GLOBAL HEALTH COMMENTARY

Impact of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement on India as a Supplier of Generic Antiretrovirals

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ABSTRACT: This is a commentary on how the trade-related aspects of intellectual property rights (TRIPS) agreement has impacted India as a supplier of generic antiretrovirals (ARVs). We provide a systematic review of the issues related to the TRIPS agreement that affects India. This includes discussion around (a) the legal landscape underpinning India as a supplier of generic ARVs; (b) supply of second-line ARVs; and (c) the future of generic drug production in India. The proclamation into force of TRIPS-compliant intellectual property law in India is likely to affect its position as a supplier of affordable ARVs, especially drugs brought to market after 2005. Currently, mechanisms exist for the generic production of almost all ARVs in India, including second-line drugs; however, the manufacture of these drugs by generic pharmaceutical companies may require additional market incentives. Compulsory licensing may emerge as an additional mechanism by which India can provide affordable versions of patented drugs to Least Developed Countries (LDCs). © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:816–821, 2011

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INTRODUCTION: THE IMPORTANCE OF GENERIC ANTIRETROVIRALS

The World Health Organization (WHO) estimates indicate that one third of the world lacks regular access to essential medicines,[1] defined as those drugs and diagnostics necessary for a basic health care system.[2] The 16th WHO model list of essential medicines for adults[3] includes medicines used to treat chronic diseases, such as antihypertensives and anti-inflammatory drugs, as well as anti-infectives, including 14 antiretrovirals (ARVs) and five fixed-dose combinations (FDCs), used for treating patients infected with HIV. Conservative estimates indicate that 10 million lives could be saved annually by promoting better access to these existing essential medicines.[4]

Although intellectual property rights are granted to reward and promote innovation, they can impede patients' ability to access the medicines they need to stay healthy. Barriers to access can arise when one manufacturer, holding one or more patents to a drug, exerts a monopoly over its production and sales for the duration of the patent(s), selling it at a high price; as a result, the drug may stay out of reach of low-income patients, especially in developing countries.

It is important to note that patents for most drugs on the WHO list of essential medicines have already expired, permitting legal generic production all over the world. Nevertheless, intellectual property considerations are of particular importance in the context of increasing patients' ability to access HAART (highly active antiretroviral therapy). ARVs used to treat HIV are a relatively new class of drugs, and are still under patent in many countries with the manufacturing capacity to produce them. While the patents for selected older ARVs, including stavudine (d4t), zidovudine (AZT), didanosine (ddI), and abacavir (ABC) have expired,[5] select patents on newer, second-line medications including lopinavir/ritonavir and raltegravir will expire as late as 2020 and 2023, respectively.[6]

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Generic production of affordable ARVs has historically been a major contributor to patients' ability to access treatment. One example that illustrates this concept is the price drop of the first-line combination of stavudine (d4t), lamivudine (3TC), and nevirapine (NVP). In 2000, the lowest originator price[7] of this combination was $10439 pppy, a sum completely out of reach of most patients living in resource-limited settings. In the same year, patient and civil society groups fought for the release of the patent on stavudine in South Africa, which ultimately allowed for the import of this combination from generic manufacturers. As early as February 2001, the humanitarian organization MSF had negotiated with the Indian generic pharmaceutical company, Cipla, a price[8] of $350 pppy, which represented a 30-fold drop over the originator price in South Africa. By 2008, the price[7] of the same combination had dropped to $87 pppy, supplied by a different Indian generic drugmaker, Hetero drugs.

However, this price drop is the first of many battles to be won in promoting access to HAART for people living in poor countries. Since 2001, new evidence has emerged indicating the health risks of stavudine, including its long-term, irreversible side effects. In light of these findings, the WHO recommended in 2009 that countries phase out the use of stavudine as first-line treatment.[9]

Currently, there are 24 different antiretroviral drugs on the market for treating HIV, and many more fixed-dose combinations of these drugs have been approved.[6]

Since the battle to make stavudine more affordable to patients, newer drugs have emerged with greater potency (including against resistant strains of HIV) and fewer side effects. These drugs have the potential to dramatically improve the quality of patients' lives. Will they be affordable to anyone but the wealthy minority of the world?

In the late 20th century, India was well-poised as a supplier of affordable generic medicines to the world. In part because of its patent laws that allowed for the reverse-engineering of medicinal compounds, the generics industry thrived, and India acted as a "pharmacy for the developing world." In 2005 to 2006, exports comprised approximately 40% of total pharmaceutical industry production[10] and approximately 350,000 people worldwide, half of all people in the developing world, who received ARV treatment, used ARVs produced in India.[11] MSF uses ARVs manufactured by Indian generic manufacturers to treat 70% of the patients in its HIV/AIDS project.

However, the patent landscape in India changed in 2005 with amendments made to the *Indian Patent Act* in order to comply with the World Trade Organization (WTO) trade-related aspects of intellectual property rights (TRIPS) agreement, which India signed in 1995. Will the more stringent patent laws prevent India from supplying affordable second-line HIV medicines to the world?

THE LEGAL LANDSCAPE UNDERPINNING INDIA AS A SUPPLIER OF GENERIC ARVS

From 1970 to 1995, India recognized process patents, but not product patents for pharmaceuticals.[12] This allowed generic manufacturers to replicate the drugs produced by originator pharmaceutical companies, as long as they did not use a manufacturing process patented in India. This legal landscape promoted competition among generic manufacturers and incenitivized the search for greater efficiencies in the processes used to make the drugs.

India joined the WTO[13] in 1995, and by doing so became a signatory on 18 international trade-related agreements, including TRIPS. Developing countries in which product patent protection was not recognized prior to TRIPS were given until 2005 to amend their patent laws,[14] which India did[12] in March 2005 (Least Developed Countries were given until 1 January 2016). The TRIPS agreement requires WTO members to provide protection for a minimum term of 20 years from the filing date of a patent application for any invention, including for a pharmaceutical product or process.[14] Under the *Indian Patent Act 1970* (enacted 1972) until 2005, patents in India were valid from 7 years from the filing date or 5 years from the date of grant, whichever was shorter.[15]

In summary, from 1970 to 1995, it was legally permissible for Indian manufacturers to produce generic versions of all medicines, as long as the processes used were not patented in India. Drugs introduced after 2005 are granted the same patent protection in India as in most developed countries, with some exceptions (for example, to patent new versions of existing medicines, manufacturers must demonstrate increased efficacy[16]).

What about drugs introduced in India during the period of 1995 to 2005? It is particularly interesting to consider how this period was treated in Indian patent law, because it marked a boom in the introduction of new ARVs; 71 of a current total of 93 patents on ARVs were filed in the US during this time.[6]

Article 70.8 of TRIPS[17] addresses situations, where there is a delay between countries joining the WTO, and amending their patent laws to conform to TRIPS. In the case of India, it applies to the period of 1995 to 2005. Article 70.8 states that countries must provide, as from their date of entry into the WTO, a means by which patent applications can be filed, and later examined once new patent laws are in effect. The application of this article in India,[12] known as the "mailbox provision," allowed inventors to file patent applications prior to the coming into force of a TRIPS