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A Briefing Paper for DFID:
Update on China and India and Access to Medicines

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Acronyms

ACTs	Artemisinin combination therapies
AIDS	Acquired Immune Deficiency Syndrome
ANDAs	Abbreviated new drug applications
API	Active pharmaceutical ingredient
ARVs	Antiretrovirals
ATM	Access to medicines
CL	Compulsory licence
DFID	Department for International Development
EML	Essential Medicines List
FDA	Food and Drug Administration
FDCs	Fixed-dose combinations
GFATM	The Global Fund for AIDS, TB and Malaria
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
IP	Intellectual property
IPR	Intellectual property rights
MNC	Multinational corporation
MOU	Memorandum of Understanding
PEPFAR	President's Emergency Plan for HIV/AIDS Relief
R&D	Research and development
TCM	Traditional Chinese medicine
TDF	Tenofovir disoproxil fumarate
TRIPS	Trade-related Aspects of Intellectual Property Rights
US	United States
WHO	World Health Organization
WTO	World Trade Organization

Please see Annex 6 for a glossary of ARV names

1 EXECUTIVE SUMMARY

1.1 Market Overview

Both India and China are important sources of medicines supply domestically, worldwide, and for products of public health importance in developing countries. China is an important source of chemical and API supply, whereas India is stronger on the finished product/formulation side.

On the research and development (R&D) side, external changes as well as internal changes in India and China present opportunities and challenges for increased R&D activity. Whilst the development of genomics and the pressure on 'big pharma' to reduce costs are creating opportunities for R&D in these countries, regulatory and technical challenges remain barriers to moving up the value-added ladder.

As for how the market overall is evolving, market share is expected to gradually transfer from smaller to larger companies, e.g. via mergers and acquisitions, between Indian firms and MNCs as well as South-South collaborations. Companies will also be selling and buying brands to increase their footprint (and pricing power) in a particular therapeutic area. A proliferation of in-licensing deals may also be expected, for example MNCs will do licensing deals with large domestic firms in order to get their product marketed in India.

1.2 Intellectual Property and Access to Medicines

The Indian Patent Ordinance, issued on 26 December 2004, caused great concern to ATM-stakeholders, as it eased standards of patentability, eliminated pre-grant opposition procedures, limited Paragraph 6 exports to only those countries that issued a compulsory licence (thereby unnecessarily excluding no-patent countries), and failed to streamline and expedite the procedures for compulsory licensing. The eventual Patent (Amendment) Act, passed by the Indian Parliament in March 2005, was more ATM-promoting, although concerns still remain. In short, India should be able to continue producing most existing generics although there are likely to be battles over some more recent products, e.g. Tenofovir. It is not yet clear what impact the requirement for 'reasonable' compensation will have on prices or on time needed to negotiate deals and start producing, as there have not yet been any cases where Indian companies are paying such compensation. (The Gleevec case is still in court.)

Production of future products will be more challenging technically but, compulsory licenses would be an option to overcome the IP-restrictions. The challenge is whether CLs will be practically feasible; this is influenced by whether and how the country has translated TRIPS flexibilities into domestic legislation and whether the product in question can be developed by generic firms in time to meet public health need.

Although enhanced IP will in fact only impact between 10% and 15% of the current value share of medicines, and an even smaller share of medicines on the WHO EML list, this percentage will obviously increase over time, as new, patented medicines become an increasing proportion of the overall market and of the EML list.

It would be a mistake to conclude, based on the above statistic, that patent status has little impact on access to medicines. The small percentage one gets from such a patent counting exercise undervalues the impact that patents have on access by taking averages of large samples of dissimilar drugs and dissimilar countries and, in

the process, discounting important variations and outliers within the sample. For example, lack of access to one drug in a combination therapy (due to patent status) can preclude appropriate treatment. Despite the fact that NVP and d4T are off-patent as individual drugs¹, GSK's patent on the ARV 3TC blocked the availability of the simplest and most affordable AIDS treatment available worldwide – the WHO-recommended fixed-dose combination of d4T/3TC/NVP. It was therefore necessary to prescribe brand-name medications that were five times more expensive, and in individual drugs rather than in co-formulated pills (thereby complicating the treatment regimen and potentially affecting compliance and therefore efficacy).² Patent-protected drugs, although few in number, actually represent a very large percentage of health budgets. Just a few expensive patented medicines can skew entire treatment budgets.

The disease areas most likely to be negatively impacted by TRIPS include

- Classes of drugs that experience a high speed of new product development due to emerging resistance, such as antibiotics and anti-infectives (e.g. ARVs, TB drugs, anti-malarials).
- Drugs for cancer and diabetes, since these are treated with relatively new drug classes which have little therapeutic competition/substitution, and therefore have significant pricing power.

Only newer, patented medicines will be effective in these categories; these will be unaffordable in developing countries.

TRIPS officially came into force in China at the end of 2002. China has a version of the Indian 'mailbox' system, called 'administrative protection', that allows back-dating of market exclusivity. There are also compulsory licensing provisions in domestic patent legislation, although practical use may be constrained due to a) limited grounds on which they can be issued b) procedural restrictions which accompany them, and b) a requirement that CLs be issued predominately for purposes of supplying the domestic market.

China plays an essential role in supplying chemicals and APIs, especially for products of public health importance in developing countries and to ATM-enhancing finished product manufacturers. Whereas domestic suppliers of finished product ARVs were few in early 2004, China now has four domestic pharmaceutical companies manufacturing six generic HIV/AIDS cocktails.³ A recent announcement from the Clinton Foundation brought to the public eye the technological capacity of China to do even more for ATM. The Foundation negotiated a deal with Mchem of China to supply the API of five products: AZT, 3TC, D4T, NVP and efavirenz.⁴ The Foundation is also offering technical assistance to Mchem on certain products (e.g. TDF, EFV, LPV/r) with the hope of adding additional products to the supply agreement at some point in the coming year. Of the eight products Mchem will be offering to Clinton partners, at least two (3TC and efavirenz) would seem to be IP-protected in China, bringing to the public eye a situation that formulators have wondered about, that is, how to interpret the meaning of China's IP.

¹ Please see Annex 6 for a glossary of ARV names

² Goemaere, Lotrofska, Marchandy, and t'Hoen in Letters to the Editor, Health Affairs, September/October 2004: 280.

³ See Annex 4 for details of ARVs made by Chinese firms.

⁴ To clarify, The Clinton Foundation does not procure ARVs. The Foundation negotiates deals and helps form partnerships. Prior to the Mchem deal, it had four partner companies: two API partners and three formulator partners (one of whom was also an API partner). Mchem became the third API partner and the fourth formulator.

Several theories, but little evidence, exist for how China can supply newer drugs or raw materials for these drugs. Some observers assume IP sophistication allows Chinese firms to legally bypass apparent IP requirements, whilst others assume either complete lack of capacity or intent to comply IP requirements.

Clearly IP is an access-constraining factor, which can sometimes be overcome through inventive means if there is the will and/or the economic incentive. There will be an increasing role for ATM-promoting solutions over time, due to a) the continuous change in spectrum of diseases and resistance patterns, requiring ever-more innovative technologies to address public health problems b) the gradual increase in the percentage of EML drugs on-patent (as the list is updated with new, patented medicines) and c) the gradual decrease in generic sources of newer medicines from quality suppliers due to changing IP in the major producing countries.

Genuine confusion about what the WTO requires from a country and the flexibilities WTO gives member states seems to be present in many developing countries, in the context of bilateral trade agreements that encourage IP standards in excess of the minimum required by WTO. Countries need political support when utilising TRIPS flexibilities for public health purposes, and technical support to adapt domestic legislation and policies in order to facilitate the use of those flexibilities.

Donors should not only encourage policies that promote value for money, but should look to better align the institutional mechanisms for financing and procurement with the most efficient way of dealing with the particular market; such alignment will result in increases supply security and often, in reduced prices as well. Other health systems and institutional issues can constrain access as well. There are many actors and processes influencing how well drug financing is used, e.g. WHO, GFATM, procurement agents, country-level policymakers and managers. Donors can play a fundamental role in improving individual agency and country capacities, but also in improving how well these agents interface with one another and work together in a harmonized way.

2 BACKGROUND

In 2004, the Department for International Development (DFID) Policy Division's Access to Medicines team commissioned a series of studies aimed at developing the evidence base in support of an integrated framework addressing institutional, policy and structural barriers to access to medicines. The intention has been to aid international and national actions by major stakeholders in improving access to medicines, especially for developing country partners, pharma and generic producers, and UK and other Organisation for Economic Co-operation and Development governments.

The DFID-commissioned study 'The effect of changing intellectual property on pharmaceutical industry prospects in India and China: considerations for access to medicines' provided evidence to show how important Indian and Chinese firms are to the supply of quality, low-priced active pharmaceutical ingredients and finished products domestically and to developing countries. It also analysed the effect of changing intellectual property regimes in these countries on companies' strategies and access to essential medicines both locally and internationally. The study is available at:

http://www.dfidhealthrc.org/shared/publications/Issues_papers/ATM/Grace2.pdf

The purpose of this piece of work is to update the previous study with information that has become available in the year since the research was done. Updating the paper is expected to yield new insights into how Trade-related Aspects of Intellectual Property Rights (TRIPS) is being implemented at country level, what effect the changes are having on firm-level strategies and in turn, what effects these changes are having on access to medicines supply. An updated paper is expected to support ongoing policy engagement by DFID on TRIPS at an international level, to support DFID-funded (International Trade Division) work to build developing country capacity to utilise TRIPS flexibilities, and support DFID country offices involved in access to medicines debates.

In the past year, there has also been increased interest in the existence⁵ and potential of domestic production in developing countries, fuelled partly by the closing window of generic supply of newer drugs from India and China in the context of evolving disease and resistance patterns, and partly by the 2016 extension given to LDCs on complying with TRIPS. Domestic production potential is obviously affected in large part by the API supply and technology transfer opportunities available from Indian and Chinese sources, hence an additional source of interest and importance of these countries.

The following research questions will be addressed in this paper:

- During the past year, what have been the major developments in the Indian and Chinese pharmaceutical industries and what are the major opportunities?
- How has TRIPS been translated into domestic law in India? How does the Patent Law differ from the original Ordinance and what are the practical implications for:
 - o The percentage of the market that is likely to be affected?
 - o The therapeutic importance of the drugs to be affected?

⁵ WHO AFRO has done a survey of production capacity in Africa that indicates that local production is widespread. http://www.afro.who.int/rc55/documents/afr_rc55_10_local_production.pdf

- How has TRIPS been translated into domestic laws in China? How do domestic policies and laws in China (especially drug selection) interface with interests to promote domestic industry, and in turn how is this interface affected by intellectual property rights (IPR)-related institutions and laws?
- With the evolution in first-line recommendations for diseases like malaria and HIV, what role will India and China be able to play for either finished product or active pharmaceutical ingredient (API) supply (or supply of intermediates), for domestic use or export, of drugs like tenofovir and artemisinin combination therapies (ACTs) for malaria?

3 MARKET OVERVIEWS: INDIA AND CHINA

3.1 A quick snapshot of the Indian market

At US\$10 billion, Indian industry ranks 4th worldwide in volume of production and 13th in value. India supplies 22% of the world's generic drugs and a significant proportion of the vaccines made for the developing world.⁶

There are 300 companies of large and moderate size and approximately 5,000 smaller companies. Four hundred bulk drugs are produced and almost all formulations are made in India. One-third of the production, or about US\$3.5 billion, is exported, and export growth averages 25% per annum. India has the largest number of units approved by the Food and Drug Administration (FDA) outside the United States (US), numbering 65. One-half of the exports are to the US alone. Large exports also go to China, Brazil, Nigeria and Mexico.

For a fuller picture of trends and business strategies, see Grace 2004: http://www.dfidhealthrc.org/shared/publications/Issues_papers/ATM/Grace2.pdf and Gehl Sampath 2005: <http://www.who.int/intellectualproperty/studies/PadmashreeSampathFinal.pdf>.

3.2 Developments on the R&D side: India

On the research and development (R&D) side, external changes as well as internal changes in India present opportunities for Indian R&D. On the positive side, the development of genomics and with that, an increasingly fragmented disease market⁸; may make smaller-scale production more economically feasible for Indian firms with a lower cost base. A small, tightly focused niche company may well do better in this environment than the historically successful 'Big Pharma'. The lower cost base also increases the potential for innovation, e.g. if it takes a firm US\$100 million, rather than US\$1 billion, to develop a drug, there is more room for experimentation and finding new ways to do research.

Revenues from the generic business, India's most productive pharmaceutical sector,⁹ are being used by some domestic companies as the means to move up the value-added ladder. In 2004, India's ten largest drug firms spent over \$170 million on R&D. This figure is expected to exceed \$200 million by 2006. Ranbaxy expects to spend 10% of its revenue on R&D in the future.¹⁰ Such increases in R&D expenditure are beginning to produce results. For all Indian companies, drugs in Phase I and II of the R&D pipeline have tripled from 5 in 2003 to 16 at present.¹¹

⁶ <http://www.nature.com/nature/journal/v436/n7050/full/436478a.html>

⁷ This firm level survey of the Indian pharmaceutical industry was produced for the Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH). The work revealed that Indian firms have been preparing for India's product patent regime over time, and their strategies have been devised to help them cope with the emerging regime.

⁸ With genomics, an individual's genomic profile is used to predict how that individual will respond to certain drugs, with the aim to enable a more personalized, safer, and more efficient approach to medication.

⁹ There have been more than 300 ANDAs from India since 1997. Thirty percent of the ANDA filings with the US FDA are from India (150 filings expected by the end of 2005). Source: BRICs: Challenges and opportunities: The Healthcare Sector, June 2005. Sahu, Keusch, Bostrom, Goldman Sachs Equity Research.

¹⁰ 'Breaking news on drug discovery: India enjoys increased drug R&D opportunities'. 21/04/2005. <http://www.drugresearcher.com/news/printNewsBis.asp?id=59570>

¹¹ Goldman Sachs, 2005.

Although R&D expenditure and outputs from that are on the rise, there are remaining challenges. Two-thirds of R&D spend is on API and formulation work, whilst only one-third is on new chemical entity research, and of that, 80% is prior art or analogue research.¹² Some Indian companies are also of the view that clinical trial stages will be too expensive to conduct independently; this view can partly explain the emergence of research partnerships between Indian and research-based multinational pharmaceutical companies, as witnessed with Novartis (Dr Reddy's, Torrent), Novo Nordisk (Dr Reddy's), GlaxoSmithKline (Ranbaxy) and Schwarz (Ranbaxy).¹³

3.3 Further opportunities for India

It has been suggested that there would be good synergy between biotech companies and Indian companies, with biotech in the R&D role and India developing cost-effective manufacturing for the toxicology studies. Others argue that large molecules – protein-based drugs – are not India's forte. Biosimilars (i.e. biogenerics)¹⁴ are also quite challenging from a regulatory standpoint. Others opine that India's diverse gene pool makes fertile ground for out-sourcing of clinical trials and using biomarkers to reduce the risk of clinical trials failures.

Whilst clinical trials in India might be an interesting commercial opportunity, there are concerns about the regulation and ethics that are necessary to have in line with the increase in such trials. According to the Indian Journal of Medical Ethics¹⁵, this is also true of India, where cost-savings and availability of treatment naïve subjects/underpaid researchers are leading to abuses, despite the presence of stringent regulations.

Interviews with manufacturers revealed another recently emerged commercial opportunity for Indian suppliers - the President's Emergency Plan for HIV/AIDS Relief Initiative (PEPFAR). Now that the risk to the generic company of being sued by the originator has been removed from the equation¹⁶, companies are more willing to make the investments to generate abbreviated new drug applications (ANDAs) for antiretrovirals (ARVs). Ranbaxy, Matrix and Aurobindo have so far taken up the offer to get generic ARVs approved by the FDA under the expedited review process set up to support PEPFAR. Aurobindo has four drugs approved for PEPFAR supply: BI's nevirapine, GSK's lamivudine, Merck's efavirenz and BMS's Zerit (stavudine). South

¹² Meaning that they lack high levels of novelty, being salts or esters (analogues) of existing compounds, or being relatively obvious to a person skilled in the art of the field in question (prior art)

¹³ 'Breaking news on drug discovery: India enjoys increased drug R&D opportunities'. 21/04/2005.

<http://www.drugresearcher.com/news/printNewsBis.asp?id=59570>

¹⁴ That is, generics of biotechnology products, often referred to as 'biosimilars', because demonstration of equivalence to regulators is more challenging versus with non-biological (small molecule) pharmaceuticals.

¹⁵ The Indian Journal of Medical Ethics, January-February 2004:

<http://www.essentialdrugs.org/edrug/archive/200401/msg00026.php>

¹⁶ In order for generic companies to be able to supply PEPFAR, the US has introduced a 'tentative approval' (versus conventional approval) process, whereby a generic manufacturer of an ARV still under patent protection in the US can get FDA approval under an expedited process, but only for supply to developing country recipients of PEPFAR funding. (The product can only be registered and marketed in the US once the patent has expired, hence the term 'tentative' approval). Normally the USFDA would not register a patent-protected product (patent-registration linkage exists), and the only way a company could attempt to register a generic version of a patent-protected product is via a 'Paragraph 4' filing, which essentially challenges the patent. However, if the company making the challenge proves to be unsuccessful, there is a risk of litigation from the patent-holder. Generic manufacturers outside the US would usually consider the expense of this potential risk to be too large.

Africa's Aspen Pharma got FDA approval in Jan 2005 for their co-packaged combination of 3TC, ZDV, and NVP.¹⁷

Companies report that they are seeing a new face of the FDA in terms of the speed of the process and the level of interaction, i.e. the FDA has been proactive in telling companies what their dossier needs to look like. The FDA inspectors have also been doing concurrent reviews of different steps in the process in order to bring down approval time.

3.4 A quick snapshot of the Chinese market

In 1998, China had 7,500 pharmaceutical factories until the government started to require good manufacturing practice certification. By the end of 2003, there were 4,296 pharmaceutical factories, of which 2,800 had obtained GMP certifications. It is expected that another 1,000 companies will lose their licenses by the end of 2005¹⁸.

In comparison with Indian firms, Chinese firms are relatively more focused on the domestic market and on chemical/API manufacture as opposed to finished product. Not one single Chinese company has filed an ANDA on the US market, although it is believed that the first Chinese company will gain FDA approval status by late 2005. However, on the API-side, the Chinese are more US-focused, with 55 FDA-approved factories and at least 20 additional factories planning to file DMFs in 2005.¹⁹ This would indicate that quality is gradually improving in China, although the remaining poor-quality suppliers create a negative image for those firms making investments²⁰ in quality.

China is the world's leading producer of API for first line ARVs, and also produces many second line APIs. Because production of APIs is the most technically demanding part of the production process for ARV drugs, it is critical that China is able to continue and indeed expand on its capacity (both in terms of technical difficulty and volume) to produce API, for existing first line and newer generation/second line ARV drugs, in order to supply formulators in India, Brazil, South Africa, and other developing countries. A good understanding of how IP affects China's supply is therefore important; if, for some reason, IPR enforcement were to reduce/restrict API supply from China, other countries/producers would find it much more difficult to continue producing, with obvious consequences for affordable generic supply and ultimately access to medicines.

3.5 Developments on the R&D side: China

Despite being behind the Indians in US penetration and international presence in the generics business, some innovative products have been coming out of China over the past year. For example, traditional Chinese medicine (TCM) research in the Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) sector has had a productive year. In April 2004, the first HIV/AIDS treatment to be derived from TCM was approved by local authorities, a Tang Herbal Tablet. In October 2004, the TCM treatment Ke'aite was approved for Phase II clinical research by the State Food and Drug Administration and CATCM-II, another TCM drug,

¹⁷ Please see Annex 6 for a glossary of ARV names

¹⁸ Capie, S., 'Outlook on China's pharma development – 2004', Journal of Generic Medicines, Vol.2, No.3, 212-218. April 2005.

¹⁹ Capie, S., 'Outlook on China's pharma development – 2004', Journal of Generic Medicines, Vol.2, No.3, 212-218. April 2005. Based on author's visits/interviews in the second half of 2004.

²⁰ The SFDA in China estimates that factories have paid, on average \$2.4-\$3.6 million to implement changes to bring them into compliance with national GMP requirements. Compliance with US GMP (cGMP) would require an even higher investment.

developed by the Chinese Academy of TCM (CATCM), has also been validated by the Ministry of Science and Technology. Another compound known as SH has been jointly developed by the Thai government and a division of the Chinese Academy of Sciences and was shown to be 89% effective in clinical trials.

The Chinese firm FusoGen Pharmaceuticals has developed a new HIV drug that aims to block the virus from entering cells. The drug - a fusion inhibitor,- is currently being tested in clinical trials. The drug is similar to Roche's Fuzeon (enfuvirtide) but employs a different molecular modelling. The drug is likely to hit the market at the end of 2006, and will be priced significantly below Fuzeon, which can cost \$20,000 per patient per year.

Another example is the anti-cancer drug, Gendicine, the only gene therapy in the world to have received regulatory approval, having been authorised by China's State Food and Drug Administration. The drug was developed by a Chinese scientist who recently returned from a visiting Professorship in the US. Gene therapy researchers in the West have reportedly expressed concern about potential lack of transparency in China's drug regulation system and potentially lower standards for clinical trials. These concerns are accentuated by commercial concerns about patent violations, particularly in the US. On the other hand, if the 'trust' factor can be addressed, and partnerships can be made to work, some see huge rewards, particularly for researching gene therapies for neglected disease, such as malaria and hepatitis.²¹

Chinese R&D is also happening in partnership with MNCs. Novo Nordisk started the trend in 2002, with a small research facility in Beijing. Astra-Zeneca then set up the first Western-owned clinical research organisation in China to collaborate on multi-site trials. In 2003, Eli Lilly struck a deal with the Chinese company ChemExplorer to purify, synthesize, and analyse compounds supplied by its researchers. And last year, Roche opened its new R&D laboratory in Shanghai.

3.6 Mergers and acquisitions activity in India and China

Analysts foresee two major market developments emerging. There will be a transfer of market share from smaller to larger companies; the market share of the top 50 companies will increase at the expense of the bottom 50.²² This will be achieved partly through mergers and acquisitions, between Indian firms and MNCs as well as South-South collaborations. There have been multiple examples of mergers and acquisitions activity in the past year:

- Matrix Laboratories of India and Mchem of China formed a strategic alliance, allowing Matrix to backward integrate into China for the manufacture of intermediates and to consolidate its position as a major supplier of active pharmaceutical ingredients worldwide.²³
- In July 2005, the largest acquisition ever executed by an Indian pharmaceutical company was witnessed. Matrix Laboratories announced acquisition of a controlling stake in the Belgian drug company Docpharma NV for \$263 million (Rs 1,157.2 crore). The Chairman and CEO was quoted as saying 'The acquisition accelerates our evolution as a growing force within the

²¹ Callan, E. 'Approval for cancer drug divides opinion: Treatment Regulation: Chinese regulators made Gendicine the first gene therapy to be authorised.' Financial Times, 1 April 2002.

²² Driven partly by government policies which will have the effect of benefiting larger companies at the expense of smaller ones – e.g. the maximum retail price excise duty, Schedule M and the tax credit on R&D spend. Similarly in China, smaller companies are exiting the market because they cannot invest to meet the higher GMP criteria and because of changes in registration requirements.

²³ 'Matrix Labs inks alliance with MCHM of China', 8 February 2005, The Hindu Business Line.

global generic pharmaceutical industry. This transaction allows us to gain direct access into the under-penetrated high-growth generic pharmaceutical markets of Belgium and southern Europe.²⁴

- Similarly, Ranbaxy cemented a southern European beachhead in June 2005 with the acquisition of a generic product portfolio containing 18 products of the Spanish pharma company Efarmes. The products belong to the cardiovascular, central nervous system and pain management segments.

In India, this transfer of market share will not only come as a result of mergers and acquisitions. Many Indian firms are owner-founder companies and will not necessarily want to sell their firms altogether, therefore companies will also be selling and buying brands. Firms like Ranbaxy and Dr Reddy's may be expected to buy in new brands in order to increase their footprint (and pricing power) in a particular therapeutic area. A proliferation of in-licensing deals may also be expected, for example smaller MNCs will do licensing deals with large domestic firms in order to get their product marketed in India.

²⁴ 'Trends: Business News', Business Today, 17 July 2005.

4 THE INDIAN PATENT LAW AND ITS IMPACT

The process of India coming into compliance with TRIPS is a long story.²⁵ Only the recent history will be covered here. Under Presidential decree, a Patent Ordinance was issued on 26 December 2004, which had essentially the same provisions as those of the Patent Bill of 2003. Concerns with the Ordinance had been that the proposed legislation did not maximise the flexibilities that would promote access to medicines. The Ordinance eased standards of patentability, eliminated pre-grant opposition procedures, limited Paragraph 6 exports to only those countries that issued a compulsory licence (thereby unnecessarily excluding no-patent countries), and failed to streamline and expedite the procedures for compulsory licensing.

The Ordinance was followed by the Patent (Amendment) Act, passed by Parliament in March 2005 without debate. Some of the access to medicines (ATM) concerns were dealt with, and the Indian generic industry was put in a more favourable position overall vs. their situation under the earlier Ordinance. The following paragraphs discuss some of the more ATM-relevant features of the Indian Patent Law.

4.1 Scope of patentability

The Patent Act aims to curb 'me-too' product patent applications by requiring one or more inventive steps and excluding derivatives such as salts, esters, ethers, polymorphs and similar forms and combinations of known substances, unless their properties differ significantly in the context of efficacy. On the one hand, this would decrease the likelihood of evergreening.²⁶ On the other hand, the inexactness of some of the language leaves scope for interpretation and therefore expensive and time-consuming litigation is likely to ensue. This is already happening with the anti-cancer drug Gleevec, as discussed below.

4.2 Pre-grant opposition

The Patent Ordinance rushed through at the end of 2004, to meet India's commitment to comply with TRIPS by 1 January 2005, had excluded the 11 formal and technical grounds for pre-grant opposition. The third amendment to India's Patents Act reinstated these grounds, thereby permitting pre-grant opposition to patent applications. A window of six months has been granted for such challenges, which must be submitted to the Patent Controller's office, rather than to the courts. However there is no fixed timeline for resolution of patent challenges.

A high profile pre-grant opposition is underway currently. The Indian firm Nacto has initiated pre-grant opposition of Novartis' patent application for Gleevec, claiming that Novartis' crystalline modification of the treatment constitutes an 'evergreening' strategy, not permitted under India's new IP laws. Nacto claims that the patent application seeks protection beyond the basic molecule, and that the 'polymorph' claimed is the same as that of a molecule with a 1993 patent priority date.

²⁵ See page 65 of Chaudhuri, S., *The WTO and India's Pharmaceuticals Industry: Patent Protection, TRIPS and Developing Countries*. Oxford University Press, 2005. This work began as a background paper to the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH).

²⁶ 'Evergreening' refers to strategies employed by originator firms to extend the patent life of older molecules, with the aim of delaying or preventing generic entry and extend market exclusivity. There are mechanisms to achieve evergreening. Some examples include: 1) the originator company develops something of marginal value (such as product line extension), and seeks a new patent, e.g. the originator introduces a capsule and withdraws the older tablet from the market, so the pharmacist cannot replace the capsule with a tablet; 2) patent stacking and litigation, e.g. most chemical entities have multiple patents, each with a different patent life – for instance, the anti-ulcer drug Tagamet had 26 patents; 3) extended exclusivity (e.g. develop a paediatric version).

4.3 Compulsory licensing

In the Ordinance, developing countries importing from India were required to issue a compulsory licence (CL), even if the original drug was not patented in their country. A late amendment to the bill allows exports if a developing country 'has by notification or otherwise allowed importation of the patented pharmaceutical products from India'. The government also redrafted a section to clarify that when CLs are granted mainly for supplying the Indian market, the licensed product can still be exported.

One remaining problem on the CL front, is the three-year moratorium during which companies are not allowed to apply for a compulsory licence; this applies from the date of patent approval and is a restriction not required under TRIPS. Even once the 3-year period is up, there are other practical difficulties in making CLs work for public health benefit. Imagine this scenario: 1) the Asian bird flu hits India, 2) the Indian government looks for supplies of Roche's Tamiflu (oseltamivir) and finds that there is a supply shortage 3) Indian government asks some local companies if they can supply generic versions of Roche's product 3) Indian companies reply that the product is not easy to synthesize and they would need some time to develop the process to make it. Meanwhile, the flu epidemic worsens, with disastrous consequences for the majority of the population. This type of potential scenario has led some to suggest that compulsory licenses granted once such an epidemic has begun would be ineffective; consequently, countries might need to develop short-lists for all life-saving drugs that are vital to the countries needs, and issue blanket CLs for all the products on that list.

Empirical firm-level evidence confirms that compulsory licenses are not very feasible economically either. In a recently conducted firm level survey of Indian pharmaceutical firms, Gehl Sampath 2005 shows that most of the wealthier Indian firms would not consider the option of producing drugs under the CL a very attractive option due to a) procedural costs associated with producing under CL b) low economic returns from such exports and c) unwillingness to invest in the process development or API acquisition, if the firm's usual product range differs from the products demanded by LDCs or emerging public health hazards.²⁷

4.4 What happens to generic versions of drugs patented between 1995 and 2005?

What is important in Indian law is not the date of marketing launch of a medicine or the patent expiry date of the molecule, but the effective date of the start of the patent.

What would happen to drugs in two categories had always been very clear: 1) drugs with patent priority dates before 1995 are not affected by the Patent Law; 2) drugs with valid patents issued subsequent to 1 January 2005 (when the new Patent Law came into force) can be launched by manufacturers in India, only with approval from the innovator company.

Prior to the actual Patent Law being passed in March 2005, the big question in everyone's mind related to the situation of drugs with patent priority dates between 1995 and 2005. The new law states that a currently marketed generic product can continue to be commercialised once the branded original has been granted patent protection, provided that domestic generic manufacturers pay 'reasonable' royalties to the patent holders, the generic firm had marketed the product prior to 1 January 2005, and the generic firm has made significant investments. Access to medicines

²⁷ Gehl Sampath, 2005, p. 62.

will benefit overall from this addition to the law through continuing availability of low cost generics, albeit perhaps with a royalty fee tacked on.

However, the difficulty of defining 'reasonable' royalties and what makes a 'significant' investment might lead to litigation. Canada has placed a cap on the reasonable royalty to be paid to the patent holder for a drug that is produced in Canada for production under CL and is exported to another country. It capped this royalty at 4% of the value of the generic product, but also tied the royalty rate to the United Nations human development index, with the aim of ensuring that a poorer country would pay a lower royalty rate than a richer country.²⁸

Whilst some observers argue that the Indian Patent Law's treatment of drugs with patent dates in the 1995-2005 window is not TRIPS-compliant²⁹, others point out that India was not actually required to implement any patents until 2005, having been granted a 10-year transition period, in 1995, to implement TRIPS. According to the latter view, the previous 'mailbox' exclusive marketing rights system and current processing of patents for pre-2005 drugs is essentially incorrect as WTO in its rules and regulations does not allow backdating.

4.5 Practical impact on specific drugs of public health concern

There are many nuances to consider when applying the Indian Patent situation to questions concerning access to medicines. Common questions include: what percentage of the overall drug market is likely to be affected?; what percentage of drugs on the Essential Medicines List (EML) will be affected?; what is the therapeutic importance of the drugs to be affected? and more micro-level questions are being asked as well, for example, what will happen to specific drugs like tenofovir, fixed dose combinations (FDCs) for treating HIV, and the anti-malarial, Coartem? These micro-level questions are arguably the all-important ones from the perspective of patients who need 2nd and 3rd line drugs.

The boxes below illustrate the last of these questions, or how the Indian Patent Law is likely to impact specific medicines.

Box 1: Practical example of potential IP impact on generic medicines: 1

A generic FDC, combining drugs from three different originator companies

An example of an important FDC is stavudine/lamivudine/nevirapine. The patents on these three individual drugs expire in 2007/2009/2010 respectively. This means that the patents were filed in 1987/1989 and 1990 respectively.

Access to medicines implication: since all three products were patented before 1 January 1995 (irrespective of the launch date), each individually can be freely marketed without any arrangement with the innovator company, irrespective of the expiry date of the patent. Indian generic companies can also develop and patent their own FDC combinations using these three base products.

²⁸ <http://www.cptech.org/ip/health/c/india/insideustrade04152005.html>

²⁹ <http://www.cptech.org/ip/health/c/india/insideustrade04152005.html>

Box 2: Practical example of potential IP impact on generic medicines: 2**Combivir**

Combivir contains AZT (patented 1985) and lamivudine (patented 1987). Since both of these drugs are pre-1995, they are not individually eligible for patents in India.

However, Combivir has a formulation (for the combination of the two in one tablet) patent with the priority date of 1997. Worldwide, no one can market this product until 2017 (2018 in the US).

However, Cipla has been making generic Combivir for five years. If GSK's Combivir, which is currently in the Indian mailbox, is granted a patent, then Cipla can continue to manufacture the drug, since Cipla made a significant investment in developing the generic version and had it on the market prior to 1 January 2005.

However, according to Indian law, Cipla would then have to start paying royalties to GSK. Cipla has two options that might allow it to avoid this: 1) when GSK's Combivir patent application comes up for review, Cipla could employ pre-grant opposition; 2) Cipla might challenge the validity of GSK's patent, asserting that the formulation should not be patentable because people have been combining these two drugs since the early 1990's and there is literature that documents it as a known combination.³⁰

Box 3: Practical example of potential IP impact on generic medicines: 3**Tenofovir**

The base patent for tenofovir is 1992, but the priority patent date on Tenofovir Disoproxil Fumerate - the ester/salt of tenofovir - is 1997.³¹ Gilead is believed to have filed a patent application in India, but it has not yet been approved. Meanwhile, Cipla launched 'Tenvir', their own brand of tenofovir disoproxil fumarate (TDF), in September, 2005. If Gilead is eventually granted an Indian patent, Gilead could take Cipla to court, alleging patent infringement. Cipla's options are to engage in pre-grant opposition, litigate against Gilead's patent validity (if granted a patent), or withdraw its product.

Box 4: Practical example of potential IP impact on generic medicines: 4**Coartem**

The FDC anti-malarial formulation, Coartem, has a 1990 patent priority date on the formulation, so it is not eligible for patenting in India. (The patents on the individual components comprising the FDC are much older.) Indian companies are therefore free to develop their own patented FDC combinations using the same individual components artemether/lumefantrine.

4.6 Percentage of drugs to be affected

At a more macro level, there are questions about the percentage of drugs (in general) on the Indian market that will be affected by TRIPS. Three data sources approach this in different ways, but come up with a similar percentage.

³⁰ In fact, Cipla recently won a similar case against GSK with the combination drug Seretide. Cipla successfully argued in a UK court that there is no novelty to the combination of a bronchodilator and a steroid – i.e. this combination is obvious to a person of reasonable intelligence with expertise in this field.

³¹ An analogous drug would be the antibiotic amoxicillin, which in the body turns to ampicillin – the effective form.

A 1993 study by Heinz Redwood offers one answer. In June 1993, Redwood studied the sales of all drugs among the top 500 (representing two-thirds of the total audited pharmacy market) to determine what proportion contained active ingredients that would have been patent-protected in the years 1987–2001, if European pharmaceutical product patents had been in force in India. The analysis revealed that 24 active substances in the top 500 products on the Indian pharmacy would have been notionally protected by patents, had European-style patent cover been in force. The combined sales value of these theoretically ‘patent-protected’ products came to Rs 328 crores (approx US\$110m), representing 10.9% of the total sales value of the Top 500 products at that time. The hospital and government tender business was not included, but Redwood opined that the greater emphasis on low-cost supplies in these unaudited sectors suggests that patented drugs would play a smaller part in them than in the author’s analysis.³²

A 2004 analysis by Dilip Shah of the Indian Drug Manufacturers’ Association (IDMA) argued that, if the Indian Law took a liberal (liberal meaning a loose versus strict definition of novelty/patentability) patenting approach, then a wider range of products would be affected. In this worst-case scenario (from an access standpoint), then overnight about 15% of the market value would be covered by patents and the Indian companies would be forced to withdraw generic copies.³³

If such a liberal patenting approach had been adopted, granting patents on post-1995 ‘inventions’ of, for example, polymorphs and salt variations of what had originally been a pre-1995 drug, this scenario would mean that entire drug ranges would have been affected, since a generic producer would not want to get held up in the courts by patent litigators coming from the originating company.³⁴

Fortunately, the eventual Patent Law does not allow these so-called ‘evergreening’ patents, so the percentage should be smaller than 15%. However, some observers opine that the way the law will be interpreted and put into practice is yet to be seen.

A third study, done by the international consulting firm, McKinsey & Company, showed that 10–20% of the market by value will be affected, compared with 5% or less by volume. This study relied on two methods:

- 1) extrapolating what happened in Poland and Brazil to India, and
- 2) studying the drug pipelines and determining how many would be affected by new patent law (how many would cause people to switch over vs. those that were substitutes).

The McKinsey study concluded that even ten years from now, 95% of drugs will be off-patent, though on the negative side, the really innovative life-saving drugs will not have generic competition.

In conclusion, between 10% and 15% seems a reasonable estimate for the current value share of medicines that will be affected by TRIPS implementation. Obviously

³² One could equally argue that the hospital sector is where drugs would be used for cancer, HIV/AIDS, and drug-resistant strains of malaria, TB and other infections, therefore the hospital sector is where newer, patented and expensive drugs would be needed.

³³ The source of this figure is unknown but is stated in a paper provided by Dilip Shah of the Indian Drug Manufacturers’ Association (IDMA), where he refers to 3,000 crores. This is equivalent to \$685,792,682 USD and is 16% of the Indian market of 4.3 billion USD.

³⁴ For more detailed information, see Abbott F, Speech given to the Federation of Indian Chambers of Commerce and Industry (provided as Annex 3 to this report.) See especially sections IV c-e.

this percentage would increase over time, as new, patented medicines become an increasing proportion of the overall market.

4.7 Percentage of EML drugs to be affected

A second related question is: what is the percentage of drugs on the Essential Medicines List that is at risk of falling under TRIPS regulations in India? The most recent data to answer this question comes from Amir Attaran's 2003 paper in *Health Affairs*³⁵ Using the World Health Organization's (WHO) 2002 Model List of Essential Medicines, 300/319, or 94% have basic patents pre-dating April 1982, are therefore not patent-protected anywhere in the world and cannot become patent-protected in the future. Attaran also finds that patents and patent applications exist for essential medicines 1.4% of the time (300 instances out of 20,735 combinations of essential medicines and countries) in the 65 countries included in the study.

This analysis can be disputed based on methodology but the errors would only be at the margins. The fact remains that only a small percentage of EML drugs are patented, and would therefore be at risk of being affected by TRIPS in India. However, many of the normative conclusions the author draws from this statistic – including that patent status has little impact on access to medicines – are flawed. Such patent-counting exercises tend to undervalue the impact that patents have on access by taking averages of large samples of dissimilar drugs and dissimilar countries and, in the process, discounting important variations and outliers within the sample.

4.8 Small percentage, big impact

To be more precise, the figures indicating the small percentage of drugs likely to be affected do not make transparent the variation within product classes, e.g. ARVs are more highly patented than other classes of drugs, so the percentages in Attaran's paper give a false impression of the under-importance of patents to access in this product group.

Second, the figures hide the importance of how lack of access to one drug in a combination therapy precludes appropriate treatment. For example, despite the fact that NVP and d4T are off-patent as individual drugs, GSK's patent on the ARV 3TC blocked the availability of the simplest and most affordable AIDS treatment available worldwide – the WHO-recommended fixed-dose combination of d4T/3TC/NVP. It was therefore necessary to prescribe brand-name medications that were five times more expensive, and in individual drugs rather than in co-formulated pills (thereby complicating the treatment regimen and potentially affecting compliance and therefore efficacy).³⁶ Lack of access to one drug in a combination can also (unwisely) encourage governments to consider less than optimal combinations as the therapeutic choice. A case in point was the situation in China with 3TC; the exclusivity afforded by intellectual property protection made 3TC unavailable in China, consequently the government initially promoted a therapeutic treatment regimen that excluded 3TC. This has had long reaching public health impacts, as described subsequently in this paper.

³⁵ Attaran A., 'How do patents and economic policies affect access to essential medicines in developing countries?', *Health Affairs*, 23(3), May/June 2004.

³⁶ Goemaere, Lotrofska, Marchandy, and t'Hoen in Letters to the Editor, *Health Affairs*, September/October 2004: 280.

An earlier study by Attaran³⁷ which had similar findings to the 2003 paper, was criticised because it had not looked at how/whether patents blocked the combinations of zidovudine/lamivudine/nevirapine or stavudine/lamivudine/nevirapine, which are widely considered to be the most appropriate for resource-poor settings because of the relatively simple dosing schedule and acceptable toxicity profile. Patents on zidovudine were found to block the combination in 33 of 53 countries studied, and patents also blocked nevirapine in 25 of these countries.³⁸

Another factor to consider is that patent-protected drugs, although few in number, actually represent a very large percentage of health budgets. Just a few expensive patented medicines can skew entire treatment budgets. Of the 14 ARV drugs on the Brazilian National AIDS Program, three new single-source products accounted for 63% of total program costs in 2003.³⁹ MSF has calculated that access to generic triple combination therapy (3TC/d4T/NVP) costs 26 times less than using the originator's triple therapy of TDF+ddl+LPV/r.⁴⁰

One must also consider the fact that patenting activity in producing countries is not of equal importance to patent activity in non-producing countries. To cite a theoretical example: if 100 countries are studied, two of which are producing countries and 98 of which are non-producing countries, and patent activity is found only in the two producing countries, we could not conclude that, 'because patents are not present in 98 countries, they are not a barrier to access'. But the point is that all countries are not equal. If the two producing countries cannot supply generics to the 98 others, then patents are most definitely a problem. Not surprisingly, more than 95% of ARVs are patented in South Africa, which has manufacturing potential useful for domestic supply and for regional export.⁴¹

It must also be recognised that the EML had, until the 13th edition, excluded most patented drugs because of cost. Therefore, since cost was a concern during 95% of the EML's life, it is understandably weighted towards non-patented products, although it can be expected that the proportion of patented drugs on the EML will increase over time. However, since only a handful of new essential drugs become available every two years (when the list is updated), it will take some time before the list becomes more weighted towards newer, and more widely patented, drugs.

It is also not surprising that patent coverage was found to be low in Attaran's study, since for most of the past twenty years there was no requirement for product patent protection in the countries studied. But with the implementation of TRIPS, patent coverage will increase.

4.9 Therapeutic importance

Other questions being asked by those concerned about the public health impact of the change in India's IP situation are:

- Which particular medicine groups are most likely to be impacted by TRIPS?

³⁷ Attaran A, Gillespie-White L., 'Do patents for anti-retroviral drugs constrain access to AIDS treatment in Africa?', *JAMA*, 2000; 286: 1886–92.

³⁸ Boelaert, Lynen, Van Damme, Colebunders, Letters to the Editor, *JAMA*, 2002; 287: 841.

³⁹ Goemaere, Lotrofska, Marchandy, and t'Hoen in Letters to the Editor, *Health Affairs*, September/October 2004: 279–80.

⁴⁰ See Annex 2 for slides.

⁴¹ Boelaert *et al.*, 'Do patents prevent access to drugs for HIV in developing countries?', *JAMA*, 2002; 287(7): 840.

- What is the relation of these groups to disease incidence in developing countries (i.e. what is the therapeutic importance of the medicines that will probably be affected by TRIPS)?

The disease areas most likely to be negatively impacted by TRIPS include cancer and diabetes, since these are treated with relatively new drug classes which have little therapeutic competition/substitution, and therefore have significant pricing power. Classes of drugs that experience a high speed of new product development due to emerging resistance, such as antibiotics and anti-infectives (e.g. ARVs, TB drugs, anti-malarials) will also be affected. This is because newer drugs in this group may have little therapeutic competition since older drugs essentially become ineffective due to resistance. A World Health Organisation study showed that in the case of pneumonia, which kills 3.5 million people annually, medications that were formerly effective now fail in 70% of cases because of drug resistance. A similar situation exists for older drugs that treat TB and malaria, where new, resistant strains are always emerging. Thus, only newer, patented medicines will be effective and these will be unaffordable in developing countries.

Access to cardiovascular and pain drugs are unlikely to be as significantly affected, as there is a high level of therapeutic competition/substitution and inter-changeability between classes within these categories.

As for how the drugs most likely to be affected match with the disease burden in developing countries, the table below offers a snapshot view of the developing country disease burden today and 20 years into the future.

Box 5: WHO expects developing country disease to mimic the West⁴²

Developed Nations 2000	Developing Nations 2000	Developing Nations 2020
Ischaemic heart disease	HIV/AIDS	Ischaemic heart disease
Unipolar depressive disorders	Lower respiratory infections	Unipolar major depression
Cerebrovascular disease	Diarrhoeal diseases	Cerebrovascular disease
Alcohol use disorders	Childhood cluster diseases	Chronic obstructive pulmonary disease
Dementia and other central nervous system disorders	Malaria	Lower respiratory infections
Malignant neoplasms	Unipolar depressive disorders	Tuberculosis
Chronic obstructive pulmonary disease	Ischaemic heart disease	Diarrhoeal diseases

⁴² Source: WHO and Goldman Sachs Research estimates as reported in BRICs: Challenges and opportunities: The Healthcare Sector, June 2005. Sahu, Keusch, Bostrom, Goldman Sachs Equity Research.

5 THE CHINESE PATENT LAW AND ITS IMPACT

With the evolution in first-line recommendations for diseases like malaria and HIV, and a narrowing window of supply over time from India, access to medicines supporters are increasingly questioning what role China may be able to play for finished product, API or intermediate supply of products of public health importance. This section will examine the factors influencing the interface between the pharmaceutical industry and access to medicines in China, focusing on China's IP legislation, other important institutions, the current ATM role China plays, and the potential role it could play.

5.1 The evolution of China's patent laws⁴³

China became a World Trade Organization (WTO) member in 2001, and TRIPS officially came into force in China at the end of 2002. In recent history, and prior to becoming a WTO member, China's IP policy was very much a result of bilateral negotiations with the US. China's first modern patent law – the Patent Law of 1984 – came about during 1979 negotiations with the US. Similar to the Indian 1970 Patent Act, it allowed for process patents whilst excluding pharmaceutical product patents.

In 1992, a Memorandum of Understanding signed with the US compelled China to amend its 1984 Patent Law to reach the protection level of TRIPS.. This amendment resulted in the 1993 Patent Law that extended patentable subject matter to include product patent protection, ten years before TRIPS would otherwise have come into force in China. It also established an administrative protection regime, protecting foreign pharmaceutical patents granted between 1984 and 1993. This administrative protection system resembles the co-called 'mailbox system' provided for in Article 70.8 of TRIPS, because it allows for retrospective market exclusivity.

The 'administrative protection' granted to foreign patent holders prohibits others from manufacturing or selling the pharmaceutical product in China. However, it does not preclude using or importing, these normally being included in the exclusive rights of a patent holder. Administrative protection offers market exclusivity for seven years and six months. There are several other requirements for eligibility. For example, the exclusive right must be obtained on a drug whose patent priority date was between 1 January 1986 and 1 January 1993. Drugs with priority dates after 1993 would be eligible for product patent protection in China, so applying for patent protection (which grants more rights and a longer period of protection than administrative protection), would be the appropriate avenue in this case.

5.2 Compulsory licensing

There are three grounds on which compulsory licenses can be granted in China.

- 1) "Where any entity which is qualified to exploit the invention or utility model has made requests for authorization from the patentee of an invention or utility model to exploit its or his patent on reasonable terms and conditions, and such efforts have not been successful within a reasonable period of time." (Article 48)
- 2) "Where a national emergency or any extraordinary state of affairs occurs, or where the public interest so requires, the Patent Administration Department

⁴³ This section draws primarily from the following paper: Wu, Zuolong, Pharmaceutical Patent in the PR China: Adjustment in Public Health Concern. Master's thesis, Faculty of Law, Lund University. Autumn 2002.

- under the State Council may grant a compulsory license to exploit the patent for invention or utility model.” (Article 49) (Ibid. Article 49)
- 3) “Where, according to the preceding paragraph, a compulsory license is granted, the Patent Administration Department under the State Council may, upon the request of the earlier patentee, also grant a compulsory license to exploit the later invention or utility model.”⁴⁴ (Article 50)

These three grounds are subject to procedural restrictions, such as a requirement to notify the patent holder, limited scope and duration, non-exclusive and non-assignable rights, payment of royalty to the patent holder, and a three-year moratorium on CLs after the date the patent is granted. The CL must also be predominately for purposes of supplying the domestic market (Rule 72, para. 4, Implementing Regulations 15 June 2001).⁴⁵

China has not incorporated legislation to allow CL issuance on the basis of public non-commercial use, although it is suggested that this would be the grounds that would pose the least procedural restriction and would therefore prove beneficial in terms of access to medicines.

Public non-commercial use and correction of anti-competitive practices are two other widely accepted grounds on which TRIPS allows CL; however, these are not provided for in the Chinese legislation.

5.3 Other institutional issues

The two other major institutions that affect the Chinese pharmaceutical industry are the registration authorities and the public health service.

5.3.1 Registration process

Chinese drug legislation, enacted in 1985, requires that new drugs be approved by the national drug regulatory authority before they can be marketed in China. Since enactment of this legislation, China has significantly altered its regulatory review process for new drugs. The Drug Registration Regulation, which is compatible with the World Trade Organisation agreement, went into effect on 1 December 1 2001. The new regulations now require qualification of the drug registration applicant, the classification of drug registration application, links between the intellectual property and the registration process,⁴⁶ and the protection of undisclosed trial data.⁴⁷ This latter ‘data exclusivity’ provision provides for 6 years of protection from the date of granting of manufacturing or marketing approval, which is above and beyond that required by TRIPS.⁴⁸

⁴⁴ NB: the law says “may” and not “shall”, meaning the earlier patentee may or may not receive a compulsory license.

⁴⁵ According to MSF, Chinese legislation has not yet been amended to take into account the Aug 30 decision, meaning that for the time being the ‘predominant’ clause holds.

⁴⁶ The applicant is required to submit: the patent information and ownership certificate for the drug submitted for registration, or for the formula and technology used in the research and manufacture of the submitted drug; the guarantee of not constituting an infringement; and the promise of assuming all infringement responsibilities. The state drug agency allows the applicant to submit a drug registration application for a drug still under patent protection, up to two years prior to patent expiry, in order to assist generic manufacturers to put their products on the market as soon as patent expiry occurs.

⁴⁷ Zhen, Li Hui, ‘The drug registration application’, *J Pharm Pharmaceut Sci*, 2003; 6(2): 211–14.

(www.ualberta.ca/csps)

⁴⁸ Using the Chinese provision as a standard, the US is allegedly currently trying to insert similar clauses into the FTAs it is negotiating with other developing countries. Data exclusivity is of concern because it is another way to block generic entry, even after a patent has expired (depending on the timing) and there is no equivalent of a compulsory license to ‘break’ data exclusivity for public interest reasons.

5.3.2 *Public health policies*

Government health policy is yet another critical piece in the puzzle of understanding the interface between the pharmaceutical industry and the access to medicines situation in China. The Chinese Government has given a high level of political commitment to tackling HIV and AIDs, including through free access to ARVs. Although this free ARV policy holds promise, implementation has been slow; only 20,000 people have been started on ARVs paid for by the Chinese government's free treatment plan. The slow increase in uptake has meant a lack of genuine orders to manufacturers, and this has in turn reduced the incentive both for domestic firms to enter the market and scale-up supply, and for foreign firms to supply the market.

A major reason for the slow start is believed to be the inconsistency between a fee-for-service health system and a free ARVs policy; service providers have no incentive to offer free drugs in such a context. Other problems have been high side effects, due to the lack of 3TC in the first year of the government's new treatment plan, and resultant therapy discontinuation which may heighten levels of resistance and propel patients into second-line drugs.

5.4 Domestic ARV production

Whereas domestic suppliers of finished product ARVs were few in early 2004, China now has four domestic pharmaceutical companies manufacturing a multitude of generic HIV/AIDS cocktails.⁴⁹ A recent announcement from the Clinton Foundation brought to the public eye the technological capacity of China to do even more for ATM. The Foundation negotiated a deal with Mchem of China to supply the API of five products (AZT, 3TC, D4T, NVP and efavirenz.) to its partner suppliers.⁵⁰ The Foundation is also offering technical and regulatory assistance to Mchem on certain products (e.g. TDF, EFV, LPV/r) with the hope of adding additional products to the supply agreement at some point in the coming year. Whether this will work depends on the technical capacity of Mchem, IP constraints in China and relative production costs to India.

Ironically, formulations of 3TC, Combivir (3TC+AZT) and efavirenz are reportedly difficult to get hold of in China, despite the fact that Chinese companies are producing the API for these for originator companies and for Indian, Brazilian and South African formulators.

⁴⁹ See Annex 4 for details of ARVs made by Chinese firms.

⁵⁰ To clarify, Clinton does not procure ARVs. The Foundation negotiates deals and helps form partnerships. Prior to the Mchem deal, it had four partner companies: two API partners and three formulator partners (one of whom was also an API partner). Mchem became the third API partner and the fourth formulator.

Box 6: Tenofovir in China**Tenofovir In China**

Gilead applied for patent protection on its tenofovir in China in 1997, but the patent has not yet been granted; so the product is currently not patented, registered nor marketed in China. However, it is rumoured that Chinese companies are producing tenofovir API and shipping it to India for manufacture of finished products there.

Since there is no issued patent in China, then one may wonder why domestic companies are not producing generic tenofovir finished product. According to some, companies are unlikely to enter into finished product production of tenofovir, because if the product patent is eventually granted, the generic firm would have to immediately stop production and lose the investment made into its process development. Nonetheless, as with efavirenz, companies do not expect that an issued compound patent in China will necessarily preclude them from manufacturing and exporting – with government permission – the APIs.

This sort of 'limbo' situation is not good for ATM, as Gilead cannot even grant a voluntary license as there is not yet a patent. NGOs are therefore calling on Gilead to grant some sort of guarantee that the firm would not seek punitive action against generic TDF generic producers in China.

If Gilead is awarded a patent tomorrow, there will be no CL possible on the patent until Oct 2008 at the earliest due to the 3-year moratorium on CLs. Gilead has not yet registered tenofovir, but as an AIDS drug its registration goes through a 'green channel' in China, the process of which takes about one year. Even if Gilead launches its registration application on the same day its patent is granted, there will be an additional 2 years (in theory) before Gilead would be exposed to the risk of a CL. (This implies less leverage for the government in negotiating lower prices).

On a related note, Gilead has licensed tenofovir and its FDC combination of tenofovir and emtricitabine to Aspen Pharma of South Africa to supply 95 countries at access pricing, but the API must be from Gilead. This is a significant issue, since approximately 70% of tenofovir's cost is in the API, therefore Aspen will not be able to offer a price significantly below Gilead's. Presumably Gilead has imposed this restriction to maintain cost (pricing) control and comfort on quality issues, as well as control of the production process IP. There is some speculation that some of Aspen's voluntary licences were offered in order to prevent Aspen doing what Mchem and Cipla are currently doing – producing competitive generics and undercutting the originator in price.

5.5 IP nuances

Given what we now know about China's IP laws and institutions, stakeholders are wondering how China is able to produce API for products that would seem to be patent-protected in a fully-TRIPS compliant regime. As a case in point, of the eight products Mchem will offer to Clinton partners, at least two (3TC and efavirenz) would seem to be protected by administrative protection and product patents respectively in China.

Even formulators who source from China are perplexed at how China can produce API for products that, in their view, would be patent-protected in a fully TRIPS-compliant regime. For example, one formulator interviewed for this study and who sources routinely from China, was under the impression that drugs with patent dates

before 2002 cannot be patented in China. Another formulator who imports routinely from China did not understand how, in IP terms, China was able to produce the API imported by his/her company. His theory was that China either had some kind of mailbox system or that China must still be in the midst of the ten-year phase-out allowable by TRIPS.

Several theories, but little evidence, exist for how China can supply newer drugs or raw materials for these drugs. Some observers assume IP sophistication allows Chinese firms to legally bypass apparent IP requirements, whilst others assume complete lack of IP enforcement.

At the more IP-sophisticated end of the spectrum, we have the example of efavirenz, which is protected by several product patents and several process patents in China, yet Chinese companies are producing the API – illegally so, it would seem. The nuance in this case is that the patents are only at the level of the API or later in the production process. Therefore production of a chemical that was one step before it became an API would not violate the patents. Although this ‘pre-API’ can benefit other countries, it does little good for the Chinese patient trying to access inexpensive efavirenz. Whilst producing ‘pre-API’ may be a legitimate IP ‘loophole’, it is reported that multiple suppliers are exporting the ‘finished’ API as well. On a related point, Chinese government negotiations with Merck for differential pricing have reportedly not yet been successful⁵¹, causing some to speculate whether a CL on the formulation would be a politically feasible alternative.

Another example where one has to look at the fine print to understand the actual situation is with lamivudine (3TC). Lamivudine is protected in China by process patents and by administrative protection (until October 2006), but not by compound patents on the molecule. A particular nuance of the administrative protection system is that it applies only to ‘drugs’ (defined as ‘drugs for human consumption’ and not to API (as API is not for human consumption), thereby leaving open the window of producing 3TC API, but not finished product. Another nuance of the Chinese administrative protection system is that it does not prevent importing generic versions for non-commercial use; in fact, Médecins Sans Frontières in China is currently looking into how this ‘loophole’ could be used to import fixed-dose combinations containing generic 3TC.

These examples highlight the need to question specifically what the domestic patent applies to. Does it apply to the entire composition of a substance (the drug and the structure of it), to a specific process, or to the drug’s medical use? Related to this is the fact that some patents are easier to bypass. For example, process patents are relatively easier to bypass, since an alternative process can be invented in many instances. It should be noted that such investigation is transaction-intensive and requires a level of IP sophistication that is in short supply, so even when there is a legitimate ATM-conducive ‘loophole’, it may never be found and used.

Many people assume that some level of IP-engineering or finagling goes on in China, whereby the Chinese companies circumvent IP restrictions by exporting intermediates, rather than fully finished products, as with the efavirenz example. So if there is a ten-step formula for arriving at an ARV, a Chinese company may take the chemical through to stage eight and then export it to India for the remainder of the processing. Up to stage eight, the product is called a chemical, not a medicine, and the originator is less likely to have taken out a patent on the early-stage chemical.

⁵¹ Merck offered the government a differential price compared to developed-country prices, but the government has been requesting an even lower price, with no success.

This is in fact happening, but according to some in the industry, it is happening for economic, not IP reasons. Intermediates are not subject to the same quality restrictions as API. So China is capable of making intermediates for ARVs, in cases where it may not necessarily have the capabilities to produce the dossier required for regulatory approval of the API. The advantages to formulators are primarily regulatory, plus the cost advantage of having several steps in the process conducted in China. It may also save a formulator time and capital investment to source intermediates from China.

Then there are the theories of complete IPR neglect. There is the (very plausible) theory that Chinese companies neglect IP for lack of capacity reasons rather than because of purposeful intent. As revealed in the examples above, pharmaceutical patent laws have many specific features requiring both scientific and legal knowledge; Chinese companies may lack the legal resources to carry out extensive patent searches to ensure non-infringing processes and they seem to so far lack the legal sophistication of the Indian firms to launch patent challenges outside of China.

Finally there are the purposeful neglect, or 'IP cowboy' theories. The stories in this category include those about changing the name of the API before export, calling it a chemical or 'raw material', thereby circumventing the IP restrictions that would otherwise apply if the originator has a patent on the API or the finished product. Even on API for export, the Chinese government allegedly applies less stringent criteria versus that applied on finished product exports. Generic companies, in weighing the probability of punishment against potential gains, may also consider: 1) whether originator companies would be likely to sue them, given the bad PR it might well create as well as the fact that big pharma sources chemicals from many Chinese suppliers and may want to maintain these supply relationships; and 2) whether there are enough ambiguities in TRIPS and domestic laws to make government intervention extremely time-consuming and difficult.

Clearly, there is a perception that China's IP algorithm in the pharmaceutical sector is not as transparent as India's. There appears to be little understanding of the official IP policy and there is also a view, in some sectors, that official policy does not mean much anyway. The Research Director of Novo Nordisk's Beijing site, for example, stated 'China has in place a series of laws related to IPR protection. But their enforcement, particularly the amount that would be paid to the damaged side, remains a problem that needs to be addressed.'⁵² The Director of McKinsey Consulting's China office echoed this view: 'The core issue is enforcement. The central government has largely followed through on its WTO commitments by creating a stronger policy framework for protecting intellectual property. However, the will and the ability to enforce the policy at the local level are often modest, to the continuing dismay of many foreign investors.'⁵³ But whilst lax IP enforcement on certain products, such as luxury goods and entertainment products, is more well-known in China, clearly IP enforcement does in fact heavily impact on the lives of patients, since – as discussed earlier - Chinese generic firms are unable to circumvent the IP restrictions on the finished product formulations of 3TC, efavirenz and tenofovir.

⁵² Yidong, G., 'Pharma moves ahead cautiously in China', *Science*, 2005; 309.

⁵³ Orr, Gordon R., 'What executives are asking about China', *McKinsey Quarterly*, 2005.

6 CONCLUDING REMARKS

Six million people need ARVs. Only 1 million get them. Something is not working – is IP the main culprit? Is lack of financing the real problem? Are health systems holding things back?

This paper has focused on the IP perspective and has revealed that clearly IP is an access-constraining factor, which can sometimes be overcome through inventive means if there is the will and/or the economic incentive. There is a need now for policymakers to encourage more 'access' activity in situations where the market fails – either where drugs are patented or single-source for other reasons – including where such drugs are a crucial part of a combination. There will be an increasing role for such encouragement over time, due to a) the continuous change in spectrum of diseases and resistance patterns, requiring ever-more innovative technologies to address public health problems b) the gradual increase in the percentage of EML drugs on-patent (as the list is updated with new, patented medicines) and c) the gradual decrease in generic sources of newer medicines from quality suppliers due to changing IP in the major producing countries.

Genuine confusion about what the WTO requires from a country and the flexibilities WTO gives member states seems to be present in many developing countries. As countries with large R&D bases, the UK and US are well placed to provide both the political support to back up countries who choose to utilise TRIPS flexibilities, and the technical support to adapt domestic legislation and policies in order to facilitate the use of those flexibilities. China is a classic example of a country that has bent to bilateral pressures and has implemented few ATM-enhancing TRIPS flexibilities in its domestic legislation. The sub-optimal domestic access to ARVs is partly a result of that.

Financing is the other side of the high-price coin, if you will. More financing would indeed improve access, but so would reduced prices, which would decrease the need for that financing. Only about 10% of Africans who need the ARV drugs get them. Of that 10%, 50–60% receive branded drugs in Africa (primarily through PEPFAR and some through the Accelerated Access Initiative) and the rest come via the Global Fund for AIDS, TB and Malaria (GFATM), primarily generics with some Combivir. In some cases, the problem is not so much lack of financing but the restrictions on the financing. Clearly, the PEPFAR financing will go a lot further if the US makes good on its commitment to buy generics that have been FDA approved.

Donors should not only encourage policies that promote value for money, but should look to better align the institutional mechanisms for financing and procurement with the most efficient way of dealing with the particular market. For example, ACTs, some vaccines and some TB drugs have similar market characteristics; supply security and reduced prices are more likely to be achieved with these drugs via pooled financing and procurement. Conversely, where the drug markets are more competitive and/or the public sector is a smaller percentage of overall demand, decentralised procurement and financing is less of a problem.

Other health systems and institutional issues can constrain access as well. There are many actors and processes influencing how well drug financing is used, e.g. WHO, GFATM, procurement agents, country-level policymakers and managers. DFID can play a fundamental role in improving individual agency and country capacities, but also in improving how well these agents interface with one another and work together in a harmonized way.

ANNEX 1: TERMS OF REFERENCE

5 July 2005

Integrating new findings into the DFID commissioned paper on China and India

Background

In 2004, the DFID Policy Division's Access to Medicines team commissioned a series of studies aimed at developing the evidence base in support of an integrated framework addressing upstream barriers to access to medicines. The intention has been to aid international and national actions by major stakeholders in improving access to medicines, especially for developing country partners, pharma and generic producers, and UK and other Organisation for Economic Co-operation and Development governments.

The DFID commissioned study 'The effect of changing intellectual property on pharmaceutical industry prospects in India and China: considerations for access to medicines' provided evidence to show how important Indian and Chinese firms are to the supply of quality, low-priced active pharmaceutical ingredients and finished products domestically and to developing countries, and analysed how changing intellectual property was affecting firm strategies and access to essential medicines in these countries.

Several things have happened since the paper was published, which would warrant an update of this paper.

- Now that the Indian authorities have made decisions about how TRIPS will be translated into domestic law, a more realistic picture can be provided of how this is affecting producers' ability to produce generic copies of drugs which fall under the product patent protection umbrella.
- Evidence compiled in support of the ATM Good Practice Framework, has revealed that, although the percentage of drugs affected by TRIPS is small, the therapeutic importance of this percentage was perhaps not made as explicit as should have been. This information should now be integrated.
- New empirical evidence has become available through CIPIH commissioned studies, with some relevant lessons for how changing IP may affect incentives for innovation and how the interface between IP policy and other policies (like price controls) may affect access.
- In addition, the major investment banks are currently compiling data on the Chinese pharmaceutical industry, similar to what had been done on the Indian industry in the autumn/winter of 2003/2004. Such information, now several years into the IP changes in China, would be quite revealing juxtaposed against the Indian data.
- There has also been a gradual evolution in first line recommendations for diseases like malaria and HIV, leading stakeholders to question what role will India and China be able to play for either finished product or API supply (or supply of intermediates) for domestic use or export of drugs like Tenofovir and ACTs for malaria.
- There has been increased interest in China and the role that it can play in ATM, leading stakeholders to ask, 'What is the exact nature of China's legal texts on IPRs?' Does China have a mailbox provision? Do its domestic laws include 30th August export provisions?

Purpose

The purpose of the consultancy is to update the study 'The effect of changing intellectual property on pharmaceutical industry prospects in India and China: considerations for access to medicines' with information that has become available in the year since the research was done. Updating the paper is expected to yield new insights into how TRIPS is being implemented at country level, what effect the changes are having on firm level strategies and what downstream effects these changes are having on access to medicines supply. An updated paper will;

- Support ongoing policy engagement by DFID on TRIPS at an international level
- Support DFID funded (International Trade Division) work to build developing country capacity to utilise TRIPS flexibilities

Method

Literature review and interviews: The consultant will rely on contacts, including those made during the recent Chatham House meeting and those within the investment banks, to gather available data and supplement this data with interviews.

Inputs

8 days

Outputs

Updated paper, addressing the bulleted issues identified in the 'Background' section above, to the degree data is available.

Timeframe

To be completed by end of August.

ANNEX 2: GENERIC TRIPLE COMBINATION THERAPY

MSF Price Calculations showing benefit of access to generic triple combination therapy⁵⁴

Prices

Country	First-line regimen	First-line price (\$/y)	Second-line regimen	Second-line price (\$/y)
Malawi	3TC/d4T/NVP	288	AZT+ddI+NFV	1875
Ukraine	3TC/AZT+NVP	500	d4T+ddI+LPV/r	—
Kenya	3TC/d4T/NVP	292	AZT+ddI+NFV	1594
South Africa	3TC/AZT+EFV	1000	ddI+d4T+LPV/r	1203
	3TC/AZT+NVP	400		
Mozambique	3TC/d4T/NVP	389	AZT+ddI+NFV	—
	3TC/d4T+EFV	463		
Cameroon	3TC/d4T/NVP	277	AZT+ddI+NFV	4763
Cambodia	3TC/d4T/NVP	350	AZT+ddI+LPV/r	1215
Thailand	3TC/d4T/NVP	352	AZT+ddI+SQV/r	3500
Honduras	3TC/d4T/NVP	426	d4T+ddI+NFV AZT+ddI+NFV	3796 (for NFV only)
Guatemala	3TC/AZT+EFV	867	d4T+ddI+NFV	1161
	3TC/AZT+NVP	520		

Prices: WHO recommended regimens

	(1 st line) 3TC/d4T/NVP	(2 nd line) TDF+ddI+LPV/r	2 nd line vs 1 st line
Western countries ¹	US\$ 8 773/year Originator products	US\$ 13 151/year Originator products	1.5 times more expensive
Developing countries	US\$ 154/year ² Triomune® (Cipla)	US\$ 3950/year ³ Originator's	26 times more expensive
Reduction	-98%	-70%	

¹ Australian EXW price, ² Clinton Foundation price (FOB) + 10%, ³ EC ddI Australian EXW price, TDF and LPV/r prices FOB prices + 10%

⁵⁴ Slides courtesy of Ellen t'Hoën at MSF

ANNEX 3: THE INDIAN PATENTS (AMENDMENT) BILL

Speech given by Fred Abbott to Federation of Indian Chambers of Commerce and Industry

India at the Crossroads: The Patents (Amendment) Bill 2003 and the Future of Public Health

Frederick M. Abbott⁵⁵
IndiaChem 2004, Mumbai
November 4, 2004

I am here to discuss the present reality of India's generic pharmaceutical industry and the impact of the January 1, 2005 TRIPS Agreement transition, having listened this afternoon to speculation about the long term future. The issue I am concerned with is whether, and in what condition, India's generics industry will survive to meet that vision of 2020.

- I. On January 1, 2005, India becomes obligated further to Article 65.4 of the TRIPS Agreement to extend patent protection to pharmaceutical products. As the TRIPS Agreement transition period expires, India is obligated to apply the ordinary obligations of a WTO Member in respect to providing patent protection. (Least developed WTO Members are not yet subject to these obligations.) The objective of the Amendments Bill is to allow India to meet its new obligations.
- II. There are several reasons why India's situation is unique among WTO Members and why the terms and implementation of the Patent Amendments Bill are especially important.
 - a. In the period of the GATT Uruguay Round negotiations, India already maintained a vibrant generic pharmaceuticals sector and was the country most likely to be affected by a change in the global pharmaceutical patent regime.
 - b. India employed a skilled negotiating team that bargained hard to secure the viability of its domestic pharmaceutical industry. The terms of the deal struck in Articles 65 and 70 of the TRIPS Agreement were India's response to pressures from the United States, Europe and Japan and their pharmaceutical industry constituency.
 - c. Alone among significant developing country producers of pharmaceuticals, India has taken advantage of the full extent of the TRIPS transition arrangements. By doing so, it has further encouraged the development of its generic pharmaceuticals sector, which is a principal supplier of low cost pharmaceuticals not only to its domestic market, but of much of the developing world.
 - d. It is the Indian pharmaceutical producers who demonstrated to the world that medicines to treat HIV-AIDS could be produced and sold at a fraction of the price being charged by the major Pharma companies, and opened the door to the possibility of comprehensive treatment of those infected with HIV. Without the efforts of the Indian generics

⁵⁵ Edward Ball Eminent Scholar Professor of International Law, Florida State University College of Law.

sector, it would not have been possible for President George W. Bush to announce in his State of the Union address two years ago that treatment around the world is now a possibility because medicines could be obtained for \$300 per person per year, a figure that is now significantly lower.

III. The Uruguay Round Bargain

- a. Before considering the details of the Patents Amendment Bill it is important to understand the bargain that was struck by India in 1993, and which entered into force on January 1, 1995. India agreed that it would initiate pharmaceutical product patent protection on January 1, 2005. It also agreed to establish a so-called patent application “mailbox” under Article 70.8 that would allow the filing of pharmaceutical product patent applications during the ten year transition period. At the end of the transition, the applications would be taken out of the mailbox and reviewed. If the application met the TRIPS Agreement standards of patentability, as implemented in national law, a patent would be granted for the remainder of the patent term counted from the application filing date in India. During the transition period, a regime would also be instituted for the grant of so-called “exclusive marketing rights” or EMRs based on the fulfillment of certain criteria, including the grant of a foreign patent and the grant of marketing approval in India.
- b. The essence of the bargain struck by India was that pharmaceuticals for which patents were granted abroad before January 1, 1995 would not be patented in India. Applications for inventions filed in India after January 1, 1995 would not be able to demonstrate novelty. (There may be borderline cases involving applications filed abroad prior to January 1, 1995, and filed in India within the one-year priority period or prior to publication. India did not join the PCT until 1998, and this eliminates certain potential complications with respect to the January 1, 1995 cut off date.)
- c. The other core element of the Uruguay Round TRIPS bargain is that patents should be granted for inventions that are new, involve an inventive step and are capable of industrial application, as well as being sufficiently disclosed. The TRIPS Agreement does not define novelty, inventive step or industrial applicability, and these are terms which have been and are applied by courts in different legal systems around the world, developed and developing, according to different rules and standards. However, there are certain core principles of patentability that can be looked at. An invention should not have been anticipated by prior art so as to defeat its novelty, and an invention must involve the critical element of “inventive step”, such that a change or improvement that would have been obvious to a person skilled in the art practiced by the invention.
- d. India in its present Patent Act has attempted to be cautious in avoiding the grant of patents for inventions that do not meet reasonable standards of patentability. Thus, in Section 3(e) of the Patents Act, “mere admixture ... of components” is not subject to patenting, and under Section 3(d) the “mere discovery” of a “new use for a known substance” is not patentable. This, of course, in addition to the present non-patentability of medicines under Section 5 of the Act.

- e. To highlight a key point, it is important to be mindful of the two-fold nature of the forthcoming transition in India. First, all medicines developed after January 1, 2005 will be subject to patenting, provided they meet the criteria of patentability. Second, all pharmaceutical product applications being held in India's patent mailbox will be taken out and reviewed by patent examiners, and those for which the criteria of patentability are met will be granted patents (as well as applications which formed the basis for existing EMRs granted in India).

IV. The Patents (Amendment) Bill and Its Implications

- a. The Patents Bill addresses the extension of patents to post-January 1, 2005 applications through elimination of the existing exception in Section 5 of the Act. (It proposes also to amend the reference to "mere" new use to "new use".) It also proposes to eliminate an important existing element of the procedure by which patents are examined and granted, and this involves the right of third parties to challenge the grant of a patent before it occurs – the so-called pre-grant opposition procedure.
- b. The provisions regarding mailbox applications are friendly to patent applicants. At Clause 12, amending Section 11B, it generally provides for the shortening of the time period under which patents should be examined, encouraging the adoption of regulations shortening the present 18 month expectation. Clause 10, amending Section 11A, allows the patent applicant to request early publication of the patent, and then grants provisional rights to the patent holder based on the published application, as if the patent had been granted, although not allowing the commencement of infringement proceedings until the patent has been granted. This places the generics producer in the position of potentially paying damages for infringement from the date of early publication, which in the case of mailbox applications may be very shortly following January 1, 1995. This arrangement may create a situation threatening to generic producers.
- c. There are some very troubling aspects of the mailbox situation that give rise to serious risks to the Indian generics sector. Although the contents of the mailbox applications are not known, it has been widely reported that 4000 applications with respect to pharmaceutical products have been filed (plus an additional 3000 with respect to agricultural chemical products.) Because most or all of the new chemical entities that constitute today's first line antiretroviral treatments were patented abroad before January 1, 1995, it has been assumed that generic versions of such drugs would be remain available from Indian generics producers after January 1, 2005. However, the large number of mailbox applications gives reason to speculate as to whether there are minor variations on the initial new chemical entity patents that are filed, and which the applicants will use to challenge existing first line ARV products. These include applications concerning polymorphs and formulations, routes of administration, and so forth. It is common practice in the OECD countries for originators to file multiple patent applications on minor variations of new chemical entities seeking to extend the effective term of the patents – so called "evergreening" practices. Whether or not the patents secured by these applications are found to be valid in litigation, their mere presence is a significant deterrent to entry of generics into the market.

- d. And consider the potential problem of combinations. The development by Indian generic producers of low cost fixed dose combination ARV treatments has been a boon to people throughout the developing world. But certain ARV combinations were patented by originator companies post-January 1, 1995, and mailbox applications may have been filed for these combinations. It is possible that the patent applications filed in India's mailbox will seek to circumvent the Patents Act restriction on combinations by asserting claims for subject matter other than the mere admixture of known substances, such as new routes of administration. While such combinations may be perfectly obvious ways to enhance patient adherence to treatment, there may be considerable possibility for litigation over such claims.
 - e. And, to be clear, the mailbox application situation does not only affect ARVs. The mailbox has been open for ten years. The number of new chemical entities for which pharmaceutical patents are granted each year is small, perhaps 25.⁵⁶ Over a ten year period, NCEs would account for perhaps 250 patent applications. What, then, constitute the remaining 3750 pharmaceutical patent applications in India's mailbox? How many of them claim minor variations on molecules already being produced by the Indian generics industry?
 - f. The risk cannot be quantified because, outside the Indian Patent Office, we do not know what is in the mailbox. But there seems to be a significant risk that a large number of patent applications could be published, and a large number of patents granted, so that Indian generics producers will be subject to a flood of inhibitions and eventual infringement litigation.
 - g. The problem of evergreening based on minor changes and the risks raised by elimination of the pre-grant opposition procedure are relevant also to patent applications first filed after January 1, 2005, but because of the immediacy of the mailbox situation I have focused on that aspect in these remarks.
- V. Ameliorating the Impact of the Transition on Indian Industry and the Public in a TRIPS-Consistent Manner
- a. To be clear, it is the interests of the Indian medicines consumer and consumers throughout the developing world that we must bear in mind. Bernard Pecoul from MSF/DND is here, and I will rely on him to address in more detail the implications of limiting access to generic medicines and the impact of higher prices on patients.
 - b. I would make three main suggestions, two of which have already been put forward by the Indian Pharmaceutical Alliance.
 - i. The Patents Act should retain its pre-grant opposition procedure to allow third parties to challenge the basis for issuing a patent. Once the patent is granted, the holder may institute infringement litigation and place the generics producer in a very costly defensive posture. Even if the Patents Act does not expressly provide a presumption of patent validity in an infringement proceeding, the mere fact of mounting a defense to a granted patent involves major risk and expense to the

⁵⁶ See National Institute for Health Care Management, Changing Patterns of Pharmaceutical Innovation (2002) relied on by the U.S. Federal Trade Commission in To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy, October 2003.

generic producer, and it may be impelled to exit the market as an alternative to costly litigation.

1. The TRIPS Agreement does not in any way prevent the use of a pre-grant opposition procedure. In Article 62.2, it provides only that procedures for the grant of IPRs not impose unreasonably delays. India has experience with the administration of its pre-grant opposition procedure, and there is no indication that it has been abused, or used in a manner that has resulted in unreasonable delays.
 2. In the case of the Amendments Bill, retention of the pre-grant opposition procedure would need to be integrated with provisions encouraging early publication and review of applications.
- ii. Second, the Patents Act could be clarified to address the potential grant of patents on minor changes to new chemical entities so as to prevent the use of evergreening techniques. There are a number of different types of changes that could be specifically addressed, including formulations, polymorphs, routes of administration, metabolites, and so forth. And, the particular issue of combinations of known substances should be addressed in greater detail than is done in the present Act to avoid leaving this to be sorted out by the courts. These clarifications would be consistent with fundamental principles of patent law and the TRIPS Agreement Article 27.
 - iii. Third, the provisions that authorize the patent applicant to request early publication and obtain provisional protection should be reconsidered in connection, at the least, with mailbox applications. If the existing provisions are retained, 4000 claims of provisional protection could come into being almost immediately following January 1, 2005, with potentially very serious consequences for the Indian generics industry. To be clear, the TRIPS Agreement does not require a country to provide provisional protection for published patent applications, whether associated with mailbox applications or otherwise, nor does it require that applicants be allowed to request early publication.
 - iv. I would also note that Clause 49 of the Amendments Bill addressing implementation of the August 30, 2003 WTO Decision on Implementation of Paragraph 6 requires a technical amendment because importing countries are not necessarily required to issue compulsory licenses. There may be no patent in the importing country, and least developed countries may elect not to enforce patents pursuant to Paragraph 7 of the Doha Declaration (thereby not requiring that compulsory licenses are issued).

VI. WTO Dispute Settlement

- a. All of the foregoing suggestions are consistent with the TRIPS Agreement, but because of pressure from U.S. PhRMA or EU Pharma, it is possible that claims might be asserted that India's January 1, 2005 implementation is inconsistent with the TRIPS

Agreement. Let us assume that the U.S. and EU might take India to WTO dispute settlement. Such an action requires an initial period of consultation, the formation of a panel, proceedings and decision by the panel, potential appeal to the Appellate Body, hearings and decision. Up to that point, the procedure requires approximately two years. Then assume solely for the sake of argument that India were to lose in dispute settlement. It would have a reasonable period in which to bring its system into compliance. The reasonable period is presumed to be fifteen months, though it can be longer or shorter depending on the circumstances. Only after a country fails to bring its rules into compliance within a reasonable period of time may the complaining party suspend concessions. The “net” of this is that if India is taken to WTO dispute settlement, it will not face the potential withdrawal of trade concessions by the United States and/or EU for two to three years.

- b. WTO Members are well known to use dispute settlement to their tactical advantage and, as a sophisticated actor at the WTO, there is no reason why India should consider itself exceptionally averse to use of the dispute settlement process as a means to validate its decision-making.

It is difficult to predict with certainty the impact of the January 1, 2005, TRIPS transition on the Indian generic pharmaceuticals sector because there are a substantial number of unknowns. However, it seems apparent that the Indian generics industry is facing a difficult period. It would seem to be in the best interests of India and its people, as well as individuals throughout the developing world in need of medicines, to manage this transition in a way that avoids severe disruption to the supply of important medicines.

ANNEX 4: ARV PRODUCTION IN CHINA

Asian Generic ARV Manufacturers

Note: The material in the Table below has been gathered from documents provided by Médecins Sans Frontières China in November 2005, whilst the company profiles below come from the website:

<http://web.amfar.org/treatment/specialreport/Appendix1.asp> , accessed in September 2005.

Companies currently producing formulations (x) and additional APIs slated for development (o)											
	AZT	d4T	3TC	IDV	NLF	ddl	NVP	EFV	RTV	LPV	TDF
Desano	x	x	o	x	o	x	x	o			
Huahai				x		x	x		o	o	o
Mchem	x	x	o	x			o	o	x	o	o
Northeas	x	x				x					

Northeast General Pharmaceutical Factory (NEGPF)

Established in 1946 and based in Shenyang, the state-owned Northeast General Pharmaceutical Factory has over 10,000 employees. Its products are sold to all provinces, municipalities and autonomous regions in China as well as 55 countries and regions worldwide. The annual export sales income of NEGPF totals nearly US\$80 million. NEGPF exports API products to developing countries in Africa, Latin America and Asia, including Korea, India and Brazil. In August 2002, the Chinese government approved the domestic production and sale of stavudine (d4T) and zidovudine (AZT). The per-patient cost of treatment is approximately US\$360–600 per year.

Northeast General Pharmaceutical Factory
No. 35 The Youth Street
Shenhe District
Shenyang, China
POD 11014
www.negpf.com

Shanghai Desano Biopharmaceutical Co.

Shanghai Desano employs 1,600 people and plans to produce enough drugs to supply 500,000 people with combination therapy each year. In September 2002, the company received approval from the Chinese government to produce ARVs for the domestic Chinese market. Treatment costs approximately US\$435–560 per patient per year. Shanghai Desano also exports seven anti-AIDS compounds to India, Thailand and Brazil. Product details listed below.

Shanghai Desano Biopharmaceutical Co.
No.78, 887 Zuchongzhi Road,
Zhangjiang Hi-Tech Park
Shanghai 201203
China
www.desano.com

Xiamen Mchem Pharma Group

In September 2002, Xiamen Mchem Pharma Group reported that it had signed a five-year contract with the Brazilian government to become the third appointed

manufacturer of antiretroviral compounds for Brazil. The company also exports antiretroviral pharmaceuticals to 13 countries in Africa.

Xiamen Mchem Pharma Group Ltd.
20F Sanjiang Bldg., 81 South Hubin Road
Xiamen, Fujian 361004
China
www.mchem.com.cn

Zhejiang Huahai Pharmaceutical Co. Ltd.

In June 2003, Huahai Pharma received approval from the Chinese government to produce didanosine (ddl) and ddl tablets (50mg and 100mg), the first ddl tablets to be produced in China under official authorization. Huahai reports that it will initially produce 200,000 tons of AIDS medications annually and expects to reach a total output of 500,000 tons under full capacity.

Zhejiang Huahai Pharmaceutical Co. Ltd.
Xunqiao
Linhai, Zhejiang 317024
China
www.huahaipharm.com

ANNEX 5: PEOPLE CONSULTED

Pascale Boulet, Médecins Sans Frontières
Ellen t'Hoën, Médecins Sans Frontières
Carsten Fink, World Bank
Dilip Shah, CEO, Vision Consulting and Secretary-General, Indian Pharmaceutical Alliance
Fred Abbott, Edward Ball Eminent Scholar Professor of International Law, Florida State University College of Law
Keith Alcorn, NAM
Equity analysts (un-named) at several investment banks
Krisana Kraisintu, former Director of the Government Pharmaceutical Organisation in Thailand
Stavros Nicolaou, Aspen Pharma of South Africa
Odilon Couzin, China AIDS Organisation
Aaron Pattillo, Clinton Foundation
Suerie Moon, MSF China
Elodie Lambert, MSF China
Dr Yusuf Hamied, Chairman and CEO of Cipla
Hans Rietveld, Novartis
Philippa Saunders, Essential Drugs Project
Connie Osborne, World Health Organisation in China

ANNEX 6: ARV GLOSSARY

Note: Bold name is the generic name, *Italic name* is the brand/trade name and the name in parenthesis is the short-hand acronym used to refer to the generic

Class	Drug	Originator
NRTI	abacavir (ABC) <i>Ziagen</i>	Glaxo Smith Kline (GSK)
NRTI	didanosine (ddl) <i>Videx</i>	Bristol-Myers Squibb (BMS)
NRTI	didanosine (ddl) <i>Videx EC</i>	BMS
NRTI	emtricitabine (FTC) <i>Emtrival</i>	Gilead
NRTI	lamivudine (3TC) <i>Epivir</i>	GSK
NRTI	stavudine (d4T) <i>Zerit</i>	BMS
NRTI	zidovudine (AZT or ZDV) <i>Retrovir</i>	GSK
NtRTI	tenofovir disoproxil fumarate (TDF) <i>Viread</i>	Gilead
NNRTIs	efavirenz (EFV) <i>Stocrin</i> 200 mg	Merck, BMS owns rights in N. America & 5 European countries as <i>Sustiva</i>
NNRTIs	efavirenz (EFZ) <i>Stocrin</i> 600 mg	Merck
NNRTIs	nevirapine (NVP) <i>Viramune</i>	Boehringer Ingelheim (BI)
Protease inhibitors	atazanavir (ATV) <i>Reyataz</i>	BMS
Protease inhibitors	indinavir (IDV) <i>Crixivan</i>	Merck
Protease inhibitors	nelfinavir (NFV) <i>Viracept</i>	Pfizer, but Roche has international contract
Protease inhibitors	lopinavir-ritonavir (LPV/r) <i>Kaletra</i>	Abbott
Protease inhibitors	saquinavir (SQV) <i>Fortovase</i> or <i>Invirase</i>	Roche
Protease inhibitors	ritonavir <i>Norvir</i>	Abbott
Co-formulated combinations		Originator(s)
tenofovir/ efavirenz/ emtricitabine (TDF/EFZ/FTC) (<i>In development</i>)		Gilead & BMS (with Merck)
tenofovir/emtricitabine (TDF/FTC) <i>Truvada</i>		Gilead
lamivudine / zidovudine (3TC/AZT) <i>Combivir</i>		GSK
abacavir/ lamivudine / zidovudine (ABC/ 3TC/AZT) <i>Trivizir</i>		GSK

Co-formulated combinations	Originator(s)
lamivudine / stavudine / nevirapine (3TC/D4T/NVP)	GSK/BMS/BI [no originator product – made by generic companies]
zidovudine/lamivudine/nevirapine (AZT/3TC/NVP)	GSK/BI [no originator product – made by generic companies]
stavudine/ lamivudine (D4T/3TC)	BMS/GSK [no originator product – made by generic companies]