

The Effect of Changing Intellectual Property on Pharmaceutical Industry Prospects in India and China

Considerations for Access to Medicines

Cheri Grace

June 2004

The Effect of Changing Intellectual Property on Pharmaceutical Industry Prospects in India and China



**Considerations for Access
to Medicines**

Cheri Grace

June 2004

The DFID Health Systems Resource Centre (HSRC) provides technical assistance and information to the British Government's Department for International Development (DFID) and its partners in support of pro-poor health policies, financing and services. The HSRC is based at the Institute for Health Sector Development's (IHSD) London offices and is managed by an international consortium of seven organisations: Aga Khan Health Services Community Health Department, Kenya; CREDES-International, France; Curatio International Foundation, Georgia; IDS (Institute of Development Studies, University of Sussex, UK); IHSD Limited, UK; IHSG (International Health Systems Group, Harvard School of Public Health, USA); and the Institute of Policy Studies, Sri Lanka.

This report was produced by the Health Systems Resource Centre on behalf of the Department for International Development, and does not necessarily represent the views or the policy of DFID.



Title: The Effect of Changing Intellectual Property on Pharmaceutical Industry Prospects in India and China: Considerations for Access to Medicines

Author: Cheri Grace
June 2004



DFID Health Systems Resource Centre
27 Old Street
London EC1V 9HL
Tel: +44 (0) 20 7251 9555
Fax: +44 (0) 20 7251 9552
E-mail: enquiries@healthsystemsrc.org
www.healthsystemsrc.org



Contents

1 Abbreviations and Acronyms	4
2 Definitions	5
3 Executive Summary	7
4 Background	10
4.1 Purpose	10
4.2 Scope	10
4.3 Methods	10
4.4 Format of the study	11
5 Why are India and China Important?	13
5.1 Domestic access to medicines	13
5.2 International access to medicines	13
5.3 Indirect benefits via market structure and overall competitive environment	15
6 The Context	16
7 Evolving Prospects of the Indian Pharmaceutical Industry	17
7.1 A snapshot of the Indian industry today	17
7.2 Strategic choices of Indian firms	19
7.2.1 Variants of the competitive business model	20
7.2.2 Variants of the co-operative business model	23
7.3 Traditional medicine	26
7.4 Risks faced by Indian firms	26
7.5 Implications for market structure and brand name multinationals	27
7.6 Conclusion: Prospects for Indian pharmaceutical firms and access to medicines	28
8 Implications of Changing IP on Product Level Access to Medicines in India	30
8.1 IP and access to existing medicines	30
8.1.1 Translation of TRIPS into domestic law	30
8.1.2 Price increases	32
8.1.3 Quality	35
8.1.4 Availability	35
8.2 IP and access to new medicines	36
9 Evolving Prospects of the Chinese Pharmaceutical Industry	42
9.1 The Chinese industry today	42
9.2 Evolving strategic options for Chinese firms	42
9.2.1 Competitive business models	43
9.2.2 Co-operative strategies	44
9.3 Conclusion: Prospects for Chinese pharmaceutical firms	46
10 Implications of Changing IP on Product Level Access to Medicines in China	48
10.1 Generic ARVs	48
10.2 Patented ARVs	49
10.3 Discussion: Emerging lessons from China	49
11 How Changes in India and China will Affect the Rest of the World	51
12 Potential Role for UK Government: Dialogue, Monitoring, Technical Assistance, Further Research	54
Annex A: References	57



1 Abbreviations and Acronyms

AIDS	Acquired Immune Deficiency Syndrome
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
ARV	Anti-retroviral
DFID	Department for International Development
DMF	Drug Master File
EMR	Exclusive Marketing Rights
EU	European Union
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
ICMR	Indian Council of Medical Research
IFPMA	International Federation of Pharmaceutical Manufacturers Association
INTECH	Institute for New Technologies of the United Nations University
IP	Intellectual Property
IPR	Intellectual Property Rights
MNC	Multi-national Corporation
MSF	Médecins Sans Frontières_
NCE	New Chemical Entity
NDA	New Drug Application
NIH	National Institutes of Health
OAPI	Organisation Africaine de la Propriété Intellectuelle (African Organisation of Intellectual Property)
PPP	Private Public Partnership
R&D	Research and Development
TB	Tuberculosis
TRIPS	Trade-related aspects of intellectual property rights
UNICEF	United Nations Children's Fund
US	United States
WHO	World Health Organization
WTO	World Trade Organization



2 Definitions

Regulated markets	Those markets with more established systems of patent laws and relatively more sophisticated regulatory systems for drug quality control – the US, EU and Japan
Unregulated (or less regulated) markets	Those markets with less well established systems of patent laws and relatively less sophisticated regulatory systems for drug quality control – most of Africa, Asia – including India and China
New Chemical Entity (NCE)	A drug compound that meets novelty criteria, as defined in national laws
Abbreviated New Drug Application (ANDA)	The registration application for a product that is less novel than a NCE – e.g. a variant on an existing formulation, a new dosage form or a new indication for an existing product
New Drug Application (NDA)	The registration application for a more novel product than those products that would qualify for an ANDA application
Drug Master File (DMF)	The registration application on an API
Active Pharmaceutical Ingredient (API)	The primary, active ingredient(s) of a final pharmaceutical product, produced in the first stage of pharmaceutical production and usually in bulk quantities
Pharmaceutical intermediates	Chemical products produced in stages leading up to production of an API. Different APIs will have a different number of stages, with more complex APIs having, for example, a dozen or more intermediate stages before production of the final API
Plain vanilla generics	Commodity generics, post-patent expiry, that offer little or no innovative value over the originator's product
Blockbuster	Pharmaceutical industry jargon for a product with very large sales – usually 1 billion or more – and on the back of which new product development can be funded. Examples: the anti-ulcer drug Zantac was a major blockbuster for Glaxo and the anti-depressant Prozac was a major blockbuster for Eli Lilly

Specialty generics	Generics that provide some innovative value over the originator's product, such as an alternative dosage formulation, or new drug delivery system
Branded generics	Generic drugs to which the generic company has attached its brand name and may invest marketing effort in differentiating the brand against other brands
Generic drugs	Off-patent drugs, which have received market approval based on proof of bio-equivalence ¹ to the originator's product
Biologics/ biologicals	Medical preparations made from living organisms and their products, such as insulin, erythropoietin, vaccines
Biogenerics	Generic versions of biological products, i.e. copies that have been proven to be therapeutically similar



3 Executive Summary

To meet obligations under the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS), China enacted regulation in 2002 extending pharmaceutical patents to twenty years, and data-exclusivity for six years and India plans to amend its patent laws by 2005 to allow for pharmaceutical product patents on any product with a patent issued after January 1, 1995.

Why is the introduction of product patents in India and China important? Firms in these countries are important suppliers of low-priced active pharmaceutical ingredients and finished products domestically and to developing countries, and many fear that the introduction of product patents will destroy these industries and lead to increased drug prices. DFID has consequently commissioned this study to answer some emerging policy questions:

- What will happen to the pharmaceutical industries in these countries? Will Indian and Chinese pharmaceutical firms be displaced as MNCs enter their domestic markets, or become multinationals themselves, governed by the same incentive structure?
- What will happen to the supply of low-priced medicines within these countries as well as internationally (where India and China export ingredients or finished products)? Will January 1, 2005 be the start of the doomsday many have feared?

The line of reasoning that connects IP, the pharmaceutical industries in India and China and access to medicines is not a direct one, so deserves clarification. Enhanced IP protection can close off certain revenue options and cause a reorientation of firms' strategies. This reorientation can affect industry structure and types of competition, and this can lead to changes in prices, quality levels and physical availability. Similarly, access to *new* medicines can also be affected by enhanced IP protection, but indirectly, through IP's influence on a firm's market orientation, and thus, the incentive structure to invest in R&D. The incentive to invest in R&D has implications for the number and type of new drugs that are developed through this investment.

This study reveals that enhanced IP protection in China and the approaching introduction of product patent law in India are already having an effect on the product and market strategies of Indian firms. The introduction of product patents means that Indian firms will have reduced revenue options for the sale of drugs domestically, since generic copies of newer drugs will become illegal. To compensate for this revenue loss, Indian firms have increased their emphasis on exporting to the more profitable regulated markets, as evidenced by the large concentration of FDA approved manufacturing

plants (more than any other country besides the US, numbering 60). There is also an increased focus on product innovation, with the most successful firms investing an increasing amount in R&D, including in partnership with MNCs, and with increasingly positive results; one-third of all FDA applications came from India in 2003, and this number is expected to be one-half in 2004. MNCs have been interested in working with Indian firms for some time, attracted by the lower cost structure – estimated to be one-eighth (in R&D) to one-fifth (in manufacturing) compared to Western firms; advanced chemistry and process engineering skills; and large market size. In conclusion, the prospects are extremely positive for the future of the Indian industry, in contrast to what many would predict.

The Chinese industry has different strengths and weaknesses versus the Indian industry. At this time, China is primarily still thought of as the lowest-cost source of pharmaceutical ingredients and plain vanilla generics, rather than the source of more innovative products. However, some of the major current domestic generic producers are migrating towards innovative R&D, at least as a longer-term goal. Within the innovative products category, Chinese firms appear to be focused on opportunities with biotech and traditional medicine primarily, with a lesser emphasis on small molecules, the traditional area of expertise of MNCs and Indian firms. Although China's expertise in selected sectors (e.g. biotech) already stands out at the international level, the industrialisation of this expertise is under-developed. Co-operative relationships between MNCs and Chinese firms are also not exactly comparable to the Indian situation either, as many MNCs are put off by the language barriers, relatively lower level of chemistry skills in China, relatively inferior quality, insecure institutional environment for intellectual property protection, long registration approval processes, and regulatory favouritism towards local firms.

Although some have feared that the advancing product and market strategies of Indian and Chinese firms would cause them to lose interest in serving their traditional low-priced/high-volume markets, there is ample reason to believe that these firms will not reject the markets that have been their bread and butter for several decades. Low-priced/high-volume markets have been and are likely to remain relatively² more attractive to Indian and Chinese firms, given the lower cost structure of these firms, their existing expertise in serving these markets, and their need to balance their more risky forays into the regulated markets with more advanced products.

There exist theoretical arguments to predict as well as some evidence to reveal what effect changing IP is having on the pricing and availability of medicines within China and India. The good news is that the availability and pricing of approximately 90% of medicines in India and China, including most the WHO Model List of Essential Medicines, should not be affected by the introduction of product patents.

With the introduction of product patents in India, the category of products that will be immediately affected will be those patented after 2005, and, depending upon how

TRIPS is translated into domestic law, perhaps those medicines patented between 1995 and 2005 as well. The latter includes some of the newer ARVs and some important anti-cancer drugs. Access may be impeded for these categories of products in terms of price or even lack of physical availability at any price. China is already experiencing access problems within the category of newer drugs. Some important ARVs are simply not physically present on the Chinese market, while others are present, but at prices aimed at skimming the wealthy market segment.

As for access to *new* medicines, as mentioned above, changing IP is influencing the business strategies of firms in India and China, and the incentive to invest in R&D in order to move up the product/market hierarchy. Thus, indications are that enhanced IP is encouraging increased development of *new* medicines, which is a good thing for access. However, there is mixed theory and evidence to support the idea that Indian and Chinese firms may be more likely than MNCs to devote R&D expenditure towards the development of products for neglected diseases.

Worldwide access to medicines, where India and China provide products or sources of price competition, is affected not only by the parameters discussed above which determine domestic access in India and China, but also by the IP situation in the importing country. Many African countries already implemented domestic patent legislation in line with the more regulated markets.³ Thus, although generic copies of, for example, older ARVs will be able to remain on the market in India, domestic legislation would not authorise generic copies in these African countries unless the patent holder has waived its rights or licensed the patents to generic firms. Where the patent holder is not willing to do this, the options include trying to access differential prices of the originator's product through 'access' programmes, pooling demand for bulk purchasing, tapping in to less expensive sources of the originator's product through parallel importing, issuing a TRIPS-compliant compulsory license, or in eligible countries, amending domestic legislation to take advantage of the TRIPS extension for least developed countries until 2016.⁴ All of these options have their practical difficulties.

The final section of the study offers ideas for initiatives that public funding bodies may wish to support with the goal of improving access to medicines.



4 Background

This study is one in a series of several studies commissioned by the UK Department for International Development and focused on answering emerging policy questions related to access to medicines.

4.1 Purpose

The objective of this study is to answer the following policy-relevant questions: How is implementation of product patents in India and China affecting access to medicines? Will generic copies of patented medicines have to be withdrawn from the market? Will prices rise? Will the domestic industry disappear? Will MNCs become more interested in working with domestic firms? What are the implications for donors?

4.2 Scope

Although this study highlights the impact of intellectual property on foreign direct investment, trade and firm strategy, with inevitable consequences for industrial development, this study is not primarily about the pharmaceutical sector's role in economic development in India and China. A wide literature⁵ exists debating the positives and negatives of the introduction of patent laws on the development of the pharmaceutical industry, technological development, and economic development in emerging markets.⁶

This study is primarily about what will happen to important sources of low-cost quality medicines coming from India and China, an analysis which requires looking at the probable strategic scenarios and options available to firms in these countries (with inevitable implications for the industries as a whole, and for economic development).

It must be recognised that the paper's focus on pharmaceutical supply and pricing is only one part of a multi-faceted system determining levels of access to medicines. For example, WHO advises that rational selection, sustainable financing, reliable systems and finally, affordable pricing are all necessary components in achieving better access to medicines.⁷

4.3 Methods

This study does not rely on country-level empirical data collection, although selected interviews were conducted with informants in order to confirm and supplement information gleaned from written reports. It was primarily a desk-based exercise, focused on a cost-effective means of gathering information from available reports,

studies, and interviews to answer a set of policy-relevant questions. What is new about this study is the way that it brings together these pieces of information, from quite varied sources, to answer these specific questions.

Methods included a review of literature, including academic, press, and equity analyst reports from the major investment banks. The research assistance of Kate Hurtig and Rabiya Hussain was helpful in gathering this literature. Interviews were held with the following categories of people: academics, pharmaceutical equity analysts based in major banks in India and London, researchers and medical practitioners based in China, operational managers as well as corporate communications individuals within research-based MNCs, the IFPMA, individuals from the Indian and South African generics industries, a patent law expert as well as an industrial development expert in India, individuals from WHO and individuals from other UN agencies who are knowledgeable in the subject areas covered. A London Business School sponsored Indian Business Forum, which had a break-out panel session on the Indian pharmaceutical industry, also provided useful information.

Helpful comments were received on an early draft of this paper in May/June 2004 by Nel Druce, Deputy Director of the Institute for Health Sector Development; Professor Lynn Mytelka, Director of INTECH; Maciej Gajewski, Policy Research Analyst, IFPMA; Dr Yusuf Hamied, Founder and Chief Executive Officer of Cipla Ltd; Professor Brook Baker, Northeastern University Law School, Boston MA; Andreas Seiter of the World Bank and Emma Back, team leader, Access to Medicines team, DFID. A second draft went through a formal review process, and benefited from feedback submitted by Hannah Kettler of the Gates Foundation; Andrew Creese at WHO; Abdul Barkat, Professor of Economics, University of Dhaka; Professor Richard Mahoney, University of California, San Diego; and Krisana Kraisintu, former Director of the Government Pharmaceutical Organization of Thailand and now an independent consultant working in three African countries to develop capacity for ARV production.

4.4 Format of the study

The study takes the format of considering the following questions in turn:

1. Why is pharmaceutical supply coming from India and China important to access to medicines?
2. What is the international context within which Indian and Chinese firms are operating?
3. What is the state of the Indian pharmaceutical industry today – its strengths, weaknesses, opportunities, threats? How are Indian firms responding to changes in IP? What are of implications for access to medicines of changes in competition at the firm and product level?

4. What is the state of the Chinese pharmaceutical industry today – its strengths, weaknesses, opportunities, threats? How are Chinese firms responding to changes in IP? What are of implications for access to medicines of changes in competition at the firm and product level?
5. How does changing IP in India and China affect the rest of world, where these countries supply ingredients or finished products?
6. What initiatives might donors consider to improve access to medicines?



5 Why are India and China Important?

Civil society has been concerned that the enforcement of WTO rules will have a negative effect on local manufacturing capacity, including in India and China.⁸ But it may not be evident to everyone why we should care about manufacturing capacity in India and China from an access to medicines standpoint. The following paragraphs provide evidence of China and India's importance to medicines supply in developing countries.

5.1 Domestic access to medicines

Since India and China together account for about half the poor people in the world, a key question is the degree to which domestic medicine consumption depends upon local producers. The domestic pharmaceutical market in India is worth approximately \$4.3 billion,⁹ 75% of which is supplied by Indian firms and the remainder by MNCs.¹⁰ In 2002, China's domestic market was worth approximately \$6.1 billion, and IMS Health projects a market growth of 18% per annum, to \$10 billion by 2005. This makes China the world's tenth largest market, ranking just after Canada and Mexico.¹¹ Like India, much of the domestic consumption in China is supplied by local firms; the US Department of Commerce puts the estimate at 70%.¹² So clearly Indian and Chinese companies are important to the supply of low-priced medicines domestically, where there exists a significant poor population.

5.2 International access to medicines

India and China are not only important to domestic consumption, but their supply is important internationally as well.

China is the second largest producer of pharmaceutical ingredients in the world, with an annual output of 800,000 tonnes in 2003. Chinese firms rank first in the world in the production of five pharmaceutical chemicals: penicillin (28,000 tonnes or 60% of world total), vitamin C (98,000 tonnes, of which 54,000 tonnes are sold abroad, or 50% of the world total), terramycin (10,000 tonnes, or 65% of the world total), doxycycline hydrochloride and cephalosporins.¹³

With overall production of \$7.3 billion (finished product domestic consumption, plus exports), Indian firms produce approximately 1.5% of the global pharmaceutical market of \$480 billion. However, this small share, in value terms, belies the importance of the Indian industry in volume terms, estimated at more than 20% of global consumption.¹⁴

The large difference between value and volume comes about due to the segment Indian companies serve – the high-volume, low-priced segment. The fact that Indian firms serve developing country markets is also evident from export statistics; in 2003, 40% of Indian finished products, by value, were exported and 60% of API, by value, was exported; and 44% of the combined API and finished product exports, by value, went to highly regulated markets (e.g. USA, Europe, Japan and Australia),¹⁵ leaving the other 56% to 'less regulated' markets, a category which applies to all developing countries.

India and China have also been important suppliers in certain product segments that treat diseases prevalent in poor countries, ensuring a competitive environment and with this, lowered prices. China is a major supplier of ingredients for antibiotics and India supplies API and finished product of many products, most notably vaccines and ARVs, to the developing and developed world. Ironically, despite problems with access to ARVs within China, as discussed in subsequent sections, China is a large exporter of ingredients for ARVs, with many Indian and developing country manufacturers now sourcing from China.¹⁶ The Government Pharmaceutical Organization of Thailand gets 90% of its raw materials for ARV production from India,¹⁷ the three South African producers currently capable of making ARVs get 100% of their raw materials from India,¹⁸ and raw material supply from India and China also dominates the Brazilian ARV market, where 90% of all tender submissions for ARV active principles come from Asian suppliers.¹⁹ More specifically, the Thai Public Health Ministry has clearly stated that their ambitious antiretroviral treatment programme would not exist without generic drugs, which would not have been possible without Indian API supply.²⁰ The government production facilities produce seven ARV preparations, which are two (nevirapine) to twenty-five (Stavudine) times cheaper than the cheapest brand equivalents. The use of locally produced generics has allowed the government's treatment programme to expand more than eight-fold in the past three years with only 40% increase in budget. As of May 2003, 13,000 patients are receiving ARV treatment, coverage is planned to increase to 70,000 people, using funds from Thai government and the Global Fund for AIDS, TB, and malaria. Thus, almost 10% of people with HIV/AIDS in Thailand will receive treatment within two years.²¹ Similarly, data from the Brazilian firm, Farmanguinhos, which supplies approximately 40% of the total Ministry of Health ARV demand, shows that approximately 74% of total ARV purchases in 2002 and 94% of total ARV purchases in 2003 were supplied by Indian, Chinese and Korean firms.²²

Indian ARV finished product supply is important to many non-producing countries as well. The case studies done as part of this series of papers revealed Indian ARV supply as crucial to the domestic ARV treatment programmes in Malawi and Kenya, for example.²³ As detailed in subsequent sections, Indian firms are also the major supplier of Expanded Programme on Immunisation (EPI) vaccines for UNICEF and have successfully developed more novel recombinant hepatitis-B vaccines as well.

It should also be recognised that, with South Africa scaling up its ARV efforts, a large shift in the market dynamics for ARVs is about to take place. Approximately 900,000



people are currently on ARV therapy world-wide (developed and developing countries), 500,000 of whom are in developed countries.²⁴ Indian firms currently supply the API or the finished product for less than half of the total, but for a large percentage of the patients in developing countries. However, approximately 100,000²⁵ new patients are expected to be started on ARV therapy by 2005 in South Africa alone, and the API for this supply will come from India in the near-term, with Chinese and South African suppliers on the horizon.²⁶ Therefore, because of the scaling up of treatment in South Africa, suppliers from India, China and South Africa will soon become more important sources of API and/or ARV finished product supply globally.

In summary, the prospects for the Indian and Chinese industry are important from the standpoint of access to medicines domestically, internationally, and more specifically, within product segments that treat diseases prevalent in poor countries.

5.3 Indirect benefits via market structure and overall competitive environment

It is not only the direct supply from these countries that is important, but also the indirect effect on the competitiveness of the marketplace. For example, generic offers sparked a price war for ARVs which brought the annual price for triple therapy down from 10,000 to 350 in a single year.²⁷ For example, in Brazil, ARV prices came down by 82% within five years after Brazil initiated local generic production (based primarily on API supply from India) and provided universal free HIV treatment to Brazilians who needed it. This price reduction was partly a result of the strong negotiations government was able to have with patent originators, based on the threat of compulsory licensing made credible by the presence of Asian API and domestic production capabilities.²⁸ Thus, the Chinese and Indian industries are important in terms of these indirect benefits as well.



6 The Context

How Indian and Chinese firms are adapting to IP changes in their own countries can be better understood in the context of changes happening in the pharmaceutical sector in developed market economies. Systemic changes happening within the regulated markets are pushing MNCs to consider new business models and at the same time, are creating opportunities for firms in India and China to approach these markets on their own merit.

For example, the escalating drug bill in the regulated markets has caused governments to look for cost savings. Increasing costs are partly a function of the incremental cost of specialist care products, with the result that secondary care is increasingly taking up a larger percentage of the overall health care expenditure. This trend is set to continue, as drugs become increasingly tailored (e.g. gene based therapies). The government squeeze on prices means that MNCs will increasingly need to offer lower prices, and so reduce their costs, if they want to maintain profitability. Sub-contracting to lower cost firms in India and China is one way to achieve this lower cost. Such pressure on pricing also means that there will be greater opportunities for high-quality firms in India and China, with their relatively lower cost structure, to find direct custom in the regulated markets.

The acceleration of patent expiries between now and 2007 presents a further opportunity. About \$60 billion worth²⁹ of blockbusters will open up to legitimate generic competition; consequently, the generics market is forecast to outperform the branded pharmaceutical sector significantly in sales growth to 2007.

The cost of R&D has also been escalating, and US based pharmaceutical companies are at an all-time low in terms of R&D productivity. Despite a doubling of R&D spend between 1995 and 2002, the FDA approved only 17 NCEs in 2002 – a disappointing fraction of the fifteen-year high of 56 NCEs approved in 1996 and the lowest number since 1983.³⁰ The implication is that MNCs will need to find ways to increase their R&D productivity, and it also means that Indian and Chinese firms with relatively novel approaches to product and process development may find opportunities opening up for them, whether through go-it-alone strategies or through co-operative R&D partnerships with MNCs.



7 Evolving Prospects of the Indian Pharmaceutical Industry³¹

While external systemic changes are creating opportunities for Indian firms, technological advancement and domestic regulatory changes are pushing these firms to adapt their business strategies as well.

7.1 A snapshot of the Indian industry today

The Indian industry has progressed through the value-added ladder of pharmaceutical production as a result of its domestic policies as well as the presence of supportive factor conditions, namely, the pool of scientific excellence available at low cost, and the large domestic demand for pharmaceuticals which enables economic viability in the scale intensive active pharmaceutical ingredient (API) production stage.

As of 1999, the Indian pharmaceutical industry accounted for 70% of the bulk drugs and 80% of the formulations in the country, making India one of the few countries in the world achieving self-sufficiency in drugs.³² The industry is highly fragmented; no single company has more than 7% market share, and the largest five companies account for just 20% of the total market.³³ The most promising firms have solid funding, fuelled by profits and early embrace of the capital markets.

India's core competencies

Complex synthesis capabilities, increasingly good manufacturing practices (GMP) and low-cost production, as detailed below, are core competencies that have led Indian pharmaceutical companies to heightened global visibility within the speciality generics and even branded pharmaceutical businesses.

Box 1: Cost advantages of Indian firms³⁴

Indian firms have lower costs – estimated to be one-eighth (in R&D) to one-fifth (in manufacturing) compared to Western firms. The following factors are the basis for this cost advantage:

Fixed asset costs: The cost of building a new manufacturing facility complying with international regulatory norms is about one-fourth the cost of setting up a similar facility in the US or Europe. Civil construction is \$8-\$12 per square foot versus \$75 in the US. Material costs (used for reactors, vessels, and other equipment) may also be lower.

Cheaper labour: The cost of an Indian based laboratory analyst/chemist is one-fifth to one-eighth of the US cost. Higher-level Indian scientists are well trained yet earn about a third of their Western counterparts' salaries. Finally, plant employees cost \$120-\$150 per month.

Chemistry/process expertise and development costs: More than three decades of reverse engineering 'on-patent' drugs (process engineering) has made Indian companies extremely proficient in speedy generic drug development, therefore more productive per unit of cost. Lower development costs result in lower regulatory filing costs, and this, combined with the increasing admissibility of Indian bio-equivalence studies to the FDA, puts India at an advantage. On the manufacturing side, continuous process improvement has also resulted in a highly efficient cost structure for India's bulk actives.

Clinical study costs: A large population of treatment-naïve patients facilitates rapid trial recruitment into large clinical studies. Cost per patient enrolled is approximately one-tenth of the cost in the US. However, neither Indian companies nor international companies have leveraged this cost advantage in any material sense – Indian companies due to nascent drug discovery research and pharmaceutical MNCs due to concerns over intellectual property confidentiality.

Cost of sales force: The average salary (including all benefits) of a typical drug representative for the Indian market is \$4,000 per year.

Driver of change: 2005 patent reform

The development of the Indian pharmaceutical industry has been shaped by the position of the Indian government on intellectual property law as outlined in the Indian Patent Act of 1970, under which only process patents were covered. Furthermore, the Act provided only seven years of process patent protection for pharmaceuticals – about half of the average 15 years required to develop and test a new drug. The result – more than three



decades of reverse engineering ‘on-patent’ products, a flourishing domestic generics market, as well as strong chemistry and process engineering expertise.

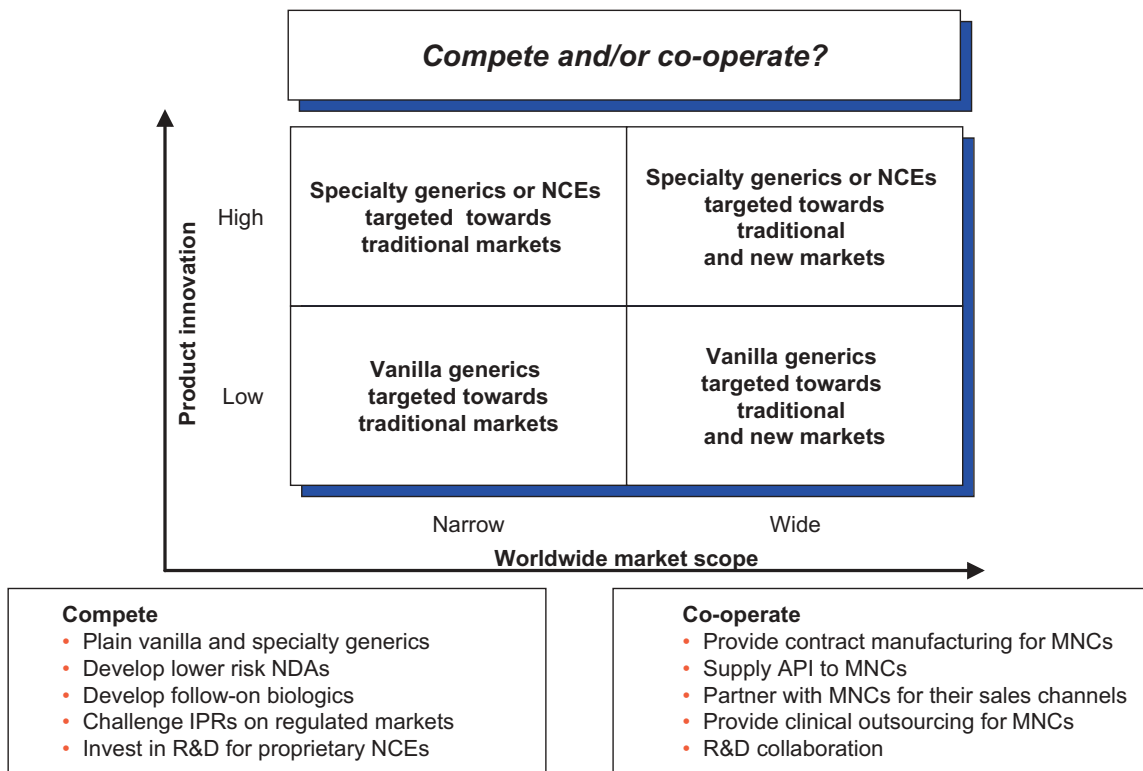
To meet its obligations under TRIPS, one of the outcomes of the Uruguay trade round (1986-94), India will have to amend its patent laws by 2005 to allow for pharmaceutical product patents on any product with a patent issued after January 1, 1995. From January 1, 2005, 20-year product patents will be awarded.

With these changes, many observers are questioning the future of the Indian industry. Will it continue being the predominant supplier to the south? Will it continue to imitate the drugs of the patent originator’s in developed countries? Or will the Indian companies innovate to a level that will allow them to compete on a par with the research-based MNCs based in developed economies? The following sections explain the evolving strategies of Indian firms and the implications of these developments for the global pharmaceutical industry. The evolving potential of India in the areas of traditional medicine and vaccines development and manufacture is discussed as well.

7.2 Strategic choices of Indian firms

The introduction of product patents has important implications for both Indian and Western pharmaceutical companies. After 2005, Indian companies will increasingly need to look beyond the domestic generics market to sustain their sales, since their traditional strategy of copying on-patent drugs will no longer be allowed. They will

Strategic choices for Indian firms



consequently need to look towards export markets and focus on product innovation. In pursuing the regulated markets, the more successful Indian firms are faced with a similar strategic choice in how to achieve such growth: whether to co-operate or compete with the large international pharmaceutical companies. However, there are multiple sub-strategies that Indian firms can choose within the framework of this strategic dilemma, and the strongest Indian firms have been able to pursue both strategies simultaneously.

7.2.1 Variants of the competitive business model

Many firms plan to meet the product patent challenge with a multi-stage strategy of moving up the product value chain³⁵ and increasing exports to regulated markets, such as the US and Europe. Leveraging their comparative cost advantages, these firms plan to target plain vanilla generics sales to regulated markets in the near-term and to develop more difficult-to-manufacture generics, (e.g. injectables), lower-risk NDAs, and follow-on biologics in the medium term. The most advanced firms hope to evolve into the area of NCE/proprietary drugs.

Targeting regulated markets

The contribution of export revenues for larger Indian pharmaceutical companies has increased significantly over the past five years, rising by 12 percentage points in the last five years to 40% in 2003. Growth in exports is expected to continue, fuelled by the impending patent law change, and made possible by India's cost advantage, regulatory filing skills, and the large concentration of FDA approved manufacturing plants (more than any other country besides the US, numbering 60).

Looking for growth, Indian companies are already targeting some European markets and the US, as evidenced by the surge in drug applications to the FDA – one-third of all US abbreviated new drug applications filed in 2003 compared with only five in 1997. Several Indian companies have also made acquisitions in Europe, in order to gain a foothold. The three markets that are under-penetrated with respect to generics (France, Italy and Spain) are expected to be especially important targets for Indian companies in the next two to five years.

Moving up the product value chain

About \$60 billion worth³⁶ of blockbusters will open up to legitimate generic competition between now and 2007, and Indian firms are expected to actively participate in supplying generic versions of these blockbusters. However, Indian firms are also looking for ways to maintain revenue growth after patent expirations peak in 2007. Because of Indian companies' strong reengineering skills, the branded prescription drug products often viewed as invulnerable because of manufacturing complexity (e.g. injectables) and regulatory hurdles (e.g. biogenerics) are increasingly likely to become targets of Indian companies, in the medium term, as are other specialty generics – e.g. reformulated



older molecules that leverage new drug delivery technologies (Cipla is a world leader in CFC free inhalers), value-added formulations and newer polymorphs/salt versions of existing chemical entities. Dr Reddy's and Wockhardt are examples of firms having in their pipeline new drug delivery technologies to develop life cycle extensions of existing molecules.

Bio-tech, bio-generics and vaccines

The biotech market in India is nascent, at \$500 million, but is expected to grow at 25-30% per year to \$9 billion by 2007-2008. There has been an explosion in the number of Indian companies involved in biotech activities, and employment in the sector is also growing, with close to 7,000 personnel currently. Annual investments in the sector are of the order of \$150 million and are growing at 25% annually. India ranks third in Asia in terms of biotech patent filings.³⁷

The bio-tech sector is more developed on the generics side, with five main Indian companies advanced in this area. Biocon, Wockhardt, Shantha Biotech, Panacea Biotech and Bharat Biotech are currently supplying the domestic market and developing countries with bio-generics. Labour and land costs for these firms are significantly below those of their Western counterparts, and the time to set up a manufacturing plant is 15-18 months, as compared to 2-3 years in the West. This has translated into reduced prices. For example, Shantha Biotech has quoted ex-US prices for insulin at \$110,000/kg compared with \$55,000/kg for insulin manufactured in India.

Despite the success in domestic and less regulated markets, Indian bio-generics companies face technical and regulatory barriers in exporting bio-generics to the regulated markets. On the regulatory side, the Hatch-Waxman Act provides the legal mechanism only for approval of drugs filed as NDAs. There is no parallel tract for biologics filed through the Biologics Licensing Application, although the FDA and the European Medicines Agency have expressed an interest in defining a mechanism for approval. A second challenge is the lack of standards for bio-equivalence. It is likely that companies developing these products will need to collect their own safety and efficacy data, making the filing requirements and cost structure for these products more like follow-on, or 'me-too' biologics rather than true generics. On the technical side, it is difficult to generate an equivalent (much less identical) biologic product, as Genetech witnessed in manufacturing Raptiva. Using the same cell line, the company's scaled-up version of Raptiva had such a difference in half-life from the compound used in clinical trials that the FDA required new Phase III trials.

India as a vaccines hub

The role of Indian firms in the vaccine sector deserves special mention, as successes in manufacturing as well as R&D have catapulted these firms to international attention.

Vaccine manufacturing

Many MNCs have pulled out of the low-margin vaccine business;³⁸ the number of players has shrunk from 26 in 1967 to 8 in 1996 and finally to 4 players in 2003.³⁹ The reasons include price controls, liability fears and opportunity costs. But the demand for vaccines is growing and developing country firms are increasingly exploiting new technologies to tap this niche market. On the manufacturing side, 60% of UNICEF's requirement for Expanded Programme on Immunisation vaccines are now fulfilled by India, Indonesia, Cuba, and Brazil, and the Serum Institute of India is believed to be the world's largest manufacturer of DPT⁴⁰ vaccines.⁴¹

Vaccine R&D

India is quickly becoming a global leader in new vaccine development as well, enabled by abundant natural and human resources, ongoing R&D in multi-disciplinary subjects, application of information and communication technologies, and growth in collaboration between academic and research institutes in public and private domains. For example, looking at the innovations that have come solely out of the ICMR in the past several years, one finds several examples of innovative new product development:

- A rota-virus vaccine is now in clinical trial phase, and should help achieve considerable reduction in diarrhoeal diseases among infants. It has been developed through a collaboration between ICMR, Bharat Biotech, Centres for Disease Control, Atlanta, the National Institutes of Health, Washington, Institute of Genomics and Integrative Biology, New Delhi, and National Institute of Virology, Pune.
- The formulations of several new combination vaccines, offering protection against influenza, Hepatitis B and DPT, are in clinical trials.
- Under the Indo-US partnership, ICMR has begun to work with the US army medical research and material command to exchange information and data on the dengue vaccine being developed by the latter in Thailand.
- The multi-caccina Ankara Epitope candidate vaccine for HIV/AIDS was developed under a tripartite agreement among the ICMR, the National AIDS Control Organisation and the International AIDS Vaccine Initiative. The pre-clinical trials of the vaccine are being carried out by a biotech company in the US.

There are other vaccines in development in India, unrelated to ICMR:

- A vaccine for HIV-1 sub-type 'C' DNA vaccine (the clade prevalent in India) is also being developed at the National HIV Reference Centre, Department of Microbiology, All-India Institute of Medical Sciences, in New Delhi. The vaccine is



still to undergo pre-clinical testing in animals.

- Indian scientists have also developed an experimental vaccine against malaria, which is likely to undergo clinical trials early next year. 'It would probably be the first time that a vaccine would go from the lab to trial site in a developing nation' said V. S. Chauhan, Director of the International Center for Genetic Engineering and Biotechnology, Delhi.
- Indian companies have successfully developed recombinant hepatitis-B vaccines.

The strength of Indian firms in this sector implies that, once the FDA and the European Medicines Agency have defined a mechanism for approval of bio-generics, India will be very well placed to dominate this field. It also suggests that donors interested in finding sources of high-quality, low-priced biologics would be well advised to give Indian suppliers every opportunity to compete for public funded procurements as well as participate in product development public-private partnerships.

Longer-term strategy: NCE/Proprietary drugs

Partly as a result of TRIPS compliance by 2005, the larger Indian companies are investing increasing sums in novel product R&D. Current R&D stands at 6% of sales for Ranbaxy and Dr Reddy's. Over the next five years, both companies intend to bring their R&D expenditure to a level over 10%. Ranbaxy has indicated that its R&D focus will be on urology, paediatrics and dermatology.

The nascent R&D effort in India is already beginning to pay off. There are currently 37 research leads for NCEs, 28 of which are in pre-clinical development, and 9 in Phase I/II trials. However, it is important to bear in mind that, overall, two-thirds of Indian R&D spend is directed towards API and formulation work, with only one-third dedicated to new chemical entities.

7.2.2 Variants of the co-operative business model

While changing legislation and technological capacity are pushing Indian firms to consider new ways of competing, there is also a pull from MNCs encouraging the same firms to achieve their growth targets through co-operative strategies. This pull factor stems from the research based MNC's increasing need to cut costs and boost productivity, and the consequent search to invest an increasing amount in external collaboration, perhaps 20% outside the company on a contract or part investment basis.⁴² This is true not only for manufacturing, but also for research. As an alternative (or, in noted exceptions, in addition) to the competition models described in the previous section, some of the Indian companies, having recognised an opportunity to meet the needs of the MNCs, have chosen to follow a more service provider/partnership-orientated model. Although the co-operative business model is clearly well established

in other Indian sectors,⁴³ India's drug-outsourcing market, at \$470 million, is still at a nascent stage. However, it is expected to grow 30% a year, hitting \$800 million by 2005, according to Bombay brokerage Kotak Institutional Equities.⁴⁴

Variants on the co-operative business model include servicing large pharmaceutical MNCs (whether research-based or generic) with API, contract manufacturing for already existing drugs or research candidates, clinical out-sourcing and research partnerships. A few firms, such as Ranbaxy and Dr Reddy's, are mixing co-operative and competitive strategies.

Why work with Indian firms?

There are multiple reasons why MNCs are drawn to working with Indian firms. India graduates approx 122,000 chemists and chemical engineers each year, and these graduates have traditionally found jobs focused on reverse engineering. With the implementation of product patent law, Indian pharmaceutical companies will have to find alternative ways to employ some of this capacity. MNCs can use these skills to re-engineer the manufacturing process for already-marketed products or to manufacture bulk-actives/intermediates for use in clinical development. Some firms are attractive as research partners; a few have even attracted out-licensing deals for clinical research for NCEs.

Box 2: Clinical trials opportunities in India

It has been estimated that the pharmaceutical industry spends up to \$800 million⁴⁵ to bring a new molecule to market. Perhaps a third of the total goes towards clinical trials, and much of that is spent on Phase III trials that use a lot of human subjects. Since the life of a patent begins to ebb away from the moment it is filed, each day saved on testing can bring millions of dollars in extra revenues to the patent holders.

Clinical trials in India ought to be cheaper and faster than those in developed markets. Contract research organisations can hire researchers, nurses and computer staff at less than a third of Western wages. The Indian population is large, ethnically diverse and suffers from both tropical diseases as well as ailments such as cancer, diabetes and heart disease that also affect rich countries. Overall clinical development costs in India are estimated to be 40–60% lower than those in the West. Tellingly, specialist contract research organisations such as Quintiles have set up shop in India. However, despite these theoretical advantages, some remain sceptical about the potential for clinical trials outsourcing in India, citing the concern over confidentiality of shared intellectual property, and the relatively limited experience of Indian hospitals in conducting clinical trials in line with FDA specifications.



Quality standards are another factor pulling MNCs to work with Indian firms. When Ranbaxy began supplying cefaclor to Eli Lilly in the 1990s, it was considered to be a rare achievement, whereas now, it is commonplace for Indian companies to supply intermediates and API to any major multinational. The idea that Indian generics are necessarily inferior to their branded counterparts, a view still fairly widespread amongst the uninformed, is clearly outdated for the majority of Indian suppliers, and particularly for those supplying ARVs pre-qualified⁴⁶ by the WHO.⁴⁷

The large market size is yet another attraction for MNCs. The 30% of Indians who can afford relatively expensive Western medicine number approximately 300 million people – larger than the US population. Those companies with strong sales forces and clinician relationships will make valuable partners to MNCs looking for Indian domestic sales.

Examples of Indian companies entering into collaborative partnerships with pharmaceutical multinationals are numerous. Divi's Laboratories does custom chemical synthesis for Merck, Abbott and GSK and makes generic anti-inflammatory and anti-arthritic formulas for other firms. International bulk drug maker Matrix Laboratories has seen its outsourcing business grow fivefold, to \$10 million, in one year. In Bangalore, having done deals with Pfizer, AstraZeneca and Bristol-Myers Squibb, Biocon has 300 scientists doing contract research, up from just 25 in 2000. Similarly, Cipla and Aurobindo tend to prefer to use India's cost advantages to act as supplier of API to US and European generic companies. Nicholas Piramal has acquired assets divested by the Western majors through periodic bouts of restructuring and aims to act as a contract manufacturer for several of these firms. Wyeth Lederle has contracted with Bharat Biotech for production of the HibTITER vaccine, and this is the first example of an Indian company contract-manufacturing a vaccine for a major research-based MNC.

Other Indian companies are collaborating in the area of R&D. On the development side, Nicholas Piramal and Divi's are aiming for a share of the clinical outsourcing market (at present, for bio-equivalence studies and Phase II & III studies). On the research side, Dabur recently announced a milestone collaborative agreement with Abbot to work on generic oncologics.

Still other Indian companies are pursuing collaborative and competitive strategies simultaneously. Although New Delhi based Ranbaxy Laboratories in March 2003 successfully challenged GSK's patent on Ceftin, in October, GSK hired Ranbaxy to research molecules that may become the building blocks for drugs. Mencef Slaoui, a GSK senior VP was quoted as saying, 'The deal fits naturally with our other collaborations around the world to complement our own resources in drug discovery'. GSK will have exclusive commercialisation responsibilities worldwide, while Ranbaxy will take the lead in India (although Ranbaxy may co-promote in US and EU, with permission from GSK). 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. The figure below captures the product and market strategies of the leading

Indian firms – illustrating the degree to which the firm is moving up the product value chain and/or adding new markets to their portfolio.

7.3 Traditional medicine

Although the present study is focused on the prospects for allopathic medicines, an analysis of how changing IP will impact access to medicines in India should make at least brief mention of the influence of IP on the traditional medicines sector. Why is this? In India, 60-80% of patients seek remedies from traditional medical practitioners or alternative medicines,⁴⁸ so any discussion around access to medicines needs to recognise this fact. Also, it has been argued that the lack of recognition for IPR has substantially contributed to the degeneration of traditional knowledge systems, incentivising traditional knowledge to be passed through descendants, rather than entering into the public domain. Therefore, the impact of the introduction of product patents is likely to create very different dynamics in the traditional medicines sector versus the allopathic medicines sector. Further, there is substantial potential for India to be competitive in this sector. Both India (Ayurvedic, Siddha and Unani) and China have prominent traditional medicine pedigrees. There is also a gap in the market: while the trend of MNCs has been towards high-throughput screening of synthetic chemical compounds held in vast chemical libraries, the field is wide open for other companies focused on R&D in traditional medicines, which requires natural material collecting and expertise with large molecule screening. The Indian government recognises this potential and has launched a programme with the objectives to promote and protect its traditional medicines sector, and evolve pharmacopoeial standards⁴⁹ for Indian Systems of Medicines and Homeopathy drugs.⁵⁰

7.4 Risks faced by Indian firms

Despite their existing competitive advantages and promising opportunities on the horizon, Indian firms have certain weaknesses and therefore face certain competitive threats, which can be summarised as follows:

1. Indian companies are relatively new to the generics business in regulated markets and there are concerns regarding their ability to manage large product portfolios, entailing numerous regulatory filings, scaling up manufacturing, forging alliances, and legal skills to win on patent litigations.
2. The US based generic industry may be able to glean the same cost advantages as Indian firms through developing partnerships or greenfield sites in India. US based generics companies such as Watson, Ivax, and Apotex have already secured manufacturing agreements with Indian bulk active/dosage form manufacturers and in the medium term, this may mitigate some of the cost advantages enjoyed by the fully integrated Indian companies like Dr Reddy's, Ranbaxy and Sun.



3. The research-based industry has also been increasingly interested in marketing their own generic alternatives to their patented products, spurred by the impending flurry of patent expirations and the knowledge that the majority of the profits of a generic drug are earned in the first six months post patent-expiry.
4. The impending deceleration in patent expiries post 2007 presents another risk to Indian firms.
5. There is a moral hazard/ tragedy of the commons⁵¹ problem – being the reputation risk that the entire industry will face if one player cuts corners with regard to GLP or GMP.
6. Pursuing the NCE strategy is risky, not least because Indian firms have a skills shortage in the area of patent writing. It has been suggested that many existing patents written by Indian professionals can be easily circumvented; so even where an Indian company has produced an innovation, it may not be protected in international settings.⁵² In addition, Indian firms are strong in chemistry, but they are relatively weak in biology and clinical research and development skills, and these are essential to compete in the innovative, NCE drug category.⁵³
7. There is a risk that the co-operative strategies employed by some firms could get in the way of the competitive strategies of these firms, especially if Indian firms do not negotiate reasonable contract terms with MNCs and/or fail to ring-fence their competitive advantages.
8. Finally, there is a risk of protectionism in developed markets, since jobs lost from US and EU will not only be those in manufacturing but also in the more skill intensive research sectors.

7.5 Implications for market structure and brand name multinationals

Changes in market structure

As a consequence of the multiple changes in the industry, pharmaceutical analysts predict that some Indian firms in this currently fragmented market (200 firms in the regulated sector, over 22,000 in the unregulated sector) are likely to experience financial pain over the next few years, culminating in market exit of the less competitive firms, and resulting in a more consolidated market structure.

Implications for large MNCs

The impact of the evolving Indian business model is likely to have both positive and negative impacts on the major generic and branded MNCs. In the commodity based

generic business, low cost is the key success factor. US and European generic companies are faced with several options: acquire or partner with Indian firms, establish greenfield manufacturing sites in India or China, or differentiate and compete, with higher costs.

Over the next few years, the effect of Indian companies on large MNCs may be more negative, as Indian companies are likely to be very competitive in the generic sector and strong patent challengers targeting branded drugs previously viewed as invulnerable because of manufacturing complexities. On the positive side, branded pharmaceutical MNCs have the potential to gain access to cheaper API and dosing formulations from Indian companies.⁵⁴ The research-based industry may also gain from R&D collaborations that result in new NCE or licensing opportunities.⁵⁵ Finally, Western patent holders can gain from increased sales to the large domestic Indian market, where such sales would previously have been impeded by generic versions of on-patent products.

7.6 Conclusion: Prospects for Indian pharmaceutical firms and access to medicines

The Indian pharmaceutical industry has traditionally been an important supplier domestically and to the less regulated markets of Africa, Asia and Latin America. Due to the forthcoming acceptance of international patent law in 2005 and the increasingly developed technological capacity of the industry, Indian firms are expected to become a major participant in the global marketplace, including on the regulated markets (i.e. US and EU) and with increasingly sophisticated products. The characterisation of Indian generic companies as copiers, lacking innovativeness, is increasingly inaccurate. Indian companies are developing new drug delivery systems or alternative formulations of existing molecules, to improve dosing regimens. Several Indian companies are investing an increasing percentage of sales in novel product R&D, and having some success as well; Novartis has in-licensed NCE candidates from Dr Reddy's and GSK and Ranbaxy are working together in R&D, a development which would not be taking place if Ranbaxy had no capacity for innovation. In summary, the future looks very bright indeed for the Indian industry so long as firms can overcome their weaknesses and effectively counter risks to their strategies.

Some observers have voiced concerns that Indian pharmaceutical firms will move away from serving their traditional low-priced/high-volume markets as they increasingly focus on the more lucrative markets, imitating the product/market focus of the research-based MNCs. However, for several reasons, this concern may be unwarranted. First, Indian firms have pre-existing infrastructure, systems and organisational comfort in serving the low-priced/high-volume segment. So the incremental investment required to continue serving these markets will differ from the incremental investment a research based MNC would need to make in order to start serving these low-priced/high-volume markets. Indian firms also have a lower cost base than research-based MNCs, so serving this segment can be relatively more profitable for them.⁵⁶ Also, these markets can serve as



a stable 'cash cow' with which to fund the riskier strategies of Indian firms.⁵⁷ For these reasons, Indian firms may not face the same tension as the MNCs have felt between serving the low-priced/high-volume less regulated markets and the high-priced markets, so it may be theoretically expected that supply to these markets may continue alongside the increased emphasis on the more lucrative, regulated markets.



8 Implications of Changing IP on Product Level Access to Medicines in India

Many fear that the implementation of patent rights in developing countries will have a negative impact on access to medicines. But what is the line of reasoning that connects IP to access? The link is not a direct one. Rather, enhanced IP protection can cause a potential change in industry structure and types of competition and this can lead to changes in prices, quality levels and physical availability. Similarly, access to *new* medicines can also be affected by enhanced IP protection, but indirectly through IP's influence on the incentive structure to invest in R&D and further downstream, the number and type of new drugs that are developed through this investment. It is important to be clear about the line of reasoning so that appropriate policies, including competition policies and incentives to encourage public health enhancing R&D, can be implemented, where needed, to ameliorate potential negative effects of product patent legislation. The previous section considered some very important factors in the overall access to medicines scheme – changing firm strategies, and changing market structure. This section unpacks other factors affected by changing IP – competition at the product level.

8.1 IP and access to existing medicines

Access to existing medicines will be affected if prices, product quality and product availability change as a result of IP's influence on firm strategy, market structure or types of competition at the level of the firm or therapeutic category.

8.1.1 Translation of TRIPS into domestic law

Types of competition will be affected in India by the degree to which generic copies of patented products will continue to be legal, and this, in turn, depends crucially upon decisions that are made regarding the legal interpretation/translation of TRIPS into Indian law. The following examples are illustrative.

Data exclusivity⁵⁸

Domestic law regarding data exclusivity is still a matter under debate in India.⁵⁹ The US is currently encouraging India to take a very restrictive view of Article 39.3 on data exclusivity, whereby the originator's data for NCEs would remain confidential and



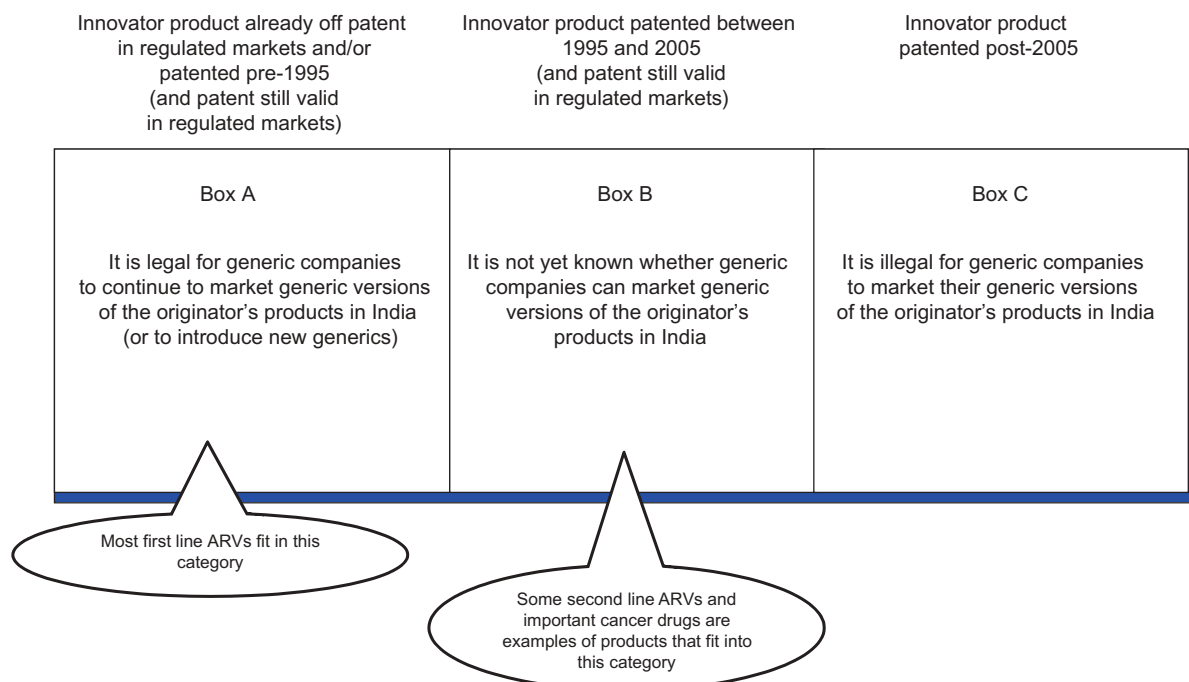
generic producers would therefore be precluded from using the earlier registrant's data to establish the safety and efficacy of the follow-on product even if the generic product is proven bio-equivalent. If the US-promoted view is translated into Indian domestic law, the practical result may be impeded or delayed entry of low-priced generic competitors.

National interpretation of product patent applicability

Changing IP will have differential effects on drugs, depending upon the date of patent filing, as outlined in the figure below. Two categories of generic products will remain legal on the Indian market after 2005, generic copies of products already off-patent in regulated markets and generic versions of products patented before 1995. It is important to note that these two categories comprise over 90% of the products on the market in India currently. There is also a category of generics that most certainly will NOT be allowed on the Indian market after 2005, and these are generics of products patented after 2005.

The contentious category relates to generics for all those products patented between 1995 and 2005. This category includes several of the protease inhibitor ARVs and important anti-cancer drugs. If Indian regulators grant a patent, post-2005, for a product that received its patent in a regulated market after 1995, then the innovator may apply for a stay order on the generic supplier to force it to stop producing the copies. This already happened with Novartis' anti-cancer drug, Gleevec, when Novartis was successful in getting a stay order to stop production of generic copies.⁶⁰

Categories of potential IP impact in India



However, national authorities have discretion regarding the criteria for patentability, particularly for defining what represents novelty. It is not yet known whether Indian regulatory authorities will take a relatively strict or lenient stance. However, if the history for granting EMR is any indication, the criteria for granting patents may be relatively strict. Fifteen EMR applications have been filed in India (as of November 2003), but the right to six of them has been denied, because they did not satisfy the eligibility conditions. Two pharmaceutical EMRs have so far been granted: one for the anti-cancer drug, Gleevec of Novartis and a second for Nadoxin, an antibiotic of Wockhardt Ltd. The rejected applications included the EMR request of GSK's blockbuster anti-diabetic drug Avandia (rosiglitazone), Swiss major Hoffmann-La Roche's application on HIV protease inhibitor saquinavir and Bayer's request for exclusive marketing rights on antibiotic moxifloxacin.

As per the provisions in the Patent Act, an EMR applicant should make a corresponding application in another country and receive marketing approvals in India as well as in that country. Further, the right is restricted to new drug molecules, meaning derivatives or alternative dosage formulations of the same molecule are ineligible.

Administrative capacity

Another area that is open to speculation concerns those products that have been placed in the 'mailbox', awaiting EMR approval currently, and patent approval post-2005.⁶¹ Over 5,000 applications have been received up until now under this stipulation for the mailbox. (This compares to 40/50 per year new molecules in the pharmaceutical field invented worldwide that would have appropriately qualified for patentability through the mailbox.)⁶² There has been some speculation that Indian authorities, lacking the capacity to approve so many applications, may take a long time to process the applications, in effect granting further time to the generic copies on the market.

8.1.2 Price increases

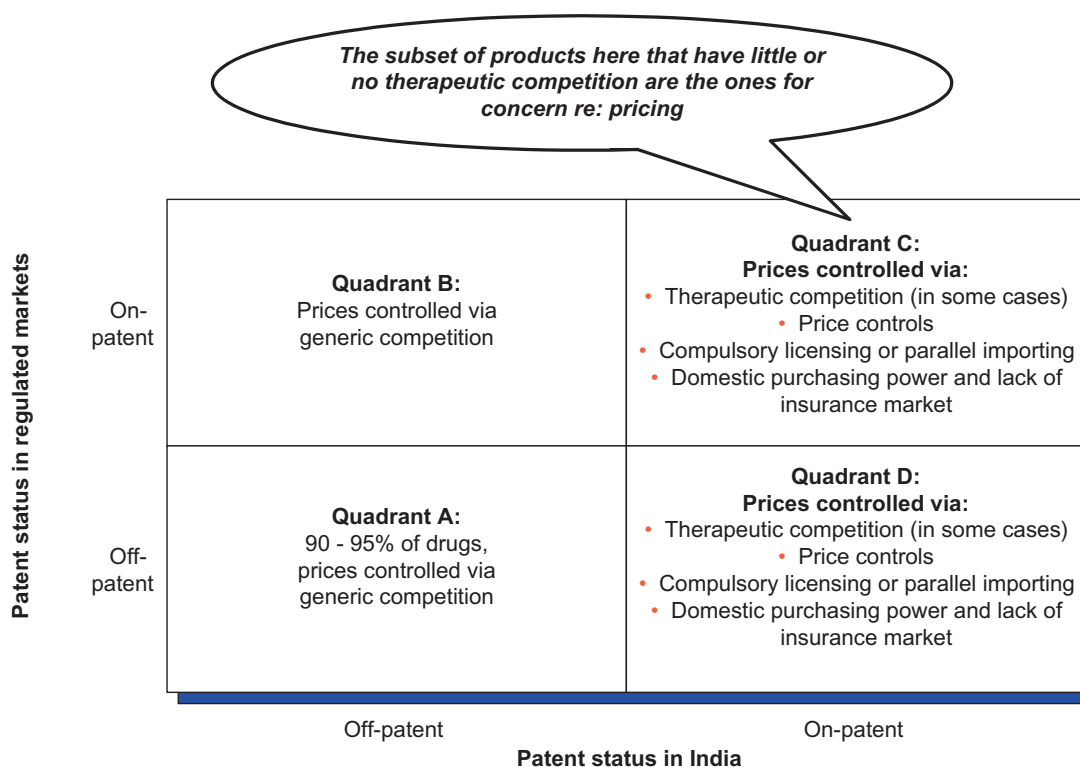
Some analysts predict mean price increases of over 200% with the introduction of product patent protection.⁶³ But this statement is misleading without unpacking how different product categories are likely to be affected. The figure below begins this unpacking process, showing several product categories, each having their respective competitive environment and thus pricing dynamics.

Price increases of the non-patented segment – 90% to 95% of market

General estimates about the patented segment of the Indian market can be derived from 1993 data showing that only 10.9% of the total sales values of the top 500 pharmaceutical products in India were comprised of drugs that were on-patent in the regulated markets.⁶⁴ Also, 95% of the drugs on the WHO Model Essential Drug List are no longer under patent protection. Referring to Box 1 in the figure, the prices of 95% of



Potential price control mechanisms



basic, essential drugs, and about 90% of drugs in general, will not be directly affected by the introduction of product patents in India, because generic competition will continue to fuel price reduction.⁶⁵ Generic price competition will also keep prices down in Box 2 – which refers to those products that are on-patent in the regulated markets, but which are not granted patent status in India after 2005, either because the patent was filed in regulated markets before 1995 or because the drug fails to meet domestic patentability criteria.

However, a general price rise could occur, even for these products in Boxes 1 and 2, if significant market consolidation takes place. Market consolidation would occur if less competitive firms are driven from the market as larger firms seek to gain increased market dominance, economies of scale and access to capital to fund R&D and then beginning to use their oligopoly powers to increase prices. Pharmaceutical analysts predict that such consolidation will take place, and academics have noted that it has already been occurring to some degree in India, and have attributed this as a partial cause to the general trend of increased prices of late,⁶⁶ suggesting that the more dominant firms are beginning to exercise their market power.

Price increases of the patented segment – 5% to 10% of market

How TRIPS is translated into domestic law will determine whether some newer drugs, like ARVs and cancer drugs, will end up in Boxes 2 and 3, and this, in turn, will affect the degree of generic competition experienced, and thus the pricing of these drugs.

Box 3 refers to those products that will be patent protected in India as well as in the traditional regulated markets; drugs patented after 2005 will fit in here, and potentially some drugs patented between 1995 and 2005 as well. Box 4 is expected to be quite a small number of products – those that have been developed and patented by Indian firms, but without the goal to export.

Of the approximately 10% of drugs that fall into Boxes 3 and 4, as noted, generic competition will not serve as a sanction on price escalation. However, other factors may still be at work to keep prices down, including the degree of therapeutic competition facing a particular product, domestic price controls, domestic purchasing power, lack of an insurance market, parallel importing and compulsory licensing. Each of these will be discussed in turn.

Therapeutic competition is a parameter of particular importance. Several studies simulate the impact of patent protection on prices and welfare in developing countries' pharmaceutical industries. These studies rely in aggregate data⁶⁷ or brand-level data⁶⁸ and simulate a transition of the patent protected segment of the pharmaceutical market towards a patent-induced monopoly by making various assumptions in the pre-patent market structure and market demand. Fink 2001 concludes that, if future drug discoveries are mainly new varieties of already existing therapeutic treatments, the impact of patents on prices is likely to be small, since therapeutic competition will keep prices down. However, where newly discovered drugs are medicinal breakthroughs, patents will allow pricing significantly above competitive levels and relatively large static welfare losses.

As for price control, the National Pharmaceutical Pricing Authority in India has the power to control the prices of drugs, if found to be excessive. However, MNCs can manipulate the import costs, and government has little ability to check for overpricing for new drugs for which the costs are not known, since there are no benchmarks with which to check the claims of manufacturers. Ultimately, the effectiveness of price control depends on the bargaining power of the government and the manufacturers. If the patentees do not want price control, they can simply withdraw from the market.⁶⁹

Domestic purchasing power and lack of an insurance market also have the potential to keep prices down. Even though India's population exceeds one billion, average per capita income is \$400 per year; 70% of people live in rural villages of less than 5,000 persons and these people rely on the 24% of GDP that comes from agriculture. Also, India's domestic healthcare system covers less than 4% of its population, and 75% of



expenditure on medicines is borne privately by patients.⁷⁰ Although these arguments support the idea that average prices post-2005 will stay below Western levels, it is just as likely that patent holders will skim the Indian market with new drugs, pricing their drugs according to incomes of the wealthy middle-class. The latter has been a common strategy of patent owning MNCs as they enter new markets, partly because they do not want to jeopardise the prices that they have been able to charge in more developed economies.

Compulsory licensing is yet another option for making sure that essential drugs are available at prices to support public health. However, many developing countries face obstacles to being able to utilise this TRIPS flexibility. The United Nations Development Programme's 2001 Human Development Report concluded that 'pressure from Europe and the United States makes many developing countries fear that they will lose foreign direct investment if they legislate for or use compulsory licenses.' Other potential problems stem from economic, legal, practical, and administrative barriers.⁷¹ Indian firms may also become increasingly antagonistic towards compulsory licensing, as they become patent originators themselves. Parallel importing is another TRIPS flexibility to access less expensive medicines; this mechanism seems to have some practical merits over compulsory licensing, with the result that it has been used more extensively and less controversially.⁷²

In summary, prices of about 90% of the drugs on the market in India will not be affected by the introduction of product patents in India, unless by the relatively longer term potential for market consolidation to an extent that would reduce general competitive levels on the Indian market. Prices of the approximately 10% of drugs that potentially will be affected by the introduction of product patents may still be held in check by other factors. The subset of products, which have few therapeutic competitors, is the subset for pricing concern.

8.1.3 Quality

Changing IP has caused firms in India to increase their export focus to regulated markets. This has created the need for greater compliance with GLP and GMP, and India now has more FDA approved plants than any other country except the US. This is likely to cause an overall upward shift in the minimum acceptable quality level on the domestic market as well, as firms begin to implement quality-enhancing systems and processes in competition with one another. Consequently, changing IP may have an indirect quality-enhancing effect, through its influence on the market orientation of Indian firms.

8.1.4 Availability

There has historically been a lag of 4–5 years between the introduction of new products on the regulated markets and introduction of generic copies by Indian firms. Indian

generic manufacturers typically wait to see what kind of market performance the product will have, and this helps inform their decision whether to invest in the development of the generic copy. Once this decision has been made, the process of clinical testing and obtaining marketing approval takes about three years for the first applicant in India.⁷³ There are exceptions – particularly where the market success is felt to be obvious before product introduction. GSK's ranitidine (Zantac) was one such exception; generic copies were available on the Indian market from the first day that GSK's subsidiary marketed the drug.⁷⁴

The introduction of product patents in India means that availability and pricing of new products on the Indian market will be completely at the discretion of the patent holder. According to some analyses, the time lag of availability of affordable versions of patented drugs under the new IPR regime could increase to 15 years,⁷⁵ and possibly even longer depending on domestic decisions regarding the interpretation of Article 39.3 of TRIPS as well as decisions taken about patentability criteria. Thus, timely availability of low-priced generic alternatives to patented drugs will be negatively affected by the introduction of the product patent regime, although the patent holder may be more willing to place the higher-priced patented version on the market in countries where IP is protected.

8.2 IP and access to new medicines

One of the theoretical advantages of introducing product patents is the increase in incentives to develop new products, thereby improving the number and quality of new drugs to treat health problems. However, the effects might differ for developed versus developing country firms. From the perspective of developed country firms, theoretical economic models (Chin and Grossman 1990, Deardorff 1992) show that the profits coming from newly available patent rights in less developed countries are only incremental to profits coming from other patent protected markets, and therefore the amount of additional innovation from MNCs, arising from product patent introduction in developing country markets, is expected to be negligible. Quite a different incentive effect may be expected for developing country firms, however. Emerging evidence on this subject follows in the next few sections.

Evolving R&D expenditure

Across the Indian industry as a whole, there has recently been a slight, but not significant increase in R&D spending, as a percentage of sales.



Industry-wide change in R&D spend⁷⁶

Reported R&D expenditure by Indian pharmaceutical firms (1991 to 2000)

Year	Amount spent (US dollars)	R&D (% of sales)
1991	\$36.5 million	1.3%
1992	\$29.4 million	1.4%
1993	\$37.0 million	1.5%
1994	\$39.8 million	1.9%
1995	\$44.6 million	2.0%
1996	\$45.5 million	1.8%
1997	\$51.5 million	1.9%
1998	\$56.0 million	1.9%
1999	\$61.2 million	2.0%
2000	\$73.6 million	1.9%

Source: Department of Science and Technology Research and Development in Industry; and Organization of Pharmaceutical Producers of India

However, the overall industry trend masks the much higher R&D activity amongst the leading firms in India, as detailed in the Table below, and explained in the next section.

R&D spend of leading Indian companies⁷⁷

Company	2002 % of sales	2003 % of sales
Ranbaxy	3.1%	6.9%
Dr Reddy's	6.1%	7.6%
Cipla	3.3%	3.3%
Sun Pharmaceuticals	1.0%	3.4%
GlaxoSmithKline	0.4%	0.0%
Wockhardt	6.2%	5.7%
Aurobindo	0.8%	1.2%
Cadilla Healthcare	3.5%	2.1%
Lupin Ltd	2.7%	2.5%
Divi's Laboratories	2.3%	2.4%
Matrix Laboratories	0.6%	0.5%
Nicholas Piramal	1.0%	1.1%
TOTAL	2.8%	3.7%

The increased R&D activity is due in part to IP changes and the strategic reorientation they induce, in part to the increasing technological capacity of the top Indian firms and in part to other domestic policies. On the latter point, in an attempt to improve the rewards for R&D, the Indian Drug Policy Control Order stipulated that innovative drugs and processes developed and produced in India would be exempt from price control for five, or in the case of new drugs, ten years.⁷⁸ The government also issued guidelines in 2000 on how Indian companies could qualify for a 10-year tax holiday on income arising from R&D.

Although R&D expenditure of 6–8% of sales is less than the average of 15% spent by the research-based MNCs, it is important to remember that Indian companies have a lower cost-base, so the productivity of this R&D investment may be relatively higher versus the MNCs. And in fact, the fruits of this R&D expenditure have already started to



pay off. There has been an acceleration of regulatory filings for the regulated markets (especially the US). For example, around 112 Indian ANDA submissions are expected in 2003, compared with 40 filings in 2001. The number of DMF filings by Indian companies as a group was 58 for the first quarter 2003, compared with 50 for the year in 2001. This emerging penetration of Indian firms into the US market is a fact that is surprising to many, as is the expectation that one-half of all FDA DMF and ANDA applications in 2004 will come from Indian firms.⁷⁹

Composition of R&D expenditure

From an access to medicines standpoint, two questions remain about the R&D spend of Indian firms. A first concern is the degree to which Indian firms are producing truly innovative products that provide health benefits. A second question relates to the degree to which Indian firms are investing in R&D for disease specific to domestic needs or the needs of developing countries. Answers to these questions require an examination of the R&D spend (inputs) and patents (outputs) at a disaggregated level.

Level of innovation

Overall, the R&D pipeline of Indian firms has principally addressed established rather than new drug targets, and has concentrated on imitating and adapting pharmaceutical products developed in foreign countries. So the 'quality', in terms of degree of innovativeness, of Indian R&D spend as well as types of 'discoveries' (as indicated by the number of DMF and ANDA filings but a dearth of NDA filings) is disappointing.⁸⁰ However, the larger Indian companies (Ranbaxy and Dr Reddy's) that are keen to move up the value chain are investing increasing sums in novel product R&D. Dr Reddy's and Ranbaxy are targeting proprietary drugs and new drug delivery systems and NCE approvals in the mid to longer term (5–6 years). Current R&D stands at over 6% of sales for both of these companies with the goal of each being 10% over the next five years.

Degree of focus on neglected diseases

The need for more investment into neglected diseases is clear. Of the 1,223 drugs introduced between 1975 and 1996, only 13 were aimed at tropical diseases. In 1998, the world spent \$70 billion on health research, but only \$300 million of this was directed at developing an AIDS vaccine and a miniscule \$100 million was devoted to malaria research.⁸¹

The hope that that developing country firms might be more likely than their Western counterparts to invest into R&D for neglected diseases is also evident. A WHO working group pointed out 'Potentially large economic and social benefits could be gained by enabling private companies and research institutions in endemic regions to contribute to R&D work on new treatment. Furthermore, research facilities based in these regions may be comparatively well placed to achieve quick solutions. This is because the

practice of health research relies heavily on close contact with other parts of the health sector, on the local epidemiological environment, and on the clinical, behavioural, and social sciences that are tied to both national and global frameworks.⁸² Hopeful observers also point to useful pockets of expertise of developing country firms and a wide variety of potentially useful medicinal plants in developing countries. For example, Vietnamese scientists extracted an effective malaria drug from a tree long used in traditional medicine.⁸³

However, views conflict as to whether this need and hope for developing country companies to invest in R&D for neglected diseases will pan out in practice. Kanavos et al take a positive view, supposing that the decreased costs of developing country firms may make it more commercially appealing for them to invest into development of products for neglected diseases.⁸⁴ Fink takes a similarly positive view: ‘...one cannot dismiss the possibility that, in the long term, patent protection in India could affect private R&D decisions and contribute to new drug discoveries – especially against diseases particular to developing countries.’⁸⁵ Another reason for optimism – some Indian firms are not under the same pressure from public markets;⁸⁶ at least, the majority of Indian companies are predominantly privately controlled. However, others take a more pessimistic view, arguing that it is just as likely that developing country based R&D programmes will focus on where the money can be made quickly and in large amounts – for diseases prevalent in the larger and richer markets.

Most of the empirical evidence supports the view that R&D spend of Indian firms will go towards diseases prevalent in rich countries. Scherer and Watal 2001 cite the fact that as of 1999, only 16% of R&D expenditure in India was targeted towards tropical diseases or developing country markets, and about half of the 16% was focused on developing more suitable products for diseases of global incidence. Kettler and Modi 2001 argue that new incentives will be necessary for Indian firms to invest into R&D for neglected diseases, just as they are necessary for companies in rich countries.⁸⁷ Similarly, Lanjouw 1998 interviewed Indian pharmaceutical executives and found that all were very clear that their target market for new drug discovery research is one-hundred percent global. This is consistent with the view of pharmaceutical equity analysts’ opinions, solicited in the course of research for this study. Indian firms have told investors that they are focusing their R&D spend on those product categories that do not require large sales forces and do not require large numbers of patients in clinical trials. So, generally speaking, development of oncology products (requiring 200 patients in clinical trials and a small sales force) is preferred to cardiovascular products (requiring 10,000 patients and a large sales force).⁸⁸ Even the Indian government-funded ‘Knowledge Partnerships’⁸⁹ are primarily concentrated on diseases like cancer, diabetes and cardiovascular problems, with only a handful targeted towards tropical diseases and TB.⁹⁰

However, small seeds of hope reside in the investor announcements a few Indian companies have made to say that their NCE research is focused on therapeutic



segments where competition is low and where market opportunities may not be big enough to attract the attention of major pharmaceutical MNCs.⁹¹ The pursuit of such 'niche' opportunities that have been overlooked by the majors offers some hope that R&D could focus on developing products for smaller markets, including those for neglected diseases.

However, publicly funded incentives are likely to be needed as well, especially for the most neglected diseases. Dr N.K. Ganguly, head of the IMRC, said, ' Even in India, the commercial pharmaceutical companies focus mostly on products for the rich, such as drugs for hypertension, obesity, ulcers...we want to change that'. He was referring to the establishment of Drugs for Neglected Diseases Initiative, a \$250 million initiative begun with MSF and a group of developing countries to research diseases ignored by Western drugs companies.⁹² The technology transfer briefing paper, another in this series commissioned by DFID, details other similar types of funding mechanisms that help provide not only technology transfer, but also incentives to engage private companies in the development and manufacture of such products.⁹³



9 Evolving Prospects of the Chinese Pharmaceutical Industry⁹⁴

9.1 The Chinese industry today

As in India, the pharmaceutical industry in China is highly fragmented. There are approximately 6,800 Chinese pharmaceutical companies, of which 5,000 produce medicines and the remainder are involved in related activities such as packaging and equipment supply. Of the 1,300 synthetic medicines produced in China, 97% are copies of originators' products. Only around 15% of firms have GMP certificates.⁹⁵

During the early 1980s, the manufacturing joint-venture was an important vehicle for inward investment in China, both for bricks and mortar and for 'software' such as effective business management techniques. This inward investment was part of China's 'open door' policy, which began under Deng Xiaoping. It is now recognised, however, that the Chinese pharmaceutical industry, like the beer industry and others in which there had been considerable inward investment in factories, has reached considerable over-capacity. Over-capacity has meant that many domestic state-funded companies are not profitable. Steps have been taken to encourage rationalisation – most notably by requiring Chinese companies to comply with GMP by June 2004. This is expected to lead to a reduction in the number of firms to around 3,500.

China started moving towards protecting intellectual property in 1993, with reform of its patent laws. Accession to WTO (and TRIPS) followed in 2002, and China has now enacted regulation extending all patents to twenty years, and data-exclusivity for six years. The evolving business strategies of Chinese pharmaceutical firms are not entirely comparable to the strategies of Indian firms, primarily due to a relatively higher level of State involvement and a relatively lower technological capacity of domestic firms in China.

9.2 Evolving strategic options for Chinese firms

As with the Indian firms, Chinese firms face two general strategic routes: compete or co-operate with foreign MNCs, although Chinese firms are much further away from making a big splash on the regulated markets.



9.2.1 Competitive business models

Generics

The importance of price in the generics market means that a gradual global migration of manufacturing to low-cost countries such as China is likely, particularly in the context of the impending surge of patent expiries from 2004–2007, and the increasing technological capacity of the Chinese industry to meet GMP standards.

Biotech

The Chinese government is encouraging a biotech industry focused on both innovative and generic biotech products. For example, the central government attempted to kick-start the sector between 1996 and 2000, investing over 1.5 billion Yuan (\$180 million),⁹⁶ through such programmes as the National Natural Science Fund, the Torch Programme, the 863 High-Tech Program and the Five-year Plans.⁹⁷ Between 2000 and 2005, the government plans to invest another 5 billion Yuan, and private money is beginning to trickle in as well.⁹⁸

Between 1966 and 1976, the Cultural Revolution did its best to erase all forms of scientific innovation in China. Many scientists left the country, and now the government is holding a recruitment drive to attract 200 scientists from abroad with Western-style salaries.

The government's strategies are starting to pay off. China's biotech expertise already stands out at the international level, with strengths in gene mapping, transgenic technology for animals and plants, gene therapy technology, stem cell research, gene chips, and gene research of some major diseases. China has a number of world-class scientific biomedical institutions – the North and South Genome Centres, the Institute of Materia Medica, Singh and Beijing Universities, for example. The Beijing Genomics Institute's industrial-scale sequencing operations played a key role in the international Human Genome Project, making China the only country in the developing world to have joined in.

However, the industrialisation of biotechnology still lags behind the Western world. The approximately 50 start-up biotech companies, mainly in and around Beijing, Shanghai and Shenzhen, are focused on generic copies, rather than NCEs, of molecules produced by cloning and fermentation processes. What China needs is an industrial base that can support research that will complement the work done in universities and academic institutions. And funding is an issue as well. Despite the government financing already mentioned, the expansion of Chinese biotechnology is still held back by lack of funding. Long development times and scientific uncertainty mean that significant funds are needed to develop a successful product. Another problem is management – finding people who have both scientific expertise and good business sense. Yet another

problem is IP protection. Although patent laws have been strengthened, IPR enforcement is weak. Finally, although the government has been working to establish national guidelines regarding bioethics, even with such regulations in place, enforcement and monitoring need to be improved.

Traditional Medicine

There are reasons for optimism in the Chinese traditional medicines sector. Shanghai's 2001–2005 development plan assumes the establishment of 10 medicinal herbal production centres and a traditional Chinese medicine test centre. With a standardised product, it is possible to envisage a greater global usage of traditional Chinese medicine, particularly where full development as a registered medicine is possible.

China is beginning to strengthen its traditional Chinese medicine with a dose of biotech as well. For example, the Shanghai Traditional Chinese Medicine Innovation Centre has been working with PhytoCeutica, an American biotechnology firm, to create a database of 9,000 traditional herbs and 150,000 recipes. In Hong Kong, the Biotechnology Research Institute is screening molecules isolated from traditional Chinese remedies to see if they have any effect on receptors known to be involved in neurodegenerative disease, via a technique that is common in Western-style drug discovery. Opportunities presented by modernisation of traditional Chinese medicine are all the more attractive considering that the approach is outside the usual core competencies of most MNCs.

NCEs

In the longer term at least, some of the major current domestic generics producers such as the 999 company, Hua Bei and Dong Bei are looking to migrate towards truly innovative R&D. The North China Pharmaceutical Group is focusing on four areas: biotech products, innovation through small molecule NCEs, traditional medicines and natural product screening, and formulation technology. A number of institutes in China have a focus on the development of small molecule NCEs, e.g. the Institute of Materia Medica. Most domestic generic companies invest around 2% of their sales into R&D.

9.2.2 Co-operative strategies

China is the world's tenth largest market, and it is expected to grow at 18% per annum, to \$10 billion by 2005. The market potential, reforms to the patent system and pharmaceutical-related regulations, and the spread of medical insurance are all factors making China an increasingly attractive market for foreign pharmaceutical investment.⁹⁹ China's capability for low-cost generic manufacture remains the primary attraction, however.

The importance of South-South partnerships deserves mention. Aware of the threat posed by lower costs in lesser-developed countries, including China, many Indian



companies are beginning to build their own base in such countries. For example, Aurobindo has a plant in China to provide cheap raw material for penicillin and many other Indian companies have subsidiaries in other third world countries (e.g. Brazil, Thailand, Nigeria) to cater to local demand.¹⁰⁰ Within the ARV segment, China has been supplying small molecule intermediates and APIs to Indian firms as well as to many developing countries with nascent ARV production capabilities.¹⁰¹

Other co-operative opportunities are starting to present themselves as well. For example, clinical trial out-sourcing holds potential in China for a number of reasons. As a major potential market, MNCs see that conducting clinical trials may assist subsequently in product registration marketing and in the appropriate use of new medicines. MNCs may also be drawn to China for clinical trials testing because of low costs and large pools of untreated patients. China also has strong links with Taiwan, with its important public sector research labs, large scale clinical test facilities, shared language and good manufacturing practice. China and Taiwan together provide the vehicle for better relationships with MNCs.¹⁰² Other parts of the R&D process provide further opportunities for collaboration, as MNCs are increasingly relying on alliances, not just for in-licensing of compounds, but for access to all kinds of developing technologies and new skills. Box 3 below illustrates selected R&D partnerships involving MNCs in China.

Box 3: Research collaboration by multinationals in China

'Accelerating innovative pharmaceutical research and development in China: A case study', IFPMA, Geneva, February 2003. D. Webber.

Shanghai Institute of Materia Medica (Chinese Academy of Sciences) and GSK: A joint project established in Shanghai in May 2001 to develop a Recombinatorial Chemistry Laboratory.

Chinese National Human Genome Centre in Shanghai with Roche: Support of \$300,000 for research into diabetes and schizophrenia.

Shanghai Jiaotong University and AstraZeneca: A large joint study designed to identify genes linked to schizophrenia, based on the University's database of DNA samples related to psychiatric disorders.

Chinese Academy of Sciences and Bayer: A scientific and technical co-operation agreement promoting joint research projects and supporting Academy scientists. Bayer provides around \$600,000 per year in joint projects with Chinese research institutes.

In addition to the above collaborations, AstraZeneca recently opened its East Asia Clinical Research Centre in Shanghai which aims to employ over 40 staff and another multinational became the first one to open a basic research centre in China.

Despite the co-operative opportunities described above, many barriers remain, from the perspective of a foreign pharmaceutical manufacturer wanting to work in China, including with Chinese firms. To start with, many MNCs prefer to conduct business in India, put off by the language barriers and relatively lower level of chemistry skills in China.¹⁰³ Further barriers to foreign investment include the uncertainty surrounding intellectual property protection and registration approval processes, and regulatory discrimination between local and overseas firms.¹⁰⁴ From the perspective of the research-based industry, problems in the area of intellectual property include:

- Copycat and generic drugs remain on the market; marketing approval by China's State Drug Administration does not require that the drug maker have a valid patent.
- The exclusive marketing period for new drugs is only five years after commercialisation (versus six years in Japan). However, foreign pharmaceutical manufacturers that import the bulk drug are excluded from this protection. Consequently, Chinese drug makers are easily able to obtain marketing approval for and commercialise generic formulations before patent protection expires.

'Problems' in the area of registration approval processes include the fact that it takes 2–2.5 years (from NDA filing to approval), compared with 1–1.5 years in Japan, Europe and the US. Foreign drug makers also feel that there is discrimination in favour of local producers. Many of the domestically produced and registered drugs do not comply with GMP standards observed on the regulated markets, thus making those who do invest in quality processes unhappy about the lack of return on their development and quality control costs. In addition, the transaction system for drug approval is thought to be skewed in favour of domestic companies, not least because of the conflict of interest that arises because the drug registration authority is charged with both drug approval and promotion of the domestic industry. For instance, it is not uncommon for data from a pending new drug application to be leaked to Chinese drug makers.¹⁰⁵

9.3 Conclusion: Prospects for Chinese pharmaceutical firms

China's strengths lie in low-cost generic ingredient and finished product production, although its chemical synthesis abilities lag behind India. Within the innovative products category, Chinese firms are strong in biotech and traditional medicine.¹⁰⁶ R&D partnerships involving MNCs are at a nascent stage; a need for better translational processes between academic centres and industry has been identified, as well as improved ability to commercialise inventions in general. The institutional environment to support IPR is not aligned with reforms to product patent laws.



10 Implications of Changing IP on Product Level Access to Medicines in China

China started moving towards protecting intellectual property in 1993, with reform of its patent laws. Accession to WTO (and TRIPS) followed in 2002, and China has now enacted regulation extending all patents to twenty years, and data-exclusivity for six years.

In terms of assessing the impact of changing IP on access to medicines in China, the same parameters that were analysed in the Indian situation are also relevant in China, namely how TRIPS is affecting market structure and competition for existing medicines, at the firm and product level, and how it affects R&D incentives for new medicines. Unfortunately there is relatively less data available on these points as compared with India.

However, some of same conclusions can be drawn – e.g. that relatively more innovative products, for which there is little therapeutic competition, are the ones for which there is likely to be an access problem. HIV/AIDS medicines fit into this category, and there are some revealing examples of the access problems that China is already experiencing in this product category.

10.1 Generic ARVs

Between three and five companies are currently believed to be supplying the Chinese market with generic ARVs.¹⁰⁷ When GSK's Chinese patent expired on AZT, Northeast Pharmaceuticals Group (Chinese company) was granted a license by Chinese regulators to sell its generic version of zidovudine (AZT). Shanghai Desano Biopharmaceutical Company (also Chinese) received approval from Chinese regulators to manufacture and sell didanosine (ddI) and stavudine (d4T). While both of Bristol-Myers Squibb's formulas, ddi and d4t, are protected by patent law in China, allegedly Desano applied to the drug administration for approval for its drug before Squibb applied for a patent. It has also been reported in the press that Desano is using a slightly different formula than Squibb uses.¹⁰⁸ A third supplier to the Chinese market is the Indian firm, Ranbaxy, which has also registered two ARVs in China: AZT (in two dosages) and nevirapine.¹⁰⁹

10.2 Patented ARVs

Despite the availability of generic versions of some ARVs, the ARV drugs available in China are therapeutically inadequate. Some drugs that are critical to WHO recommended guidelines are either missing from the market (lamivudine) or very expensive (efavirenz). The four drugs that are now being produced in China are not on the WHO's list of recommended first-line treatments for HIV/AIDS; two of the drugs are even on a 'not recommended' list on the latest US National Institutes of Health treatment guidelines.¹¹⁰

Lamivudine

For example, the GSK product, lamivudine, indicated for Hepatitis B and HIV/AIDS on Western markets, is available in China, but only for the Hepatitis B indication and only in the 100mg dose for Hepatitis B.¹¹¹ Therefore, the medical practitioner takes on increased risk if he/she prescribes it for HIV/AIDS, and the patient must become involved in a more complicated dosing regimen, involving breaking up pills. Also, it means that post-marketing surveillance data will not be collected on the HIV/AIDS indication. The reasons for GSK's decision remain unclear; what is clear is that GSK's monopoly position, enabled by product patent protection and domestic production of the product from the primary stages,¹¹² allows it to control the product's usage (via the indication for which the product is registered), in support of GSK's strategy for the product, and thus, IPR is an indirect barrier to the availability of product for HIV/AIDS.

Viracept

A similar example relates to Roche's ARV, Viracept. Although Roche has an 'access' pricing policy¹¹³ for Viracept in China, the programme is meaningless on a practical level, since Viracept is not even registered in China. Drugs that are not registered cannot be imported into China, so the product is not physically available in China.¹¹⁴

Efavirenz

A third example relates to Merck's ARV efavirenz. Merck offers an 'access' price for efavirenz in China, however, there are two problems with the offer: 1) The offer has not been widely advertised, so that procurement people are unaware of it, and 2) the difference in price between the preferential price and the normal procurement price amounts to \$7/box, which would not compensate for the increased time and effort taken to access the preferential price.¹¹⁵

10.3 Discussion: Emerging lessons from China

Access barriers relating to registration and the practical details of 'access' policies, are the type that are not immediately linked to changing IPR regimes, but in fact they are



directly related to the patent holders' monopoly rights, and the market control this provides.

As discussed in Section 9.2.2, foreign firms working in China are concerned about the level of IP protection in practice as well as the favouritism shown to domestic firms. The flip side of this is that domestic firms have quite a bit of latitude in terms of being allowed to place generics on the market legally. If the patent holder does not produce its API domestically, then the local firms can place a copy on the market, for example. The question arises as to why domestic firms are not doing this more often, for example, with the ARVs mentioned above. One answer may be that, unlike India, domestic firms do not have the same level of technological ability.¹¹⁶ So one answer to increased access to medicines in China, under current IP conditions, must be that Chinese firms need to upgrade their technological capacity. However, given IP concerns, they are unlikely to receive technology transfer, for proprietary drugs, from the research-based industry. Another possibility is that generic producers have developed ARVs, but that these are not yet on the market due to being caught up in the lengthy registration process.¹¹⁷ A third possibility is that the market has only recently looked commercially interesting to generic manufacturers, since the government has only recently acknowledged the scale of the epidemic, and begun to release official figures.

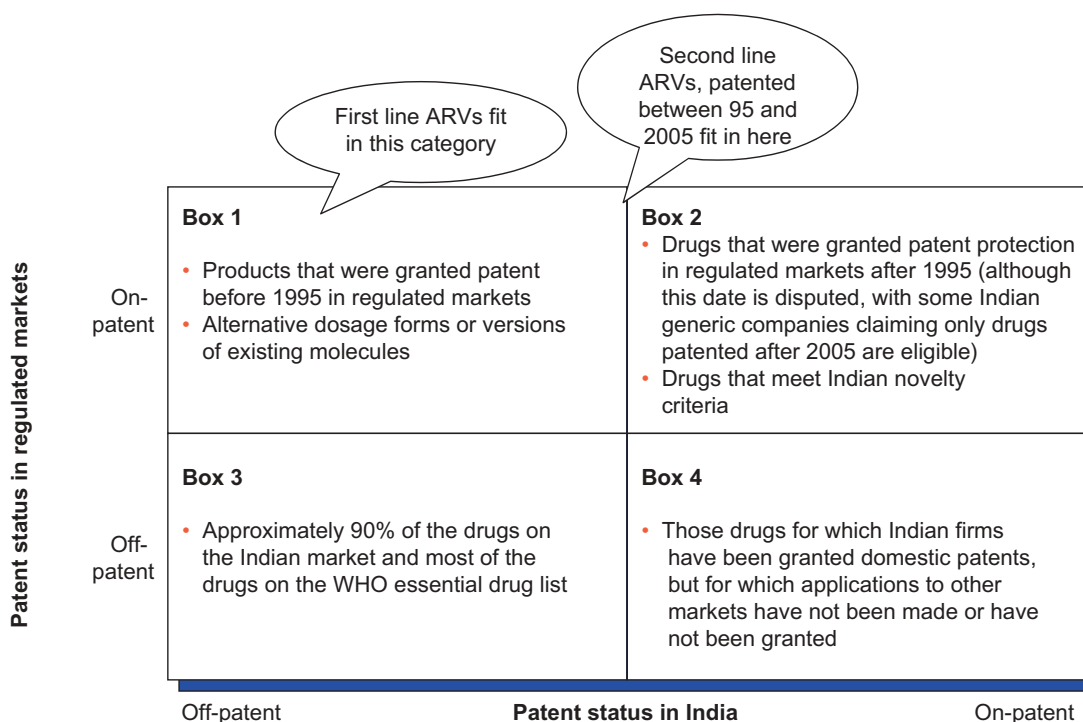
It is ironic that, despite the fact that China started respecting pharmaceutical product patents more than two years ago, the regulatory and legal infrastructure to support IPR lags behind. The implication is that the introduction of a product patent system, when not accompanied by an institutional environment that supports IPR, may make the intended gains from compliance with TRIPS¹¹⁸ illusory in the short to medium term, whilst the welfare losses from reduced access to certain medicines may be more immediate and obvious. A second implication is that a multitude of country-specific institutions and processes influence the practical impact from compliance with TRIPS, therefore we are likely to see some very different experiences and impacts as countries implement pharmaceutical product patent protection.

11 How Changes in India and China will Affect the Rest of the World

As Chapter 5 revealed, the availability of quality, low-priced generic ingredients and finished products has without a doubt been a major benefit to access within India and China as well as to other countries.

As for how changing IP will affect the type of help that Indian and Chinese companies have been able to provide, for example towards the ARV efforts described above, it is relevant to consider not only the patent situation in the exporting country (India, China) but also that of the importing country.

Post-2005 world-wide IP status



Referring to Box 1 above, some African countries have already implemented patent laws in line with the more regulated markets.¹¹⁹ Thus, although generic copies of pre-1995 patented products, like some first line ARVs, will continue to be produced and exported from India, domestic patent laws in the more regulated countries (including some in



Africa) will make it illegal to import the drugs, unless the patent holder has waived its rights or licensed the patents to generic firms.¹²⁰

Some importing countries are finding ways to get around the access problem, and enable the importation of generic version of ARVs that are under patent domestically, including finding IP loopholes in domestic legislation. For example, the South African Medicines Control Council gave a 'Section 21 exemption' to allow MSF to import normally illegal copies of patented ARVs from Brazil.¹²¹ Kenya also found a loophole in domestic legislation – something called the 'Industrial Properties Act', which gives the ability to override a patent, thereby allowing generics to be imported.¹²² The regional grouping OAPI says that there is no conflict between Doha and OAPI, since OAPI allows for government use, a variant of compulsory licensing, to import generic copies.¹²³ Brazil has yet another way of getting around patents; Brazil requires foreign firms to manufacture drugs – or any other patented product – within Brazil, or lose that right to a local competitor after three years. Voluntary licenses also have the potential to get around the IP problem, although there must be certain conditions present to induce the originator to offer licenses, and these conditions are arguably only present in the large market economies with certain pre-existing manufacturing capabilities.

Other options for accessing less expensive supply include trying to access differential prices of the originator's product through 'access' programmes, pooling demand for bulk purchasing, tapping in to less expensive sources of the originator's product through parallel importing, issuing a TRIPS-compliant compulsory license, or in eligible countries, ensuring that domestic legislation allows the country to take advantage of the TRIPS extension for least developed countries until 2016.¹²⁴ For those patented medicines that become unavailable from Indian sources, domestic production may prove to be another option, perhaps used in conjunction with a compulsory licensing or 2016 extension, but only by those few less developed countries who are able to develop some domestic ARV manufacturing capacity.¹²⁵ China may provide an alternative supply of intermediates or API in this situation.¹²⁶ All of these options have their practical difficulties.

On the subject of world-wide access, although this paper focuses on access to medicines in developing countries, it is probably worth devoting one paragraph to point out that, ironically, consumers in the regulated markets, particularly the US, France, Italy and Spain, stand to benefit from the introduction of product patents in India and China. As explained earlier, Indian and, to a lesser extent, Chinese firms have begun to increase their focus on exports to the regulated markets, in response to the diminishing growth potential from future domestic sales. The end result of this export focus will most certainly be more competition and lower prices in the US and Europe for generics and for alternative dosage forms, delivery systems and even perhaps, alternative chemical varieties of the more innovative products.

Some observers have commented that the implementation of TRIPS, and the attention

that it has drawn to the ARV price differential between the developed country price and the Indian generic company's prices, may be the start of the undoing of the current intellectual property system.¹²⁷ This is an important risk for the research-based MNCs. However, a more immediate, and perhaps less recognised, risk for generic and research based MNCs alike, and brought on partly by TRIPS, will be the loss of revenues felt as Indian firms begin to encroach on what has traditionally been their turf.



12 Potential Role for UK Government: Dialogue, Monitoring, Technical Assistance, Further Research

The following paragraphs provide ideas for monitoring, dialogue, technical assistance and further research that the UK government could potentially lead or contribute towards.

Initiatives to help link up universities with industry

As mentioned in the China section, universities are engaged in some very good technical work, however, better links between industry and universities are needed. Since the productivity of an industry is a function not only of the efficiency of its component institutions, but also the ways in which they interact, improving upon these linkages should not only increase productivity but should also allow better commercialisation of products discovered within universities in developing countries.¹²⁸ How exactly to create and structure these links, however, would need to be investigated for each country, taking into consideration the underlying country resources and policy settings which set the framework for IP implementation.

For example, a number of Organisation for Economic Co-operation and Development governments have shown considerable interest in emulating the Bayh-Dole Act of 1980, a piece of legislation that is widely credited with stimulating significant growth in university–industry technology transfer and research collaboration in the United States. However, efforts to emulate the Bayh-Dole Act elsewhere, particularly in developing countries, are likely to have modest success at best without greater attention to the underlying structural differences among the higher education systems of different nations.¹²⁹

Help in negotiating contract terms

Developing country firms are in the weak negotiating position when it comes to negotiating contract terms, and in particular, license fees. There may be a role for international assistance here.

Technical assistance in determining royalty rates and finance for royalty payments

If voluntary or compulsory licenses are sought, there is very little precedent in terms of setting economic royalty rates. Technical assistance may be needed to help assess an appropriate rate. If the rate is very high, donors may also help provide finance for the royalty.¹³⁰

Patent processing expertise

Developed country governments could help developing countries improve their expertise in judging whether a patent application is justified. Collaboration with the United Kingdom Certified Institute of Patents Agents might be useful, since they provide training to patent professionals in law, science, engineering, and patent infringement.

Monitoring the impact of TRIPS

The WHO co-ordinates a network of academic institutions, responsible for monitoring the impact of TRIPS implementation, but some of the country data has been difficult to interpret thus far.¹³¹ Monitoring price changes in India and China, overall and for specific product categories will be very important, as will monitoring the R&D spend (aggregate and composition) and patent activity (overall, and by type of patent – including traditional medicines and for products for neglected diseases) in markets where patents have recently been introduced.

Monitoring the impact of bilateral negotiations on how TRIPS is translated into national law, and the balance struck between industrial and health policy will also be important for the international community as a whole.

Patent bank¹³²

There currently exist a few sector-specific brokers who specialise in linking up patent holders with lesser-cost producers in developing countries to develop or produce drugs for neglected diseases (e.g. WHO/Special Programme for Research and Training in Tropical Diseases and Medicines for Malaria Venture), in cases where a patent or technology is of use to developing countries, and the patent owner is interested in divesting of the technology. The possibility could be explored to create an umbrella patent bank, with a service component, dedicated to the search for potential partners in the developing world to whom the technology and its related tacit knowledge component could be transferred. Existing technology transfer brokers and networks would make excellent partners for such an initiative.

Advocacy

This study has provided the evidence that Indian and Chinese firms have the potential to be quality, low-cost suppliers. Donor-funded purchasing activities should therefore



avoid raising barriers to entry for these firms to supply publicly funded programmes. More ideally, donors could more proactively seek to lower barriers to entry for these suppliers, since their lower-cost structure makes them more obvious and sustainable partners for publicly-funded programmes concerned with cost.

Product development public–private partnerships

Many product development public–private partnerships exist to bring products for neglected diseases to market, but despite the recognition that low prices will be needed to facilitate access to these products, once developed, these partnerships often take place between donors and firms with higher cost structures, located in developed countries. The results of this study make a strong case for donors to increase their consideration of low-cost, high-quality researchers and manufacturers, particularly in India, as legitimate partners in developing and manufacturing products that address public health needs. This study goes some way in unpacking some of the peculiarities of Chinese and Indian pharmaceutical firms, but further and more detailed research would be needed to tailor and determine the impact that specific incentive packages for R&D into neglected diseases would have, given the specific comparative advantages, strategies and cost structures of these firms. Once implemented, monitoring the impact of push/pull incentives for neglected diseases on research spend and patent activity would also be necessary.

Further research

This study offers a wide scoping of the current situation and emerging trends with two of the world’s major medicine supplying countries. However, given the dearth of available information on China, primary research would be needed in order to better understand the capacity and strategies of Chinese firms, insofar as this would answer questions about changing market conditions and competition that have downstream effects on access. The Chinese ARV situation, in particular, warrants further research to determine why the capacity to supply generic API for export has not translated into better ARV supply for the domestic market.



Annex A: References

Acharya, T., *The TRIPS Agreement: Implications for Public Health in India*. Thesis presented to the faculty of the department of epidemiology and public health, Yale University, 1999.

Baker, B., *Processes And Issues For Improving Access To Medicines: Willingness And Ability To Utilize TRIPS Flexibilities In Non-Producing Countries*. A Paper for the Department for International Development, August 2004.

Business Week online, *India: Big Pharma's New Promised Land? Drugmakers are heeding the siren call of its well-trained, cheap chemists*, January 12, 2004.

Chin, J., Grossman, G. 'Intellectual Property Rights and North-South Trade' in R. W. Jones and A.O. Kruegar (eds) *The Political Economy of International Trade: Essays in Honour of Robert E. Bladwin*, Cambridge, MA: Basil Blackwell, pp. 90–107, 1990.

Cockburn, I., 'The changing structure of the pharmaceutical industry', *Industry Priorities* magazine, January/February 2004.

Deardorff, A., 'Welfare Effects of Global Patent Protection' *Economica*, vol. 59, pp. 35–51, 1992.

Dechamp, J., 'Facts and issues concerning access to ARVs (antiretrovirals) in China. A critical analysis of Main ARVs in China: an MSF Working Document', draft, September 1, 2003.

Dechamp, J., Couzin, O., 'Access to HIV/AIDS Treatment in China: IPR, Generics, and Barriers to Effective Treatment', Chapter prepared for HIV/AIDS in China, draft June 2004.

Dhar, B., Rao, C.N., *Transfer of Technology for Successful Integration into the Global Economy*, UNCTAD report 2002. See: http://www.unctad.org/en/docs/iteipcmisc22_en.pdf

Dimasi, J., Hansen, R., Grabowski, H., 'The price of innovation: new estimates of drug development costs' *Journal of Health Economics*, vol. 22, pp.151–185, 2003.

Fink, C., 'Patent Protection, Transnational Corporations, and Market Structure: A Simulation Study of the Indian Pharmaceutical industry' *Journal of Industry, Competition and Trade*, vol. 1:1, pp. 101–121, 2001.

Ford, N., 'Patents, access to medicines and the role of non-governmental organisations' *Journal of Generic Medicines*, vol. 1, no. 2, pp. 137–145, January 2004.

Ford, N., Wilson, D., Bunjumng, O., Angerer, T., 'The role of civil society in protecting public health over commercial interests: lessons from Thailand'. *The Lancet*, vol. 363, no. 9408, pp. 560–563, February 14, 2004. See: <http://www.essentialdrugs.org/edrug/archive/200402/msg00041.php>

Globalization and Access to Drugs, 1997. See: www.haiweb.org

Goldman Sachs, *Global Healthcare: Indian Pharmaceuticals, Passage from India*, March 16, 2004.

Grace, C., *Equitable Pricing of Newer Essential Medicines for Developing Countries: Evidence for the potential of different mechanisms*, World Health Organization, February 2003. See: http://www.who.int/medicines/library/par/equitable_pricing.doc

Grace, C., *Leveraging Private Markets for Public Health: A Briefing Paper for the Department for International Development on Technology Transfer in the Pharmaceuticals Sector*, September 2004.

Guimier, J., Lee, E., Grupper, M., *Processes and issues for improving access to medicines: The evidence base for domestic production and greater access to medicines. A Paper for the Department for International Development*, June 2004.

Hill, S., Johnson, K., *Emerging Challenges and Opportunities in Drug Registration and Regulation in Developing Countries. A Paper for the Department for International Development*, May 2004.

JP Morgan, *Medicines and Frontiers: Notes from the Indian Pharma Tour 2003*, December 18, 2003.

Kanavos, P., Mrazek, M., Mossialos, E., *Pharmaceuticals: a global industry with local interests. Paper presented at the Nuffield Trust/Royal College of Physicians Conference on Global Health: a local issue*, London, England, January 31, 2000.

Keayla, B.K., *TRIPS patent system and Doha declaration, implementation process by India*, 2004. See: www.patentmatics.com/pub2004/pub1b.doc

Kettler, H., Modi, R., 'Building local research and development capacity for the prevention and cure of neglected diseases: the case of India. *Bulletin of the World Health Organization*, vol. 79, no. 8, 2001.

Lanjouw J., 'The Introduction of Pharmaceutical Product Patents in India: Heartless Exploitation of the Poor and Suffering?', National Bureau of Economic Research (NBER) Working Paper No. 6366, 1998.

Lettington, R., Banda, C., A survey of policy and practice on the use of access to medicines related TRIPS flexibilities in Malawi. A Paper for the Department for International Development, June 2004.

Lettington, R., and Munyi, P., Willingness and ability to use TRIPS flexibilities: Kenya case study. A Paper for the Department for International Development, April 2004.

Lucchini S, Cisse B, Duran A, de Cenival M, Comiti C, Gaudry M, Moatti JP. Decrease in prices of anti-retroviral drugs for developing countries: From political "philanthropy" to regulated markets? In: Economics of AIDS and Access to HIV/AIDS Care in Developing Countries, Issues and Challenges, International AIDS Economics Network, 2003: 169–212.

Maskus, K., Konan, D., 'Trade-Related Intellectual Property Rights: Issues and Explanatory Results' in A.A. Deardorff and R.M. Stern (eds), Analytical and Negotiating Issues in the Global Trading System, Ann Arbor: The University of Michigan Press, pp. 401–454, 1994.

Mercer Management, 'Lessons learned: new procurement strategies for vaccines, presentation to the GAVI (Global Alliance for Vaccines and Immunization) Board', March 11, 2002.

Morgan Stanley, Pharmaceuticals: Global Insights, Implications from Emerging Indian Pharma, October 16, 2003.

Morgan Stanley, Healthcare: China: Potential Huge, but Intellectual Property an Issue, April 9, 2004.

Mundy, J., Attawell, K., 'Provision of anti-retroviral therapy in resource-limited settings: a review of experience up to August 2003'. Prepared by the Health Systems Resource Centre for DFID in collaboration with the World Health Organization, November 2003.

Nogues, J., Social Costs and Benefits of Introducing Patent Protection for Pharmaceutical Drugs in Developing Countries, 'The Developing Economies 31(1). pp. 24–53, 1993.

Orsi, F., Hasenclever, F., Fialho, B., Tigre, P., Coriat, B., Intellectual Property Rights, Anti-AIDS Policy and Generic Drugs, Lessons from the Brazilian Public Health Programme, June 2003.

Oxfam briefing paper no. 26: Generic competition, price and access to medicines? The case of ARVs in Uganda, July 10, 2002.

Porter, M., *Competitive Advantage: Creating and Sustaining Superior Performance*, Simon & Schuster, Inc., The Free Press, 1985.

Prakash, S., *Trade and Development Case studies (India) 1998*. See: <http://www.itd.org/issues/india5a.html>

Quick, J., Hogerzeil, H., 'Twenty-five years of essential medicines'. Powerpoint presentation, WHO Essential Drugs and Medicines Policy, May 2002. See: [http://www.who.int/medicines/organization/par/briefing/tbs2004/\(1\)/001-25_years_of_essential_medicines.ppt](http://www.who.int/medicines/organization/par/briefing/tbs2004/(1)/001-25_years_of_essential_medicines.ppt)

Ramesh, J., *New Convert to Reforms in India Today*, India Today, December 7, 1998. See: <http://www.India-today.com/itoday.com/07121998/jairam.html>

Rao, S., *India races to be a global vaccines hub*. 2003 See: <http://biospectrumindia.com/cgi-bin/printer.asp?id=54364>

Read, P., 'India in perspective: the pharmaceutical sector' ARANCA Pharmaceutical Reports, April 2004.

Saha, R., Satyanarayana, K., Gardner, C.A., *Building a "Cottage Industry" for Health (and Wealth) The New Framework for IP Management in India*. IP Strategy Today No. 10, pp. 23–58, 2004.

Scherer, M., Watal, J., 'Post-TRIPS options for access to patented medicines in developing countries. Draft working paper for Working Group 4 of the Commission for Macroeconomics and Health. World Health Organization, 2001.

Singh, Y., 'Pharma Generics: emerging from the shadows of brand power' ARANCA Pharmaceutical Reports, April 2004.

Subramanian, A., 'Putting Some Numbers on the TRIPS Pharmaceutical Debate' *International Journal of Technology Management* 10(2/3) pp. 252–268, 1995.

Subramanian, A., 'Medicines, Patents and TRIPS: Has the intellectual property pact opened a Pandora's box for the pharmaceutical industry?' *Finance and Development*, pp. 22–25, March 2004.

TAC and MSF import generic antiretrovirals from Brazil in defiance of patent abuse' January 29, 2002. See: <http://www.essentialdrugs.org/edrug/archive/200201/msg00090.php>

Wade, C., 'China to produce generic AIDS drugs' United Press International, September 24, 2002. See: <http://ww2.aegis.org/news/upi/2002/UP020907.html>

Watal, J., 'Introducing product patents in the Indian pharmaceutical sector: implication for prices and welfare' *World Competition, Law and Economics Review*, vol. 20, no. 2, pp. 5–21, 1996.

Watal, J., 'Pharmaceutical patents, prices and welfare losses: policy options for India under the WTO TRIPS Agreement' *World Economy*, vol. 23, no.5, pp. 733–752, 2000.

Webber, D., 'Encouraging pharmaceutical R&D in developing countries' IFPMA, Geneva. February 2003. (a)

Webber, D., 'Accelerating innovative pharmaceutical research and development in China: A case study. IFPMA, Geneva. February 2003. (b)

WHO, Investing in health research and development: report of the ad hoc committee on health research relating to future intervention options (unpublished document Special Programme for Research and Training in Tropical Diseases/GEN/96.1), Geneva, 1996.



References with no listed author:

Confederation of Indian Industry. Note on Biotechnology, June 2004, distributed at the London Business School India Business Forum, held June 30, 2004.

Economist, November 8, 2001.

Economist, 'Biotech's yin and yang', December 12, 2002. See:
http://www.economist.com/printerfriendly.cfm?story_ID=1491569

Economist, 'China's biotech industry is growing fast, but faces several challenges', December 12, 2002.

Financial Times, April 16, 2003.

Financial Times, June 26, 2003.

'Glaxo acts over S. Africa drug row', CNN, October 7, 2001. See:
<http://www.essentialdrugs.org/edrug/archive/200110/msg00023.php>

<http://indianmedicine.nic.in>

<http://www.India-today.com/btoday/19990822/pharmrep.txt>

Information Memo on the Enforcement of the Revised Bangui Agreement. See:
<http://www.essentialdrugs.org/edrug/archive/200206/msg00062.php>

Open letter from Chinese people with HIV/AIDS to pharmaceutical companies in China, February 3, 2004. See:
<http://www.essentialdrugs.org/edrug/archive/200402/msg00034.php>

Pharmaceutical Business News, 'China expands raw materials production', July 1, 2004.

Scrip magazine, Article on Chiron vaccines in India, March 21, 2003.

Shanghai Daily news:
<http://english.eastday.com/epublish/gb/paper1/665/class000100022/hwz86287.htm>

Treatment Action Campaign Press Release, December 10, 2003. See:
<http://www.essentialdrugs.org/edrug/archive/200312/msg00017.php>

Notes

- 1 See: <http://www.fda.gov/cder/guidance/1716dft.pdf> for definition
- 2 Relative to how attractive these markets would be to a developed country based MNC with a higher cost structure
- 3 Although some of these countries are not required to until 2016, according to Paragraph 7 of the Doha Declaration on TRIPS and Public Health
- 4 Although there are certain practical difficulties to utilising this extension, as discussed in Grace 2003
- 5 The following links may be useful to readers interested in exploring these subjects further:
<http://www.unctad.org/Templates/StartPage.asp?intltemID=2983&lang=1>
<http://www.iprsonline.org/resources/technologytransfer.htm>
http://www.london.edu/cnem/Working_Papers/working_papers.html
<http://people.brandeis.edu/~jefferso/RDandFDI.pdf>
- 6 The arguments (briefly) for product patents include the development of the science and technology base, attracting foreign investments in technology and research, reversing brain drain, and resultant economic development. However, more cautious literature on the subject talks of the need for the right kind of foreign investment – the sort that induces backward linkages into the host economy, as well as the transfer of appropriate technologies, that can be well integrated and built upon by domestic firms. Critics of product patent introduction also cite the fact that many countries' economies took off under weak IP systems – Japan, Taiwan, South Korea, even the US and Europe – using strategies of technological imitation, which some believe is a necessary stage in the process of becoming innovative
- 7 Quick 2003
- 8 Ford 2004
- 9 IMS data for May 2003 – May 2004, moving annual total figure
- 10 Goldman Sachs 2004
- 11 Morgan Stanley 2004
- 12 <http://www.buyusa.gov/china/en/pharmaceuticals.html>
- 13 Pharmaceutical Business News 2004
- 14 Goldman Sachs 2004, page 1. Note that volume data is difficult to derive, given the extent of dosage form mix. One way of equalising Indian and US data in order to compare market sizes: If the US market is approximately \$130 billion, and Indian prices are generally 5% of US prices, then the US market is worth \$6.5 billion (5% of \$130 billion) in Indian prices. Since the Indian domestic market is worth \$4.3 billion, this means that the Indian market size is approximately 65% (4.3/6.5) of the US market size
- 15 Read 2004
- 16 For example, a Chinese company called MCHM in Xiamen, China is now manufacturing the following APIs: AZT, 3TC, nevirapine, d4T, ddI and indinavir, and will soon be manufacturing Titonavir, lopinavir, nelfinavir mesylate, efavirenz, and adefovir dipivoxil. (I am grateful to Krisana Kraisintu, ARV scientist and production consultant, for this information)

- 17 Achara Eksaengsri, Deputy Director of the Research and Development Institute, Government Pharmaceutical Organization of Thailand, personal communication
- 18 Mr. Stavros Nicolaou, Director Aspen-Pharmacare, personal communication. Note that eventual supply will be obtained from China and South Africa
- 19 Orsi 2003
- 20 Krisana Kraisintu, former Director of the Government Pharmaceutical Organization of Thailand and ARV scientist and production consultant, personal communication - See also Ford et al 2004
- 21 The Lancet 2004. See:
<http://www.essentialdrugs.org/edrug/archive/200402/msg00041.php>
- 22 Eloan Pinheiro, Former Director of Farmanguinhos, personal communication
- 23 Lettington and Munyi 2004 and Lettington and Banda 2004
- 24 See: <http://www.avert.org/aidsdrugsafrika2.htm>
- 25 100,000 is a rough benchmark between the announcements made by public officials of 53,000 and the public tender document's request of enough ARVs for 120,000 new patients (including paediatrics).
- 26 I am grateful to Stavros Nicolaou, Director Aspen-Pharmacare, for this information
- 27 Oxfam 2002. See also Luccini 2003
- 28 Orsi 2003
- 29 Singh 2004
- 30 Cockburn 2004
- 31 Unless otherwise indicated, references in this section come from the following equity analyst reports: JP Morgan 2003, Goldman Sachs 2004, and Morgan Stanley 2003
- 32 Annual Report, Dept of Chemicals 1999, quoted from Acharya 1999
- 33 Prakash 1998
- 34 Adapted from JP Morgan 2003
- 35 'Moving up the product value chain' here refers to developing and marketing increasingly complex/innovative products, differentiated from competitors, and for which consumers are willing to pay a premium. See 'Competitive Advantage', Porter 1985, chapters 1 and 2 for more detail on the firm value chain concept and structural analysis of industries
- 36 Singh 2004
- 37 Confederation of Indian Industry handout distributed at the London Business School sponsored Indian Business Forum 2004
- 38 Mercer Management 2002
- 39 Rao 2003
- 40 DPT is the combination vaccine against diphtheria and pertussis (whooping cough) and tetanus toxoids
- 41 Mercer Management 2002 and Rao 2003
- 42 Webber 2003 (b)
- 43 There were over 2,000 joint ventures between UK and Indian companies in the past decade. Even in the drugs sector, there are numerous examples of UK/India collaboration, e.g. Biocon has its origins at a Scottish University. (Presentation given

by Sir Michael Anthony Arthur KCMG, British High Commissioner to India, at the London Business School sponsored conference 'Invest India', 30 June 2004.)

44 Business Week online 2004

45 Dimasi 2003

46 The WHO prequalification project establishes the quality of products that are intended for supply through a number of international agencies (eg UNICEF); interested suppliers must provide WHO with specified data for each product, and if they meet the standards required which include, but are not limited to GMP, the product is recognised as 'pre-qualified' for purchasers to consider

47 See 'AIDS in Russia: In sickness and in chaos', July 8, 2004 edition of the Economist, quoting Aleksei Mazus, director of the Moscow AIDS centre for just such a view. Referring to Indian generics, Dr. Mazus said, 'Do these people understand the difference between normal medicines and fakes?'

48 Webber 2003 (b), page 26

49 Pharmacopoeial standards in this case would establish the botanical characterisation, primarily encompassing the botanical nomenclature, plant part, and other specific requirements necessary for ensuring identity and quality. When known, minimum qualitative or quantitative chemical specifications would be provided, and in some cases, upper maximum quantitative limits established

50 See <http://indianmedicine.nic.in>

51 The term 'tragedy of the commons' refers to the situation where individuals or groups share a common good, and where one individual (or firm) may act to maximize personal short-term gain, but in the process, may cause longer-term harm to the environment, others and ultimately himself. The intellectual roots of the concept trace back to Aristotle who observed that 'what is common to the greatest number has the least care bestowed upon it'. The concept applies in its broader sense to many modern environmental problems. The potential for 'tragedy of the commons' exists in pharmaceuticals because of information asymmetries between patients and producers, which make it possible for the producer to skimp on quality standards without the consumer/patient realizing it. If one Indian producer starts skimping on quality standards, this can have reputational effects on the entire industry (reputation being the shared common good)

52 Globalization and Access to Drugs 1997 as quoted in Acharya 1999

53 Consensus of a panel of experts on the Indian pharmaceutical industry at the London Business School sponsored Indian Business Forum, June 2004

54 Although there may be concerns in the near term about sourcing API in the pre-launch phase for highly proprietary or technologically advanced products, due to concerns over confidentiality

55 Webber 2003 (a) provides a framework for assessing developing country potential in pharmaceutical R&D

56 And little upward cost pressure can be expected in the short to medium term, since the huge labour surplus in India (including in the pharmaceutical sector) implies that real wages will not rise very much

57 The theoretical arguments presented in this paragraph were confirmed as valid in

conversation with Dr. Swati A. Piramal, Director – Strategic Alliances & Communications, Nicholas Piramal India Limited

58 Prohibition against use of data submitted to secure regulatory approval and/or against relying on a prior regulatory approval to establish the safety and efficacy of a generic product – see Baker 2004 and Hill 2004 for further details

59 Professor B.K Keayla, Convener of the National Working Group on Patent Laws, India, personal communication

60 Although it should be noted that this is still under dispute in the courts, so depending on the decision, the stay order could be overturned

61 To comply with TRIPS requirements, during the transitional period India amended its Patent Act 1970 through Patents (Amendment) Act 1999 and incorporated subsection (2) under Section 5. This incorporation provided for a mailbox facility from 1.1.1995 for receiving product patent applications for pharmaceuticals and agro-chemical products

62 Keayla 2004

63 Ford 2004

64 Fink 2001. Note that this figure is a hypothetical market share, referring to the drug sales of chemical entities, which at the time of the underlying study (1993) were protected by patent rights in Europe. Since India at that time did not protect pharmaceutical (product) patents, the actual patented market share in India would obviously have been zero

65 Assuming that market structure remains fragmented enough to allow continued competition

66 Professor Biswajit Dhar, personal communication. Price rise evidence also presented in Acharya 1999 but linked with changes in the Drug Control Price Order

67 Nogue (1994) assumes a perfectly competitive pre-market structure. Maskus and Konan (1994) assume that in the absence of patents, a dominant foreign-owned firm competes with a domestic industry. Subramanian (1995) uses an upper bound scenario (perfect competition) and a lower bound scenario (duopoly) as alternative pre-patent market structures

68 Watal 1996, Watal 2000 and Fink 2001

69 Grace 2003

70 Ramesh 1999

71 See the other studies in this series, esp. Baker 2004, Lettington and Munyi 2004 and Lettington and Banda 2004

72 Lettington and Munyi 2004

73 Lanjouw 1998

74 Lanjouw 1998

75 Prakash 1998

76 Dhar 2002

77 Morgan Stanley 2003

78 Lanjouw 1998

79 Goldman Sachs pharmaceutical equity analyst, personal communication

80 However, the US based pharmaceutical companies are also at an all-time low in

terms of R&D productivity. (Cockburn 2004)

81 Economist, 2001

82 WHO 1996

83 Economist, 2001

84 Kanavos 2000

85 Fink 2001

86 The short-termism of financial markets is notorious; investors pressure pharmaceutical companies to deliver quarterly earnings results and there is intense scrutiny of the drug pipeline, looking for delivery of the next blockbuster. In contrast, many of the major Indian companies are still primarily founder-owned and managed, and some of these are notorious for caring about public health as much as about the next quarter's earnings (a position, some would argue, that is helped by the fact that financial performance of these companies has been so spectacular). (Equity analyst from First State Investments, personal communication)

87 Kettler 2001

88 Goldman Sachs equity analyst, personal communication

89 Government sponsored networks between industry, academia, and government, such as the *Drugs and Pharmaceuticals Management Programme* (promoting R&D in the pharmaceuticals sector), the *Technology Development Board* (encouraging the development and commercialisation of indigenous technologies), the *Programme aimed at Technological Self-reliance*, and the *New Millennium Indian Technology Leadership Initiative*

90 Dhar 2002

91 JP Morgan 2003

92 Financial Times 2003

93 Grace 2004

94 Unless otherwise indicated, references in this section are drawn from Webber 2003 (b)

95 Pharmaceutical Business News, 1 July 2004

96 This compares to the \$15.7 billion invested in R&D in 2001 alone by the US biotech industry

97 Economist, 'Biotech's yin and yang', 2002

98 Economist, 'China's biotech industry is growing fast, but faces several challenges', 2002

99 Morgan Stanley 2004

100 It should be remembered that similar modes of south-south technology transfers were instrumental in allowing Asian firms to move up the value-added ladder in the textiles industry during previous decades

101 I am grateful to Krisana Kraisintu, ARV scientist and production consultant, for this information

102 I am grateful to Lynn Mytelka, Director of INTECH, for providing information on the importance the Taiwan–China relationship in the pharmaceutical sector

103 China has fermentation process skills, but it lags in process chemistry skills

104 These points were included on a list of needed regulatory reforms, submitted to

the Ministry of Health, Labour and Welfare in September 2003 by the Japan Manufacturers Association (Morgan Stanley 2004)

105 Morgan Stanley 2004

106 The majority of today's medicines (at least Western medicines that dominate the global market) are chemically synthesised, small molecular weight entities. By contrast, the majority of biotech products and traditional medicines are large molecular weight entities often prepared by extraction or fermentation

107 There are many more companies registered to supply ARVs, but only five companies are believed to be currently supplying the market. (Personal communication with a researcher who is just beginning a study on ARVs in China as of May 2004)

108 Wade 2002

109 <http://english.eastday.com/epublish/gb/paper1/665/class000100022/hwz86287.htm> and Dechamp 2003. See also: <http://ww2.aegis.org/news/upi/2002/UP020907.html>

110 Open letter from Chinese people with HIV/AIDS to pharmaceutical companies in China, February 3, 2004

111 Dechamp and Couzin 2004

112 GSK has built a greenfield GSK-owned site in the eastern Chinese province of Jiangsu which conducts all stages of the manufacturing process: See: www.pharmaceutical-technology.com/projects/suzhou

113 A differential pricing policy aimed to address the tension between health need and inability to pay of the least developed countries – see Grace 2003 for more details on such policies

114 Dechamp and Couzin 2004

115 Jean-François Dechamp, formerly with Médecins Sans Frontières, personal communication. According to Dechamp and Couzin 2004, drugs accessed via differential pricing programmes usually need to be imported from the patent holders' central office. For non-governmental organisations (NGOs) and other non-governmental actors, the importation of foreign ARVs can be problematic, including constraints for the purchaser (additional costs, uncertainty on the final price, unpredictable delivery dates, length of the procedure), the importer (burdensome administration) and the manufacturer (the product must comply with the dossier of the Chinese Marketing Authorization and there might be specificities other than a Chinese labeling). Bureaucratic or other delays for any reason may impede a steady supply, which can compromise the effectiveness of the treatment and can cause resistance to develop

116 Chinese firms only started making API for ARVs two years ago; prior to that, they made some intermediates (the Worldwide Project Head for HIV at Ranbaxy, personal communication)

117 Ranbaxy has several ARVs in the lengthy registration pipeline (the Worldwide Project Head for HIV at Ranbaxy, personal communication)

118 Proponents of TRIPS argue that, by aligning with the prevailing IP protection standards in the world's developed countries, developing countries stand to gain through development of the science and technology base, attracting foreign

investments in technology and research, reversing brain drain, and resultant economic development. Opponents of TRIPS argue that, even where patent protection is implemented in a developing country with supportive IPR institutions, technology transfer and development is not automatic with increased MNC interaction, and anyway, multinationals have neither by incentive nor obligation been compelled to delocalise their activities to the south

119 Although some are not required to until 2016 according to Paragraph 7 of the Doha Declaration on TRIPS and Public Health

120 Therefore the agreements negotiated by the Clinton Foundation are legal, from the exporting side. The programme has projected coverage of one million patients in five years at US\$150–170 per patient per year. The management of Matrix has told investors that it is the primary supplier for Ranbaxy, Cipla and Aspen for this programme and expects profit before tax margins of 12–15% for supplying for this initiative. Note that earnings before interest and tax/profit before tax margins of 25–30% are more the norm for Indian pharmaceutical companies (Goldman Sachs 2003 and confirmed in conversation with Goldman Sachs analyst). Assuming all aspects of the agreement are met, Ranbaxy, Cipla and Matrix reportedly expected to begin supplying the Clinton initiative the second quarter of 2004 (JP Morgan 2003). However, it is not clear how some African countries would be able lawfully to import the drugs. South Africa appears to have resolved the issue via the ‘voluntary’ licenses that several ARV patent holders have been induced to offer (see Grace 2004 for more details on the latter)

121 ‘TAC and MSF Import Generic Antiretrovirals from Brazil in Defiance of patent abuse’ 29 January 2002. See:

<http://www.essentialdrugs.org/edrug/archive/200201/msg00090.php>

122 Mundy 2003

123 Information Memo on the Enforcement of the Revised Bangui Agreement. See:

<http://www.essentialdrugs.org/edrug/archive/200206/msg00062.php>

124 Although there are certain practical difficulties to utilising this extension, as discussed in Grace 2003

125 See Guimier 2004 for some considerations in establishing local pharmaceutical production in Africa

126 See footnote 16 for data on which ARV intermediates are available from Chinese firms

127 Subramanian 2004

128 See Saha 2004 for a detailed treatment of this subject

129 Mowery 2004

130 This idea comes from Biswajit Dhar, Professor and Head, Centre for WTO Studies, Indian Institute of Foreign Trade, personal communication

131 Cecelia Oh, WHO, personal communication

132 This idea comes from Professor Lynn Mytelka, Director INTECH, personal communication