

WTO TRIPS and its effect on the supply and development of medicines in China

A recent conference at the University of Hong Kong just prior to the December 2005 World Trade Organization (WTO) talks renewed attention on the WTO's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), in particular in relation to China. Here we provide an introduction to TRIPS, discuss compulsory licensing, and take two angles to view how TRIPS affects the supply and development of medicines in China. We look at both recent positive developments in the Chinese pharmaceutical and biotechnology industry, and also at how TRIPS can hamper the supply of medicines using HIV treatment as an example.

Introduction to TRIPS

As ideas and knowledge gain prominence in global trade, intellectual property (IP) rights are becoming increasingly important. During the 1986-1994 Uruguay Round, the WTO negotiated the Agreement on TRIPS to provide an initial framework for IP regulation. Five broad issues were addressed within the original agreement in an attempt to bring IP protection under common international rules¹:

1. How basic principles of global trade and other international IP agreements should be applied;
2. How to adequately protect IP rights;
3. How countries should enforce those rights within their own territories;
4. How to settle IP disputes between WTO members; and
5. Transitional arrangements to apply while the new system is implemented.

Compulsory licensing

Most relevant to the medical profession are TRIPS' effects on patent protections. Patents usually apply for at least 20 years and are available for both products and processes, although certain diagnostic, therapeutic, and surgical methods cannot be protected by patents. One of the TRIPS agreement's major provisions is compulsory licensing: a government may license the production of a patented product or process without the consent of the patent owner, provided the owner receives a reasonable royalty.

Compulsory licensing has existed since 1995 with the provision that compulsory licenses be granted to mainly supply domestic markets. The original agreement drew criticism for what many saw as a failure to communicate with the developing world. India, and to some extent China, were exceptions because of their established pharmaceutical industries capable of manufacturing generic drugs. Compulsory licensing was initially a major obstacle for underdeveloped countries without the capability to produce

pharmaceuticals: how could they import pharmaceuticals if the countries capable of manufacturing them were not allowed to export?

A major revision was provided in the 2001 Doha Ministerial Conference, which made it possible for countries unable to manufacture pharmaceuticals to import cheaper generic copies. All WTO members are allowed to import under the compulsory license agreement, but most developed countries have signed a waiver agreeing not to do so. Hong Kong was one of a number of signatories on a partial waiver stating that compulsory licensing would only be used in a national emergency. A further amendment within the Doha agreement allows least-developed countries (China is not classified as a least-developed country) to delay protecting pharmaceutical patents until 2016.

How do TRIPS and compulsory licensing relate to Hong Kong and China?

While Hong Kong is a founding member of the WTO, the TRIPS agreement has had little local impact due to the small size of the city's pharmaceutical industry and the relatively high purchasing power of Hong Kong residents. China officially joined the WTO on 11 December 2001, but had applied patent protections on medicine generally since 1993. Entrance into the WTO compelled China to enforce IP protections, leading to a number of high-profile litigation cases. In October 2003, Glaxosmithkline Limited (GSK) blocked a number of Chinese drugmakers from obtaining licenses for the type-2 diabetes treatment, Avandia.² It has been suggested that such actions are driving innovation within the Chinese pharmaceutical industry by shifting focus from generics manufacturing to developing independently patented biotech drugs.² Entrance into the WTO may have catalysed the recent progress of China's biotechnology industry.

However, the enforcement of IP protections also raises concerns regarding access to medicine. Médecins sans Frontières (MSF) has highlighted the problems they have confronted with the TRIPS agreement, particularly in relation to HIV/AIDS treatment in China.³ In 2003, the country had around 840 000 cases of HIV,⁴ and approximately 10% of those patients have AIDS. The Joint United Nations Programme on HIV/AIDS (UNAIDS) has estimated that China could have 10 million cases by 2010. China has a number of major health care concerns—a crumbling health system, poorly trained medical staff, too little emphasis on adherence, lack of confidentiality, and stigma/discrimination. Perhaps most critically, the cost of treatment blocks access: approximately two thirds of the population

has no health insurance, making the cost of treatment prohibitive.

Recognising the threat of HIV, the Chinese Government launched a national antiretroviral treatment (ART) programme to provide free drugs to those most in need.⁵ When the scheme was first launched in 2003, first-line treatment was the combination of stavudine (d4T) or zidovudine (AZT) + didanosine (ddI) + nevirapine (NVP).⁵ All four drugs are locally produced and not patent-protected. However, this combination is plagued by drug resistance, as highlighted in recent reports revealing an alarming 62.7% rate of drug-resistant mutations in a group treated for 6 months in Henan.^{6,7} Furthermore, this combination has particularly strong side-effects and is potentially dangerous for hepatitis B patients. All first-line WHO-recommended HIV treatments now incorporate 3TC (lamivudine), a drug patented by GSK that MSF reports remains fairly inaccessible in China.⁸ 3TC is a cheap and effective component of HIV programmes in Africa, India, Thailand, and elsewhere that is available as a generic at US\$65/year from the manufacturer Hetero. Critics asserted that GSK was protecting 3TC's other (lower-dose) use—the treatment of hepatitis B—which is particularly widespread in China.^{9,10} A recent report indicates that 80% of patients currently receiving ART in China are on the older treatment regimen excluding 3TC; no indication was made of the number of patients (<20%) receiving a WHO-mandated regimen that includes 3TC.⁵

In December 2004, GSK negotiated a supply deal with China, and committed to donating 3TC for the next 5 years in order to scale up ART in China.¹¹ Officially, the first-line treatment is now AZT + 3TC + NVP, with an annual average cost of US\$460 to US\$480 per patient, supplied free by the government to low-income patients under the 'Four Frees and One Care' policy.¹¹ However, MSF reports 3TC is still not widely available in China's national health programme, making one of the developing world's most commonly used and effective fixed-dose combinations (FDC)—3TC + d4T + NVP (taken as a single pill twice a day)—also difficult to obtain.⁸ MSF has recently succeeded in negotiating special authorisation to import FDC for use in its own clinics, but beyond the MSF clinics, FDC remain virtually unavailable and are not marketed legally anywhere in China (personal communication). Access to formulations for HIV-infected children also remains unavailable, and alternative and second-line drugs, including lopinavir/ritonavir (Kaletra), stavudine (Zerit) and tenofovir (TDF), remain practically inaccessible.³

Furthermore, because China is considered a middle-income developing country, tiered-pricing discounts are not available despite the country's massive population of rural and urban poor. However, China does have a number of generic producers, including Desano, MChem, North East, and Zhejiang Huahai, capable of high-capacity manufacturing to international standards. Indeed, these four

companies actually manufacture AZT, d4T, indinavir, ddI, and NVP, both for the domestic market and for export.⁸ China has amended its patent law to allow production under compulsory licensing, but to date no compulsory licenses have been issued. HIV patients in China are left without access to a number of patent-protected HIV drugs.

China's domestic pharmaceutical industry

Most Chinese pharmaceutical companies produce generics, but research into innovative drugs is rapidly expanding, particularly in the biotechnology sector.¹² In 2004 there were an estimated 139 drugs in China's pipeline (of approximately 700 in clinical development worldwide), although only 13 were in phase 3 trials.¹³ China's drug development industry has a number of advantages: a large patient population, insight from traditional Chinese medicine,¹⁴ and lower costs of labour and clinical trials. Furthermore, the approval process has proved to be shorter in China compared with the US, and Chinese trials can meet international standards. This is a necessity for Chinese biotechnology companies, as the Chinese market alone is often insufficient to fund research and development costs, and drugs must meet international standards to reach international markets. The primary challenge of Chinese drug development industry is raising venture capital.¹² Foreign investors are particularly concerned with monetary controls that do not allow capital to leave China, but this situation is changing.

One particular success for the Chinese drug industry was the first approval of a gene therapy for commercial production. In early 2004, the Chinese biotechnology company Shenzhen SiBono GenTech received approval for Gendicine, a treatment for head and neck squamous cell carcinoma. As of 31 July 2005, Gendicine had been used to treat over 2600 patients.¹⁵

China must be considered both as a generics producer, which is presently the major business of its pharmaceutical industry, and also as a developer of innovative drugs competing with the developed world. It is clear that over the coming years, innovation rather than generics will increasingly drive the Chinese pharmaceutical industry.

The WTO needs to facilitate access to medicine as well as free trade

Both TRIPS and entrance into the WTO present opportunities and challenges for China's health care system. Increased competition from the international pharmaceutical industry may be driving innovation in the Chinese biotechnology sector, but it is also presenting problems with access to medicine. Compulsory licensing mechanisms are in place to domestically produce drugs needed by the Chinese population. However, to date compulsory licensing has not been used in China, perhaps through fear of trade or diplomatic repercussions. Such restrictions on compulsory licensing have recently been noted by the United Nations

in relation to US trade policy.¹⁶ The WTO must take further steps to 'ringfence' compulsory licensing in order to effectively improve access to medicine in China and the developing world.

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Corrigendum

"Magnetic resonance venogram of intravenous leiomyomatosis" (December 2005;11:524-6). On page 524, in the first paragraph, line 21 should have read "IVC (Fig 1), left common and internal iliac veins" rather than "IVC (Fig 1), left common vein, and iliac veins" as printed.