collaborative agreement for drug discovery with Japan's aRigen Inc. The agreement outlines a multi-year joint drug development program whereby the company would prepare compounds to determine the lead compound and supply samples to aRigen.
2. Themis Medicare Ltd signed a long-term agreement with Schering-Plough Animal Health Corp. (SPAH), for a new drug delivery system. Themis would transfer all ownership rights, title and interests, patent rights and formulations to the worldwide animal health business of Schering-Plough Corp.
3. Panacea Biotec Ltd entered into a tie-up with U.K.-based Cambridge Biostability Ltd for manufacturing of vaccines using the "stable liquid technology".
4. Orchid Chemicals and Pharmaceuticals entered into a seven-year Master Research and Development agreement with Pfizer International LLC. Under this agreement, Orchid will provide research and development services to Pfizer's Animal Health business
5. Dr Reddy's teamed up with the UK's Argenta Discovery to jointly develop a novel approach to the treatment of chronic obstructive pulmonary disease
6. Dr Reddy's Laboratories entered into a co-development and commercialisation agreement with the Denmark-based Rheoscience A/S for joint development and commercialisation of Balaglitazone, a molecule for the treatment of type-2 diabetes.
7. Dr Reddy's licensed two anti-diabetic compounds to Novo Nordisk and one to Novartis between 1997 and 2001.
8. Ranbaxy licensed uroselective  $\alpha$ -blocker to Shwarz Pharma AG
9. Torrent sold first right of refusal for an advanced glycosylation end (AGE) breaker compound being developed primarily for hypertension to Novartis
10. Glenmark licensed a PDE-4 compound for asthma and COPD to Forest Labs.

**4.2 Governmental measures for Promoting Pharmaceutical R&D**

Government's role in promoting pharmaceutical R&D has been two-fold. One, providing incentives to the pharmaceutical industry for increasing R&D spending, and, two, facilitating collaboration between the private sector and the large network of publicly funded research institutions, in particular, those functioning under the Council for Scientific and Industrial Research (CSIR).

#### **4.2.1.1 Incentives for Increasing R&D Spending**

The Government has provided incentives to the pharmaceutical firms to increase spending on R&D principally in two forms. In the first place, products of the firms that have been more actively involved in R&D activities were exempted from the price control mechanism. Secondly, fiscal instruments have been used to provide incentives for R&D spending.

The pharmaceutical industry in India had been subjected to rigorous price controls since 1970 through the adoption of the Drugs Price Control Order or DPCO. The DPCO was aimed at fulfilling two objectives. The first and more obvious objective was to ensure that drugs were available at reasonable prices in India. The second was to create an incentive structure for domestic producers to produce new formulations and to use, as active ingredients, new drugs that were products of original research in India<sup>81</sup>. However, since the late 1980s, the focus of the Drug Policy adopted by the Government was more on providing market-based incentives to the Indian pharmaceutical industry.

Accordingly, the number of drugs under price control was reduced. Some of the criteria that were used to exclude drugs from being covered by the DPCO were as under:

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

The second dimension of Government's incentive for firms engaging in R&D activities was the tax breaks that firms could enjoy. Under the existing laws, pharmaceutical (and biotechnology) firms having in-house R&D facilities can benefit from a weighted deduction of 150% on any expenditure on scientific research (excluding cost of land or building) until March 31, 2007. And, R&D units can enjoy exemption from income tax for the same period. Furthermore, any company carrying on scientific R&D is allowed 100% deduction on profits for a period of 10 years if it is approved by the Ministry of Science and Technology before April 1, 2007.

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<sup>81</sup> Dhar Rao (2002).

For several years, the industry has been arguing for extending the fiscal benefits that the Government has been providing. The main argument of the industry has been that results of R&D efforts can be realised only after a considerable lag and therefore it would be appropriate to extend the tax exemptions and other concessions that the Government provides at present by another 10-years<sup>82</sup>.

#### **4.2.1.2 Public-Private Partnership in Promoting R&D**

During the past six decades, India's R&D infrastructure has been built around the network of institutions created under the CSIR<sup>83</sup>. In addition, the Indian Council of Medical Research (ICMR), around 25 universities and a few pharmacy colleges, funded largely by the Government, provided the additional sinews to the R&D efforts. With the maturing of private enterprise in the country, there was recognition of the need to build effective synergies between R&D efforts undertaken by the state-funded organisations and those that the private sector had put in place.

However, the concrete manifestation of this need came relatively recently. In 1999, the Government set up a Committee, the Pharmaceutical Research and Development Committee (PRDC) under the Chairmanship of Dr. R.A. Mashelkar, Director General, CSIR, which, among other things was expected to "suggest mechanisms for establishing organic linkages between private sector and government organisations/laboratories/universities with a view to synchronising and synergising national R&D efforts in pharmaceuticals"<sup>84</sup>.

The PRDC made two major contributions. First, it tried to set India's priorities for pharmaceutical R&D. Secondly, and perhaps more importantly, the Committee tried to identify the institutional mechanism that was needed to undertake R&D activities. A key element of the latter exercise was the identification of the publicly funded research facilities that were in existence.

The most prominent among the recommendations made by the PRDC was the setting up of an autonomous Drug Development Promotion Foundation (DDPF). It was suggested that the Foundation be managed jointly by the industry and the Government-supported institutions, would have several key responsibilities. The more important of these were: (i) enhancing the basic research component with special emphasis on risk-taking in discovery and development of new drug delivery systems, plant based preparations, etc., and (ii) providing international co-operation in discovery and development of new drug delivery systems and plant, mineral, animal and herbal based preparations to reduce risks, costs, and development duration.

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<sup>82</sup> FICCI (2005).

<sup>83</sup> The CSIR has 40 laboratories spread all over the country.

<sup>84</sup> The terms of reference of the PDRC also included the following: (i) to appraise the current status of R&D in the Indian pharmaceutical sector and to suggest measures to boost it in the context of drug price control regime and changes in laws on Intellectual Property Rights, and (ii) to suggest new and innovative fiscal and non-fiscal measures for boosting R&D in pharmaceutical sector. See Government of India (2001).

The PRDC also recommended that the Foundation should be financed through the Pharmaceutical R&D Support Fund (PRDSF), which should have an initial corpus of Rs 5 million to be funded by the Government. PRDSF was eventually operationalised in 2004-05 with an initial corpus of Rs 15 million. The management of the PRDSF was entrusted to Drug Development Promotion Board (DDPB)<sup>85</sup> that comprised of all the relevant Ministries/Departments of the Government and had, as industry representatives, only the three associations representing largely the “Indian” pharmaceutical industry<sup>86</sup>.

The idea of participatory research involving both the public and the private sector that the PRDC was intending to promote, and which was critically dependent on the autonomous DDPF and PRDSF, has undergone significant dilution on two counts. One, the DDPB was established with an overwhelming majority of institutions representing the Government, which raised questions about its “autonomous” character. And, two, the PRDSF, which was to provide the “corpus” for supporting R&D activities, was discontinued in 2006. It and was replaced by an annual government grant “for furthering R&D activities in the country and for defining areas of relevance and value to the Indian populace and intensifying the work in such areas by synergizing the core competence of the constituents for developing the synergies between the various actors involved in the area of pharmaceutical research”<sup>87</sup>. The moot point here is whether these changes have resulted in another state-funded and managed structure that has failed, in the past, to ensure effective participation of the pharmaceutical industry.

The eventual outcome of the initiatives taken by the PRDC to encourage public-private partnerships in the area of pharmaceutical R&D notwithstanding, there are growing evidence of collaboration Government institutions and pharmaceutical firms in recent years. The three laboratories, which are most active in area of pharmaceuticals viz., Central Drug Research Institute (CDRI), Indian Institute of Chemical Technology (IICT), and Centre for Cellular and Molecular Biology (CCMB)<sup>88</sup>, have established several collaborative ventures with the pharmaceutical firms (Annex Table 2 gives the details). These ventures are a pointer to the fact that the public-private partnerships in the Indian pharmaceutical industry have overcome the limitations of the policy-induced initiatives for promoting pharmaceutical R&D in the country. The real issue is whether this partnership can deliver s efficiently as has been provided in its blueprint.

The discussion in the foregoing indicates that the future holds much promise for the Indian pharmaceutical firms. At the same time, however, several issues of concern remain, particularly when the perspective is one of access to medicines at affordable prices. We had mentioned at the outset that the major concerns in India about the future

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<sup>85</sup> Rajya Sabha (2005).

<sup>86</sup> The industry associations included in the DDPB were: (i) Indian Drug Manufacturers Association (ii) Bulk Drug Manufacturers Association and (iii) Indian Pharmaceutical Alliance. These associations essentially represent the interests of the pharmaceutical firms that are owned and controlled by Indians. In other words, they do not include firms that are affiliates/associated of foreign firms.

<sup>87</sup> Government of India (2006).

<sup>88</sup> Apart from these institutions, National Chemical Laboratory (NCL), Pune has also been involved in this area.

of its domestic pharmaceutical industry in the new TRIPS-consistent patent regime arose from this above-mentioned perspective. Hence, policy makers were intensely lobbied by the public interest groups to evolve a patents regime that fully took cognisance of the flexibilities in the TRIPS Agreement, which could be used to address critical issues like access to medicines. While a number of flexibilities were included in the amendments introduced to usher in a TRIPS-consistent patent regime, there are others, which have remained unimplemented.

It may be argued that the developments in the Indian pharmaceutical industry enumerated in this paper may not entirely assuage the concerns pertaining to access to medicines at affordable prices for two significant reasons. First, the penchant for patenting displayed by some of the larger firms like Ranbaxy and Dr Reddy's, could create intrusive monopolies in a market that should have available for competition among the generic producers. These firms have already taken patents in the US on incrementally modified drugs, and if the patent examination procedures in India are not rigorous enough, these patents may find their way in this country as well. For instance, Ranbaxy had submitted a product patent application on its NDDS on ciprofloxacin and had even argued for the grant of EMRs, which was rejected<sup>89</sup>. This implies that although the public interest groups are arguing for the adoption of a narrow definition of "pharmaceuticals" to eliminate the possibility of patenting of older drugs like ciprofloxacin, their efforts could eventually be neutralised by the "research-oriented" Indian pharmaceutical firms.

The second weakness of the Indian pharmaceutical industry, viewed from the public health perspective, is that their increased collaboration with the foreign firms would hardly help them focus on the "neglected diseases". Although in recent years, this issue has received renewed attention because of the global initiative taken, among others, by the Médecins Sans Frontières (MSF)<sup>90</sup>, it seems improbable that the Indian pharmaceutical industry would be a meaningful partner in this global initiative.

These weaknesses notwithstanding, the Indian industry has made noteworthy contributions in the global action against HIV/AIDS. The following section provides the details in this regard.

## **5 Access to HIV/AIDS Drugs and the Indian Pharmaceutical Industry**

Universal access to drugs is a well-recognised strategy to counter the spread of HIV/AIDS. It was a bold decision of the Brazilian government in 1996 that paved the way for free ARV treatment movement. Even though, Brazil started the free ARV treatment programme using drugs from the brand name firms, it later shifted to generic

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<sup>89</sup> LEX ORBIS (2006)

<sup>90</sup> The MSF launched the "Drugs for Neglected Diseases Initiative" or DNDi, to address the need for research and development of new field-adapted, effective, and affordable drugs for patients suffering from "neglected diseases". The initial idea was to harness accumulated knowledge and cutting-edge science and technology to develop critically needed drugs for neglected diseases, making sure they are suitable for and accessible to the poorer patients of the world. The essential element of this initiative is to collaborate predominantly with developing country organizations and governments.

drugs to ensure the sustainability of the programme. The high cost of patented ARV drugs threatened the sustainability of free ARV programme. The cost of ARV drugs till 2000 was between US\$10,000 to 15,000 for per person per year (ppy). As a result, free treatment programmes were beyond the reach of most of the countries. The high cost of patented ARV drugs forced the Brazilian government to start the domestic production of ARV drugs. Thus Brazil introduced first generic version of ARV drugs, which was priced at US\$ 3000 ppy. This showed for the first time that ARV drugs can be produced at a lower price than the patented drugs and it accelerated the demand for cut in the ARV drug price.

It was the initiative taken by the Indian firm, Cipla, to reduce the prices of ARV drugs, which triggered the “domino effect”. In February 2001, Cipla announced that it would sell the triple combination<sup>91</sup> for US\$ 350 ppy. This shattered many myths on drug prices. Even the announcement itself forced brand name firms to cut ARV drug prices. This led to fall in the price of ARV drugs. The fall in the prices of ARV drugs encouraged many governments and non-governmental organisations to initiate free ARV treatment programmes. Generic ARV thus became the focal point of all free ARV treatment programmes including USA’s PEPFAR. Presently a first line triple combination is available at US\$132 ppy.

### **5.1 Indian Pharmaceutical Industry and ARV Drugs**

Indian pharmaceutical firms brought three path breaking contribution to the availability and accessibility of ARV drugs. Firstly, Indian firms started the production and marketing of the generic version of first line tippel combination drugs at an affordable price. This triggered the price war in ARV drugs segment. It was Cipla which first to announce the introduction of generic ARVs in February 2001. Secondly, Indian firms introduced fixed dose combinations (FDCs) of ARV drugs. As result, the number of pills had been reduced from six pills per day to two per day. FDCs not only improved the adherence but also reduced the price of ARV drugs. Thirdly, Indian firms also introduced the paediatric formulation of ARV drugs.

Producers of ARV drugs in India benefited from the fact that the Indian Patents Act did not allow patenting of pharmaceutical products until the Act was amended in 2005.

Following the lead given by Cipla, other Indian pharmaceutical firms also entered in the ARV drugs segment. Currently there are 14 firms active in the ARV drugs production. Out of these 14 firms, 8 firms are active only in the API segment of ARV production. The following table shows the list of firms active in the ARV drugs production.

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<sup>91</sup> Cipla’s triple combination included stavudine, lamivudine and nevirapine.

**Table 15: Firms active in ARV Drugs Production**

| Name of the Company          | API | Formulation |
|------------------------------|-----|-------------|
| Cipla Ltd                    | X   | X           |
| Ranbaxy Laboratories Ltd     | X   | X           |
| Aurobindo Pharma Ltd         | X   | X           |
| Strides Arcolab Ltd          | X   | X           |
| Hetero Drugs Ltd             | X   | X           |
| Emcure                       | X   | X           |
| Zydus Cadila Healthcare Lt   | X   |             |
| Sun Pharmaceutical Inds. Ltd | X   |             |
| Samarth Pharma Ltd           | X   |             |
| Matrix Laboratories Ltd      | X   |             |
| IPCA Laboratories Ltd        | X   |             |
| Dr. Reddy's Laboratories Ltd | X   |             |
| Eastern Surgical Company     | X   |             |
| Mac Leods                    | X   |             |

Source: Annual Reports of Firms

Possibly the most significant dimension of the operations of the Indian firms in the market for ARV drugs is that they have emerged as a major source of supplies to the affected countries. Six firms have obtained registrations for supplying ARV drugs as of October 2005, the details of which are provided in Table 16.

**Table 16: Approvals Received by Indian Firms for supplying ARV Drugs**

| Firms                      | Total Drugs Registered | WHO pre-qualified Drugs |
|----------------------------|------------------------|-------------------------|
| Aurobindo Pharma Ltd       | 41                     | 3                       |
| Cipla Ltd                  | 31                     | 10                      |
| Eastern Surgical Company   | 22                     | ...                     |
| Emcure Pharmaceuticals Ltd | 16                     | ...                     |
| Hetero Drugs Ltd           | 23                     | 1                       |
| Ranbaxy Laboratories Ltd   | 21                     | 7                       |
| Strides Arcolab Ltd        | 11                     | 4                       |

Source: WHO, The Regulatory status of Antiretroviral Drugs Database, (last update on 25<sup>th</sup> October, 2005)

The largest number of registrations has been granted to Aurobindo Pharma, although it is Cipla, which has the largest number of WHO pre-qualified drugs. The other noteworthy feature of the registrations granted to the Indian firms is that all firms, with the exception of Eastern Surgical and Emcure, have registered their presence in most countries of Africa, which is by far the most affected region.

The Indian firms have also proved their capabilities in terms of supplying the ARV drugs to the affected countries. Since the Global Fund to Fight AIDS, Tuberculosis and Malaria (henceforth “Global Fund”), started providing funds for the free treatment programme, Indian firms emerged as the major suppliers of ARV drugs. Between June 2003 and

January 2006, more than 1300 consignments of ARV drugs were supplied using the Global Fund and of these Cipla is the largest supplier<sup>92</sup>. Table 17 gives the list of top 10 suppliers of ARV drugs under the Global Fund.

**Table 17: Top 10 Suppliers of ARV Drugs under Global Fund in terms of Consignments (June '03 to Jan '06)**

| <b>Firms</b>              | <b>No. of consignments</b> |
|---------------------------|----------------------------|
| Cipla Ltd.*               | 342                        |
| Aspen Pharmacare*         | 221                        |
| Bristol Myers Squibb      | 158                        |
| GlaxoSmithKline Ltd.      | 144                        |
| Abbott Laboratories       | 88                         |
| Merck                     | 73                         |
| Ranbaxy Laboratories Ltd* | 45                         |
| Hetero Drugs Ltd*         | 35                         |
| Roche                     | 32                         |
| Boehringer Ingelheim      | 25                         |

\* Supplied from a single source

Source: Global Fund

Although three Indian firms were among the ten top suppliers of ARV drugs under the Global Fund in terms of the number of consignments, only two figured in the top 10 suppliers in terms of value of drugs supplied. Table 18 provides the details.

**Table 18: Top 10 Suppliers of ARV Drugs under Global Fund in terms of Value (June '03 to Jan '06)**

| <b>Name of manufacturer</b> | <b>Total value (in US \$ million)</b> |
|-----------------------------|---------------------------------------|
| Bristol Myers Squibb        | 8.0                                   |
| Cipla Ltd.                  | 7.4                                   |
| GlaxoSmithKline Ltd.        | 3.9                                   |
| Roche                       | 3.5                                   |
| Merck                       | 3.1                                   |
| Aspen Pharmacare            | 3.1                                   |
| Abbott Laboratories         | 0.8                                   |
| Ranbaxy Laboratories Ltd    | 0.7                                   |
| Boehringer Ingelheim        | 0.6                                   |
| Abbot Laboratories Ltd      | 0.5                                   |

Source: Global Fund to Fight AIDS, Tuberculosis and Malaria

During the period June 2003 and January 2006, the Global Fund provided nearly US \$ 34 million for procurement of ARV drugs and the share of the Indian firms was close to 25%. This establishes the point that Indian firms have become major global suppliers of

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<sup>92</sup> A part of Cipla's supplies were met by its marketing joint venture in South Africa, Cipla Medpro.

ARV drugs, particularly in the recent years. The future of the Indian pharmaceutical therefore becomes important not only for the fact that it has a critical role to play in the India's quest for obtaining drugs at affordable prices, but now as its pivotal position as global suppliers of ARV drugs to some of the most affected regions. The following section looks at the future of India's ARV drugs production capacities under the products patent regime.

## **5.2 Products Patents and Future of ARV Generics**

Introduction of product patent regime in India has created serious doubts on the future supply of generic ARV drugs. Generic availability of ARV drugs is required to meet both the domestic and export markets. Further, many countries that are among the worst affected by HIV/AIDS, do not possess the technical expertise to produce ARV drugs. These countries have, therefore, to depend upon the countries like India, Brazil and China<sup>93</sup> for the supply of ARV generics, even in the absence of a product patent protection at the domestic level. In other words the access to drugs in many countries depends upon the flexibility available in the patent laws of major generic producing countries.

Our contention is that introduction of product patent in India raises several concerns. These include: (i) whether product patent regime would affect supply of generic ARVs from India; (ii) whether Indian firms can produce ARV drugs, which are currently available, but are not produced in India; (iii) whether India can export ARV drugs to countries having no or insufficient manufacturing capacity in the pharmaceutical sector<sup>94</sup>; and (iv) how will Indian firms produce new ARV drugs in pipeline.

## **5.3 Future of Existing Supply**

All ARV drugs, which are currently available for the treatment were invented and patented in the USA or other developed countries before 1995. Hence, these drugs *per se* are not eligible for patent protection in India because the TRIPS Agreement requires India to consider grant of products patents on drugs which were invented after 1<sup>st</sup> January 1995. Annex Table 3 shows the patenting status of ARVs as listed in the US FDA's Orange Book. However, Annex Table 3 shows that the ARV drugs have been covered by multiple patents and that the applications for the recently granted patents were made post-1995. In other words, India would have to recognise the latter patents, should applications be made in this country. It may, however, be argued that the latter patents would be in the nature of improved formulations and are not eligible for the grant of patent in India, following the provisions of Section 3 (d) of the Indian Patents Act, 1970, as amended. According to this section, a *mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that*

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<sup>93</sup> It may be pointed out that China's existing strength is in production of API and not formulations.

<sup>94</sup> As provided in the Doha Declaration on TRIPS Agreement and Public Health. See WTO (2001) for details

*substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant*<sup>95</sup>.

This Section, however, qualifies the exclusion with efficacy requirements. As result, if the applicant proves that the claimed invention increases the efficacy of the known substance, patent can be granted on the invention concerned. In this context, it needs to be pointed out that the Indian Patent Office is yet not well equipped to evaluate claims on efficacy, and that the patent applicants may eventually get a favourable nod from the authorities. Further, patents are filed before the marketing approval of drugs therefore, it is not possible to make claim on efficacy at the time of filing. Pharmaceutical firms could use this exception to claim patents on the known substance to extend the patent monopoly. For instance, in the dispute on the patent on Gleevec, which was discussed earlier, it was observed that the patent applicant Novartis relied on the efficacy argument to defend their claim on a beta-crystal format of a known substance invented in 1993. The Controller accepted the efficacy argument but rejected Novartis claim on lack of evidence in this regard.

In India, several firms have filed patent applications claiming that their inventions constitute improvements of known substances in India. Table 19 provides a non-exhaustive list of pending patent applications on ARV drugs in the mailbox. Indian Patents Office is currently examining these patent applications. These applications have claimed patents either in the salt form or in the form of combinations or isomers. Therefore patents on any of these claims may affect the availability of existing ARV drugs. Even though the Indian Patents Act provides immunity to the existing producers of ARV drugs, patent on such drugs would increase the cost of such drugs since payment of royalty to the patent holder is entailed. We had argued earlier that the patent holder could try to extract supernormal rents by way of royalty payments, given that the language of Article 11A of the Patents Act, which operationalises the “immunity provision”, allows such possibilities. These supernormal rents could reflect in the price of generics price. Further, in the absence of clear ceiling on royalty the patent holder may raise the higher percent of royalty. This may lead to situation where the existing patients on the ARV treatment may end up in paying an increased price.

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<sup>95</sup> The explanation accompanying this Section provided further clarification as regards the scope: “For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy”.

**Table 19: Pending Product Patent Applications for ARV Drugs filed in India**

| Substance Name               | Title  | Indian application No | Priority Date          | Applicant            |
|------------------------------|--|-----------------------|------------------------|----------------------|
| Lamivudine + Zidovudine      | Pharmaceutical Compositions  | 2044/cAL/1997A        | 31/10/1996UK           | Glaxo                |
| Nevirapine / Hemihydrate     | Pharmaceutical Suspension Comprising Nevirapine Hemihydrate            | 2485/DEL/1998A        | NA                     | Boehringer Ingelheim |
| Trizivir                     | Antiviral Combinations   | 1206/CAL/1997A        | NA                     | Glaxo                |
| Tenofovir-3 applications     | Nucleotide Analog Composition  | 986/DEL/2002A         | 25/7/97/US             | Gilead               |
|                              | Nucleotide Analog Composition  | 963/DEL/2002A         | 25/7 /97/US            | Gilead               |
|                              | A method for preparing Form 2 or Form 4 Crystalline Adefovir Dipivoxil | 989/DEL/2002A         | 25/7 /97/US            | Gilead               |
| Lamivudine                   | Pharmaceutical Compositions  | 479/CAL/1998A         | 24/03/1997& 26/03/1997 | Glaxo                |
| Amprenavir +AZT + Ziagen     | Antiviral Combinations   | 1206/CAL/1997A        |                        | Glaxo                |
| Amprenavir+AZT+3TC+FT C      | Vaccine  | 2172/MAS1998A         | 26/09/1997             | SmithKline Beecham   |
| Amprenavir                   | Pharmaceutical Formulations  | 727/DEL/1997A         | 22/03/1996 USA         | Glaxo                |
| Abacavir                     | A Novel salt   | 872/CAL/98            | 17/5/97 UK             | Glaxo                |
| Lexiva Fosamprenavir Calcium | Calcium (3S)   | IN/PCT/2001/00039     | 18/7/1998 GB           | Glaxo                |
| Lopinavir                    | Process and Intermediates for preparing retroviral Protease Inhibitors | 259/MUMNP//2003       | 31/08/2000             | Abbott               |

Source: Patent Office.

#### 5.4 Production of Existing ARVs

As stated earlier, the introduction of generics have brought down the price of first line ARV drugs. However, patients who are already on first line ARV drugs needs to change to the second line treatment. The second line treatment is very costly. For instance, until recently, Brazil spent 63% of its ARV drug budget on only three second-line ARV drugs.

The following table shows the comparative price difference in first line and second line drugs. It shows that the price of second line drugs is exorbitant and people who develops resistance to the first line drugs many not able to easily switch over to the second line. The high cost of ARVs could also raise serious questions on the sustainability of the second line treatment by countries that have initiated the free treatment programme. It hardly needs to be emphasised that this issue should be addressed to avoid a public health catastrophe.

**Table 20: Price Comparisons of the “First” and “Second Line Regimen”**

| Country  | First line regimen | Price in US\$(ppy) | Second line                   | Price in US\$(ppy) |
|----------|--------------------|--------------------|-------------------------------|--------------------|
| Cameroon | 3TC/d4T/NVP        | 277                | AZT+ddi+NFV                   | 4763               |
| Malawi   | „                  | 288                | „                             | 1875               |
| Kenya    | „                  | 292                | „                             | 1594               |
| Cambodia | „                  | 350                | AZT+ddi+LPV/r                 | 1215               |
| Thailand | „                  | 352                | AZT+ddi+SQV/r                 | 3500               |
| Honduras | „                  | 426                | D4T+ddi+NFV or<br>AZT+ddi+NFV | 3,796 NFV only     |

Source: Medecins Sans Frontieres (MSF)

Table 21 shows that Indian firms are producing 13 ARV drugs out of 20 ARV drugs, which are currently available for treatment. Most of these drugs are started production prior to 2005 and therefore eligible for immunity clause under Section 11A of the Patents Act, 1970, as amended. However, immunity clause would not apply to drugs, which have not been produced prior to 2005. 7 ARV drugs are outside the scope of the immunity clause. Currently, Indian firms are producing 7 types of fixed dose combinations, which are used for the first line treatment (Table 22). But fixed dose combinations required for the second line treatment are also not eligible for immunity. Likewise, Emtricitabine, Tenofovir and Saquinavir have only one producer. Hence, Indian firms cannot start producing and marketing these drugs if patents are granted. Therefore, the future of the “mailbox” applications would determine the accessibility of these drugs. As table 19 shows, a number of patent applications on Lopinavir and Amprenavir, including those that are in the “mailbox”, are awaiting examination.

Further, production of fixed dose combination also would be affected if patents on the combinations were granted. Table 19 shows that at least one such combination, which may be useful in the future, has its patent application pending in the mailbox. Hence, application of Section 3(d) of the Patents Act would determine the availability of those 7 drugs and the fixed dose combinations for second line drugs.

**Table 21: Existing ARV Drugs Production Capacities of Indian Firms**

| Drugs   | Cipla | Ranbaxy | Aurobindo | Strides | Hetero | Emcure |
|---|-------|---------|-----------|---------|--------|--------|
| <b>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</b>      |       |         |           |         |        |        |
| Abacavir  | X     | X       |           |         | X      |        |
| Didanosine (ddl)  | X     | X       |           |         | X      |        |
| Lamivudine  | X     | X       | X         | X       | X      | X      |
| Stavudine (d4T)   | X     | X       | X         | X       | X      | X      |
| Zalcitabine (ddC)   |       |         |           |         |        |        |
| Zidovudine (AZT)  | X     | X       | X         | X       | X      | X      |
| Emtricitabine (FTC)   |       |         |           |         | X      |        |
| <b>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</b> |       |         |           |         |        |        |
| Delavirdine   |       |         |           |         |        |        |
| Nevirapine  | X     | X       | X         | X       | X      | X      |
| Tenofovir   |       |         |           |         | X      |        |
| Efavirenz   | X     | X       | X         | X       | X      | X      |
| <b>Protease Inhibitors</b>                                      |       |         |           |         |        |        |
| Amprenavir  |       |         |           |         |        |        |
| Indinavir   | X     | X       |           | X       |        |        |
| Nelfinavir  | X     |         |           | X       | X      |        |
| Ritonavir   | X     |         |           | X       | X      |        |
| Saquinavir  |       |         |           | X       |        |        |
| Lopinavir + Ritonavir   |       |         |           |         |        |        |
| Atazanavir  |       |         |           |         |        |        |
| Fosamprenavir Calcium   |       |         |           |         |        |        |
| <b>Fusion Inhibitors</b>  |       |         |           |         |        |        |
| Enfuvirtide   |       |         |           |         |        |        |

Source: Annual Reports of the Firms

**Table 22: Production of “Fixed Dose Combinations” by Indian Firms**

| Combination                          | Aurobindo | Cipla | Ranbaxy | Strides | Hetro | Emcure |
|--------------------------------------|-----------|-------|---------|---------|-------|--------|
| Lamivudine + Stavudine + Nevirapine  |           | X     | X       | X       | X     | X      |
| Lamivudine + Zidovudine + Nevirapine |           | X     | X       |         | X     | X      |
| Abacavir + Lamivudine + Zidovudine   |           |       | X       |         | X     |        |
| Lamivudine + Stavudine               |           | X     |         | X       | X     | X      |
| Lamivudine + Zidovudine              | X         | X     |         | X       | X     | X      |
| Lopinavir + Ritonavir                |           |       |         |         | X     |        |
| Emtricitabine + Tenofovir            |           |       |         |         | X     |        |

Source: Annual Reports of the Firms

This brings the focus on the back to the compulsory license regime in India. To follow the above strategy there is a need for simple and easy to use compulsory regime. However, the present regime does not provide a useful compulsory license regime, a

point that was emphasised earlier. It was pointed out that generally, a compulsory license is available only after 3 years from the date of grant of the patent. The only exception is national emergency, extreme emergency or public non-commercial use. Even though, HIV/AIDS is in effect a national emergency for India, the Government has not officially recognised it as such.

## **6 Conclusions and Recommendations**

The Indian generic pharmaceutical industry emerged as one of the strongest industries in the developing world during the past three decades. The growth of the industry and its subsequent consolidation, particularly since the 1990s, was contributed to a considerable extent by the country's Patents Act enacted in 1970. This Patents Act has two key features that facilitated the growth of the generic industry in India. First, only process patents were allowed for chemical entities, including pharmaceuticals, and two, the term of patent protection was made shorter for the pharmaceutical patents. However, the commitments taken by India under the WTO Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) forced a change in this regime, bringing to the fore a major challenge for the country's pharmaceutical industry.

This study analysed the likely impact that the change in the country's patent regime could have on the Indian generic pharmaceutical industry. The limitations imposed on the extent to which "me-too" processes can be developed by the Indian industry imply that the firms would have to adopt radically different strategies in the new regime. Emphasis on technology generation would have to take the front seat, which means that the firms' R&D activities would have to register quantum jump.

Our analysis showed that the leading firms of the industry have been showing considerable dynamism during the past decade. The consolidation of the Indian firms, which began in the first half of the 1990s, improved considerably since the beginning of the current decade. Particularly noteworthy was the increase in the R&D spending of some of the leading firms, in particular, Ranbaxy and Dr Reddy's. As a result, R&D intensities of the firms have improved significantly.

The R&D efforts of the leading Indian firms have borne considerable fruits. Market approvals in both the US and the UK, in particular, have increased in the past few years. Both Ranbaxy and Dr Reddy's have developed improved generics and Novel Drug Delivery Systems (NDDS), which have opened the doors for collaboration with the pioneer producers. India is fast emerging as the hub for contract research and manufacturing with a number of pharmaceutical majors establishing joint ventures with the Indian generic producers.

Although Indian firms are yet to make a mark in the area of new drug discovery, the firms seem to be on course for major developments even on this front given the sharp increase in their patenting activity of late. This activity could be strengthened by the increased efforts made by the Government to participate in the R&D activities involving the industry.

This focus on Government participation in the R&D activities came in the aftermath of the report presented by the Pharmaceutical Research and Development Committee (PRDC) that was established in 2000. One of the focus areas of the PRDC was the increase in spending by the Government on the R&D. Complementing the focus areas that the PRDC had identified was the increase in the R&D collaboration between the Government-owned research laboratories (mostly under the CSIR) and the industry.

These efforts taken with a view to strengthening the technological sinews of the Indian pharmaceutical industry should stand the industry in good stead as it evolves strategies to meet the challenges posed by the post-TRIPS patent regime. Improvements in the generic versions of proprietary drugs has become the established strength of the Indian pharmaceutical industry and with the prospects of faster growth of the market for generics in the near future, the industry should be looking at major gains.

One area where the Indian industry has got its act in place is the market for ARV drugs. Supplying these drugs at prices that the population of the affected regions can afford has become a priority and several of the Indian firms have met considerable success. With the global community now focused on obtaining drugs at affordable prices, it does appear increasingly probable that the pharmaceutical industries in the developing world, like the one existing in India, would offer the much-needed solutions.

These successful forays of the Indian pharmaceutical firms would have to be assessed in the context of its role in accessing medicines at affordable prices. We have indicated that the penchant for patenting, involving the incrementally modified drugs at that, does focus on the bleak side of the industry. Besides, the R&D priorities are being increasingly set in tune with the global trends, and this focus has increased since the firms have enhanced their level of collaboration with the foreign firms. Particularly affected in this process would be the “neglected diseases”.

The above-mentioned concerns arising from the successes of the Indian pharmaceutical industry has important policy lessons for the developing countries. In the first instance, it is necessary to provide sufficient flexibilities in the patent laws so that the domestic pharmaceutical industries can get a chance to develop. It must be recognised, however, that the advantages that the Indian policy makers could provide to their nascent pharmaceutical industry in the 1970s, by way of introducing a process patent regime cannot be replicated in a TRIPS-determined patent system. But at the same time, these countries can provide an enabling environment for the domestic industries by carefully designing provisions that relate to patentable subject matter and compulsory licences.

In our discussion, we have tried to provide a detailed template of a possible developing-country patent regime. At the same time, it must be emphasised that the dimensions of problems for the domestic pharmaceutical industries that we tried to highlight by using India’s post-TRIPS patent regime as a case, could change once sufficient experience is gained from implementing this regime. In other words, countries must be prepared to make course corrections while they are implementing their TRIPS-consistent laws.

For countries like India having matured pharmaceutical industries, the challenges are even more formidable. Besides engaging in a constant process of reviewing the newly

amended Patents Act, India would have to take complementary measures to ensure that the firms are not able to secure benefits that run contrary to the realisation of the fundamental objective of access to medicines at affordable prices. A legal regime for preventing misuse of patent monopoly would be an essential component of such measures. In this regard, India needs to go a fair distance given that the Competition Law of the country, which was enacted in 2002, contains explicit provisions to exclude intellectual property laws. Countries would also have to develop effective mechanisms to implement Article 40 of the TRIPS Agreement dealing with “Anti-Competitive Practices in Contractual Licences”.

The structure of the patent regime and the nature of its impact on the prices of pharmaceutical products may require initiatives that are beyond the scope of patent legislation. The controversial issue of statutory control over the prices of drugs becomes relevant in this context.

But above all, developing countries would need to ensure that their TRIPS-consistent patent laws provide a balance of rights and obligations. While several of the obligations would be country-specific, in our view, inclusion of obligations for ensuring the realisation of the objective of access to medicines at affordable prices would, remain the touchstone of their patent laws.

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## **Appendix: The Hatch-Waxman Act**

An innovator drug applicant must include in its new drug application (NDA) information about any patents that claim the drug that is the subject of the NDA, or the use of such drug product (21 USC 355(b)(1) and (c)(2))<sup>96</sup>. The FDA publishes this patent information upon approval of the NDA or a supplemental NDA in “Approved Drug Products with Therapeutic Equivalence Evaluations”, which is better known as the “Orange Book”.

An applicant for a abbreviated new drug application (ANDA) must include a patent certification (better known as paragraph I-IV certification) as described in section 505(j)(2)(A)(vii) of the Hatch-Waxman Act. Paragraph I certification requires the applicant to declare that the product for which approval is sought does not have an accompanying patent. Paragraph II certification requires the applicant to declare that the product in question is based on an expired patent. Paragraph III certification is applicable when the applicant has expressed his/her desire to market the product in question after the expiry of a patent. And, finally, Paragraph IV allows the generic manufacturer to either challenge the validity of applicable patents or certify that the generic equivalent product will not infringe any patent held by the pioneer drug company. The generic manufacturer is required under the Paragraph IV provisions to notify the innovator manufacturer that it is filing a Paragraph IV certification with its ANDA.

Paragraph IV thus established an incentive for generic manufacturers to file ANDAs and to challenge listed patents as invalid, or not infringed, by providing for a 180-day period of marketing exclusivity. The first generic company that files an ANDA can obtain a market exclusivity period of 180 days during which it can exclude any other prospective generic market entrant from marketing a generic product based on the same pioneer drug. The 180-day exclusivity commences upon a generic manufacturer’s first sale of its product after obtaining FDA’s approval for its ANDA. However, under the original Hatch-Waxman provision, if the generic company holding the exclusivity period never put the drug up for sale, all other generic manufacturers who have filed ANDAs for the same drug would be precluded from marketing another generic version of the same pioneer drug.

However, the pioneer manufacturer can obtain a 30-month stay of FDA approval of an ANDA if, upon the receipt of a notice of a generic applicant’s paragraph IV certification, it files a suit for patent infringement within 45 days of that notice. Filing of the lawsuit stays FDA’s approval of the ANDA until: (1) the date the patents expire; (2) a determination of non-infringement or patent invalidity by a court in the patent litigation; or (3) the expiration of 30 months from the receipt of notice of the paragraph IV certification. The earliest of the three dates is used as a reference.

In 2002, the Federal Trade Commission conducted a study to determine if the 180-day exclusivity and the 30-month stay provisions of the Hatch-Waxman Amendments have been used strategically to delay consumer access to generic drugs. The study had two

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<sup>96</sup> US Department of Health and Human Services (2003)

major findings: (i) there was increasing evidence of ANDAs being subjected to 30-month stays, (ii) there were more multiple 30-month stays than in years past, and (iii) more patents on average are now being litigated per generic drug application than in the past<sup>97</sup>.

The new rule will limit an innovator drug company to only one 30-month stay of a generic drug applicant's entry into the market for resolution of a patent challenge. For the generic drug producers, this change in the rule pertaining to the 30-month stay has provided them with greater latitude to seek decisive market entry in the US.

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<sup>97</sup> Federal Trade Commission (2002).

**Annex Table 1: Select Contract Manufacturing Deals in India**

| <b>Indian Company</b>                        | <b>Manufacturing for<br/>(Company Name)</b> | <b>Product(s)</b>                                 |
|--|---|---|
| Lupin Laboratories Ltd                       | Fujisawa                                    | Cefixime  |
|  | Apotex                                      | Cefuroxime Axetil, Lisinopril (Bulk)              |
| Nicholas Piramal Ltd                         | Allergan                                    | Bulk and formulations                             |
|  | Advanced Medical Optics                     | Eye Products                                      |
| Wockhardt Ltd                                | Ivax  | Nizatidine (anti-ulcer)                           |
| Dishman Pharmaceuticals and<br>Chemicals Ltd | Solvay Pharmaceuticals                      | Eprosartan Mesylate                               |
| IPCA Laboratories Ltd                        | Merck                                       | Bulk Drugs  |
|  | Tillomed                                    | Atenolol  |
| Orchid Chemicals &<br>Pharmaceuticals Ltd    | Apotex                                      | Cephalosporin and other injectables               |
| Sun Pharmaceutical Inds. Ltd                 | Eli Lilly                                   | CVS Products, anti-infective drugs<br>and Insulin |
| Kopran Laboratories Pvt. Ltd                 | Synpac Pharmaceuticals                      | Penicillin –G Bulk Drug                           |
| Cadila Healthcare Ltd                        | Altana Pharma                               | Intermediates for Pantoprazole                    |
|  | Boehringer Ingelheim                        | Gastrointestinal and CVS Products                 |
| Biocon Ltd                                   | Bristol Myers Squibb                        | Bulk Drugs  |

**Annex Table 2: Foreign Acquisitions by Indian Pharmaceutical Firms (2004-2006)**

| Year | Acquirer                                  | Target                                   | Target's country |
|------|---|--|------------------|
| 2006 | Aurobindo Pharma Ltd                      | Milpharm Limited                         | UK               |
| 2005 | Dishman Pharmaceuticals and Chemicals Ltd | Synprotec DCR Ltd                        | UK               |
| 2006 | Dishman Pharmaceuticals and Chemicals Ltd | Pharma services business of Solutia Inc. | Switzerland      |
| 2004 | Dr. Reddy's Laboratories Ltd              | Trigenesis Therapeutics Inc              | US               |
| 2005 | Dr. Reddy's Laboratories Ltd              | Roche's API business                     | Mexico           |
| 2006 | Dr. Reddy's Laboratories Ltd              | Betapharm Arzneimittel GmbH              | Germany          |
| 2004 | Glenmark Pharmaceuticals Ltd              | Clonmel Healthcare Ltd                   | Ireland          |
| 2005 | Glenmark Pharmaceuticals Ltd              | Laboratorios Klingler                    | Brazil           |
| 2005 | Glenmark Pharmaceuticals Ltd              | Napo Pharmaceuticals                     | US               |
| 2005 | Glenmark Pharmaceuticals Ltd              | Servycal S.A.                            | Argentina        |
| 2004 | Hikal Ltd                                 | Marsing & Co                             | Denmark          |
| 2004 | Jubilant Organosys Ltd.                   | PSI group                                | Belgium          |
| 2005 | Jubilant Organosys Ltd.                   | Target Research Associate                | US               |
| 2005 | Jubilant Organosys Ltd.                   | Trinity Laboratories Inc                 | US               |
| 2006 | Kemwell Private Ltd                       | Pfizer Health AB                         | Sweden           |
| 2005 | Malladi Pharmaceuticals Ltd               | Novus Fine Chem                          | US               |
| 2006 | Marksans Pharma Ltd.                      | Nova Nova Pharmaceuticals                | Australia        |
| 2005 | Matrix Laboratories Ltd                   | MCHEM Pharma (Group) Ltd                 | China            |
| 2005 | Matrix Laboratories Ltd                   | Docpharma N.V.                           | Belgium          |
| 2005 | Matrix Laboratories Ltd                   | Explora Laboratories S.A.                | Switzerland      |
| 2006 | Natco Pharma Ltd                          | NICK's Drugs Store                       | US               |
| 2004 | Nicholas Piramal Ltd                      | Rhodia's anaesthetics business           | UK               |
| 2005 | Nicholas Piramal Ltd                      | BioSyntech Inc                           | Canada           |
| 2005 | Nicholas Piramal Ltd                      | Avecia Pharmaceuticals                   | UK               |
| 2004 | Ranbaxy Laboratories Ltd                  | RPG Aventis                              | France           |
| 2006 | Ranbaxy Laboratories Ltd                  | Terapia S.A.                             | Romania          |
| 2006 | Ranbaxy Laboratories Ltd                  | Unbranded generic business of Allen SpA  | Italy            |
| 2006 | Ranbaxy Laboratories Ltd                  | Ethimed N.V.                             | Belgium          |
| 2006 | Shasun Chemicals and Drugs Ltd.           | Customs synthesis business of Rhodia     | UK               |
| 2004 | Shreya Life Sciences                      | SciGen Ltd                               | Singapore        |
| 2005 | Strides Arcolabs Ltd.                     | Beltapharm SpA                           | Italy            |
| 2005 | Strides Arcolabs Ltd                      | Biopharma                                | Venezuela        |
| 2004 | Sun Pharmaceutical Inds. Ltd              | Three niche brands from US based         | US               |

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|      |                              | Women's First Healthcare |              |
|------|------------------------------|--------------------------|--------------|
| 2005 | Sun Pharmaceutical Inds. Ltd | Able Laboratories Inc    | US           |
| 2005 | Sun Pharmaceutical Inds. Ltd | ICN Hungary Co.          | Hungary      |
| 2005 | Torrent Pharmaceuticals Ltd. | Heumann Pharma GmbH & Co | Germany      |
| 2004 | Wockhardt Ltd                | Esparma GmbH             | Germany      |
| 2004 | Zydus Cadila Group           | Alpharma France          | France       |
| 2005 | Zydus Cadila Group           | Bouwer Bartlett Pty Ltd  | South Africa |

**Annex Table 3: Collaboration between Government Research Organizations and the Pharmaceutical Industry**

| <b>CDRI (Lucknow)</b>                      | <b>IICT (Hyderabad)</b>                   | <b>CCMB (Hyderabad)</b>                    |
|--|---|--|
| Novo Nordisk, Denmark                      | Dr. Reddy's Laboratories, Hyderabad       | Shantha Biotechnics Pvt. Ltd., Hyderabad   |
| Krebs Biochemicals Ltd., Hyderabad         | Lupin Laboratories Ltd., Mumbai           | Dr. Reddy's Research Foundation, Hyderabad |
| Avon Organics Ltd., Hyderabad              | Cadila Laboratories Ltd., Ahmedabad       | Bangalore Genei Pvt. Ltd., Bangalore       |
| Cipla Ltd., Mumbai                         | SOL Pharmaceuticals Ltd., Hyderabad       | Dabur Research Foundation, Sahibabad       |
| Dabur India Ltd., Ghaziabad                | Neuland Laboratories, Hyderabad           | Biological Evans Ltd., Hyderabad           |
| Duphar Interferan Ltd., Mumbai             | Cipla Ltd., Mumbai                        | Sun Pharmaceuticals Ltd., Mumbai           |
| Hindustan Latex Ltd., Thiruvananthapuram   | Nectar Laboratories Ltd., Hyderabad       |  |
| IPCA Laboratories Ltd., Mumbai             | Orchid Chemicals, Chennai                 |  |
| Lupin Laboratories Ltd., Mumbai            | Trident Laboratories Pvt. Ltd., Hyderabad |  |
| Malladi Drugs and Pharmaceuticals, Chennai | Unichem Laboratories Ltd., Mumbai         |  |
| Nicholas Piramal India Ltd., Mumbai        | Armour Chemicals Ltd., Mumbai             |  |
| Lumen Marketing Co., Chennai               | Bombay Drug House, Mumbai                 |  |
| Ranbaxy Laboratories Ltd., New Delhi       | Cheminor Drugs Pvt. Ltd., Hyderabad       |  |
| Themis Medicare Ltd., Mumbai               | Torrent Pharmaceuticals Ltd., Ahmedabad   |  |
| Torrent Pharmaceuticals Ltd., Ahmedabad    | Coromandal Pharma, Hyderabad              |  |
| Unichem Laboratories Ltd., Mumbai          |   |  |
| Wockhardt Ltd., Aurangabad                 |   |  |

**Annex Table 4: ARV Drugs & Patent Status : Orange Book Listing**

**I: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**

| <b>Generic Name</b> | <b>Brand Name</b>  | <b>Firm</b>      | <b>US patent Nos.</b>   | <b>Patent Expiry</b>   |
|---------------------|--|------------------|---|--|
| Abacavir            | Trizivir (Abacavir + Zidovudine+ Lamivudine) & Ziagen (Plain Abacavir) | GSK              | 4818538<br>4833130<br>5034394<br>5089500<br>6417191<br>5905082<br>6180639<br>6294540            | Sep. 2005<br>Sep 2005<br>June 2009<br>June 2009<br>May 2016<br>May 2016<br>Jan 2018<br>May 2018          |
| Didanosine (ddl)    | Videx  | BMS              | 5616566<br>5254539<br>5880106   | Aug 2006<br>Aug 2006<br>Jul 2011   |
| Lamivudine          | Combivir (Zidovudine + 3TC) & Epivir (3TC alone)                       | GSK              | 4724232<br>4818538<br>4828838<br>5047407<br>5859021<br>5905082<br>6113920<br>6180639<br>6004968 | Sep 2005<br>Sep 2005<br>Sep 2005<br>Nov 2009<br>May 2016<br>May 2016<br>Oct 2017<br>Jan 2018<br>Mar 2018 |
| Stavudine (d4T)     | Zerit  | BMS              | 4978655   | June 2008  |
| Zalcitabine(ddC)    | Hivid  | Hoffman La-Roche | 4879277<br>502659   | Nov 2006<br>July 2008  |
| Zidovudine (AZT)    | Retrovir   | GSK              | 4818538<br>4833130<br><u>4828838</u><br><u>4837208</u>  | Sep 20<br>Sep 2017   |
| Emtricitabine (FTC) | Emtriva  | Gilead Sciences  | 5210085<br>5814639<br>5914331<br>6642245  | May 2010<br>Sep. 2015<br>Sep. 2015<br>Nov.2020   |

## **II: Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

| <b>Generic Name</b> | <b>Brand Name</b> | <b>Company</b>          | <b>US patent Nos.</b>  | <b>Patent Expiry</b>   |
|---------------------|-------------------|-------------------------|--|--|
| Delavirdine         | Rescriptor        | Pfizer                  | 5563142<br>6177101   | Oct 2013<br>June 2018  |
| Nevirapine          | Viramune          | Boehringer<br>Ingelheim | 5366972  | Nov 2011   |
| Tenofovir           | Viread            | Gilead                  | 4808716<br>5977089<br>6043230<br>5935946<br>6057305<br>5922695 | Apr 2006<br>July 2017<br>July 2017<br>July 2017<br>May 2017<br>July 2017 |
| Efavirenz           | Sustiva           | Merck                   | 5519021<br>5663169<br>6238695<br>6555133<br>6639071            | May 2013<br>Sep 2014<br>Apr 2019<br>Apr 2019<br>Feb 2018                 |

### III: Protease Inhibitors

| Generic Name             | Brand Name   | Company                    | US patent Nos.   | Patent Expiry   |
|--------------------------|--|----------------------------|--|---|
| Amprenavir               | Agenerase  | GSK                        | 5585397<br>5646180<br>5723490  | Dec 2013<br>July 2014<br>May 2015   |
| Indinavir                | Crixivan   | Merck                      | 5413999<br>6645961   | May 2012<br>May 2018  |
| Nelfinavir               | Viracept   | Agouron<br>Pharmaceuticals | 5484926<br>5952343<br>6162812  | Oct 2013<br>Oct 2013<br>Oct 2013  |
| Ritonavir                | Norvir   | Abbott                     | 5846987<br>5541206<br>5948436<br>5635523<br>5648497<br>5484801<br>5674882<br>6037157<br>6232333  | Dec 2012<br>July 2013<br>Sep 2013<br>Jun 2014<br>July 2014<br>Jan 2014<br>Oct 2014<br>June 2016<br>Nov 2017   |
| Saquinavir               | Invirase<br>(Saquinavir<br>mesylate) &<br>Fortovase) | Hoffman La-<br>Roche       | 5196438<br>6352717<br>6008228  | Nov 2010<br>Nov 2019<br>June 2015   |
| Lopinavir +<br>Ritonavir | Kaletra  | Abbott                     | 5914332<br>5886036<br>5846987<br>5541206<br>5635523<br>5648497<br>5674882<br>5914332<br>6037157<br>6284767<br>6232333<br>6284767<br>6458818<br>6521651 | Dec 2005<br>Dec 2012<br>Dec 2012<br>Jul 2013<br>Jun 2014<br>Jul 2014<br>Oct 2014<br>Dec 2015<br>July 2016<br>Feb 2016<br>Nov 2017<br>Feb 2016<br>Nov 2017<br>Nov 2017 |
| Atazanavir               | Reyataz  | BMS                        |  |   |
| Fosamprenavir<br>Calcium | Lexiva   | GSK                        |  |   |

#### **IV: Fusion Inhibitors**

| <b>Generic Name</b> | <b>Brand Name</b> | <b>Company</b>                 | <b>US Patent</b>              | <b>Patent Expiry</b>                |
|---------------------|-------------------|--------------------------------|-------------------------------|-------------------------------------|
| Enfuvirtide         | Fuzeon            | Hoffman La-Roche<br>& Trimeris | 5464933<br>6133418<br>6475491 | June 2013<br>June 2013<br>June 2017 |