A Manufactured Solution?
The Transfer of Technology to Developing Countries for the Local Production of Affordable Antiretrovirals: Case Studies from Tanzania and South Africa

By

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

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A Manufactured Solution? The Transfer of Technology to Developing Countries for the Local Production of Affordable Antiretrovirals: Case Studies from Tanzania and South Africa

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Abstract

Statement of the issue: Facing large HIV-infected populations, Sub-Saharan African countries are producing antiretroviral (ARV) drugs under provisions of the World Trade Organization’s Agreement on the Trade-Related Aspects of Intellectual Property (TRIPS). Article 7 states that the protection of intellectual property should increase technology transfer to developing countries. This clause and the debate over domestic manufacturers’ ability to provide low-cost ARVs need examination.

Methods: Case studies from ARV manufacturing initiatives in Tanzania and South Africa analyzed conditions affecting two outcomes: the type of technology transfer arrangement entered (voluntary license or imitation) and the affordability of ARVs. Data were collected and analyzed from documents, key-informant interviews, and observation. Chi-squared and phi correlation statistics were then conducted across developing countries to test the association of voluntary ARV licensure with TRIPS-compliant patents and domestic firm ownership (state or private).

Results: Tanzania’s weak patent system and poorly-financed, partially state-owned firm dissuaded industry investment, but attracted a non-government organization to transfer technology through imitation. Donor-financed ARV tenders, however, restrict competition to international quality-accredited products not produced by the firm. Without large volumes and
manufacturing capacity, it cannot achieve economies of scale to reduce prices below imported 
ARVs.

In South Africa, civil society challenged the strong patent system and poor government 
commitment that inhibited an ARV rollout. This and a well-financed, publicly-traded firm 
leveraged voluntary licenses. With international quality approval, the firm increased first-line 
ARV affordability; however, limited domestic competition keeps treatment prices above those of 
neighbouring countries.

A multi-country analysis found 321 generic ARV manufacturing initiatives in 86 firms across 25 
developing countries. Voluntary ARV licenses had a strong positive association with TRIPS-
patent compliance ($\phi=.56$, $p<.0001$) and a weak negative association with state-ownership 
($\phi=.19$, $p<.0001$). Firms in South Africa and India were granted 77% of licenses and accounted 
for most quality accredited generic ARVs.

**Conclusion:** Despite positive association, technology transfer does not readily result from 
patent protection, particularly to state-owned firms. Developing countries must enact policies to 
enable affordable ARVs; yet, they must be cautious using local production to increase ARV 
access, as most initiatives cannot compete with high-volume generic manufacturers.
Acknowledgments

There are many individuals and institutions I must thank for their tremendous support and guidance on this journey. I would first like to thank my supervisor, Jillian Kohler, along with the members of my advisory committee, Tom Einarson, David Zakus, and Joe Wong, who have each contributed a great amount of time and insight, for which I am grateful. To Jillian – your determination and positive outlook amaze me. Thank you for pulling me back when I “put the cart before the horse” and thank you for your unfailing faith in my ability to accomplish the tasks at hand. I thank you Tom, for your ardent attention to detail, David, for your commitment and endless laptop battery life, and Joe, for your inspiring and thoughtful perspectives.

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<tr>
<td>3TC</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Disease</td>
</tr>
<tr>
<td>ANC</td>
<td>African National Congress</td>
</tr>
<tr>
<td>ALP</td>
<td>AIDS Law Project</td>
</tr>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredients</td>
</tr>
<tr>
<td>ARVs</td>
<td>Antiretrovirals</td>
</tr>
<tr>
<td>AZT</td>
<td>Zidovudine</td>
</tr>
<tr>
<td>BEE</td>
<td>Black Economic Empowerment</td>
</tr>
<tr>
<td>BI</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>BMS</td>
<td>Bristol Myers Squibb</td>
</tr>
<tr>
<td>BRELA</td>
<td>Business Registration and Licensing Association</td>
</tr>
<tr>
<td>CHAI</td>
<td>Clinton HIV/AIDS Initiative</td>
</tr>
<tr>
<td>CIF</td>
<td>Cost of Insurance and Freight</td>
</tr>
<tr>
<td>COMESA</td>
<td>Common Market for Eastern and Southern Africa</td>
</tr>
<tr>
<td>COSTECH</td>
<td>Commission on Science and Technology</td>
</tr>
<tr>
<td>CSR</td>
<td>Corporate Social Responsibility</td>
</tr>
<tr>
<td>d4T</td>
<td>Stavudine</td>
</tr>
<tr>
<td>DoH</td>
<td>Department of Health</td>
</tr>
<tr>
<td>ddI</td>
<td>Didanosine</td>
</tr>
<tr>
<td>DRA</td>
<td>Drug Regulatory Authority</td>
</tr>
<tr>
<td>DST</td>
<td>Department of Science and Technology</td>
</tr>
<tr>
<td>DTI</td>
<td>Department of Trade and Industry</td>
</tr>
<tr>
<td>EAC</td>
<td>East African Community</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (United States)</td>
</tr>
<tr>
<td>FDC</td>
<td>Fixed-Dose Combination</td>
</tr>
<tr>
<td>FDI</td>
<td>Foreign Direct Investment</td>
</tr>
<tr>
<td>GATT</td>
<td>General Agreement on Trade and Tariffs</td>
</tr>
<tr>
<td>GCR</td>
<td>Global Competitiveness Report</td>
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<tr>
<td>GDP</td>
<td>Gross Domestic Product</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practices</td>
</tr>
<tr>
<td>GPO</td>
<td>Government Pharmaceutical Organization</td>
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<tr>
<td>GPRM</td>
<td>Global Pricing Reporting Mechanism</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
</tr>
<tr>
<td>HEARD</td>
<td>Health Economics HIV/AIDS Research Division</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HIVAN</td>
<td>Centre for HIV and AIDS Networking</td>
</tr>
<tr>
<td>IFC</td>
<td>International Finance Corporation</td>
</tr>
<tr>
<td>IP</td>
<td>Intellectual Property</td>
</tr>
<tr>
<td>JSE</td>
<td>Johannesburg Securities Exchange</td>
</tr>
<tr>
<td>JSI</td>
<td>John Snow Inc.</td>
</tr>
<tr>
<td>LDCs</td>
<td>Least-Developed Countries</td>
</tr>
<tr>
<td>MCC</td>
<td>Medicines Control Council</td>
</tr>
<tr>
<td>MoHSW</td>
<td>Ministry of Health and Social Welfare</td>
</tr>
<tr>
<td>MoTI</td>
<td>Ministry of Trade and Industry</td>
</tr>
<tr>
<td>MoST</td>
<td>Ministry of Science and Technology</td>
</tr>
<tr>
<td>MSD</td>
<td>Medical Stores Department</td>
</tr>
<tr>
<td>MSH</td>
<td>Management Sciences for Health</td>
</tr>
<tr>
<td>MSF</td>
<td>Médecins sans frontières</td>
</tr>
<tr>
<td>MTP</td>
<td>Medium-Term Plan</td>
</tr>
<tr>
<td>NACP</td>
<td>National AIDS Control Program</td>
</tr>
<tr>
<td>NGO</td>
<td>Non-Government Organization</td>
</tr>
<tr>
<td>NSI</td>
<td>National System of Innovation</td>
</tr>
<tr>
<td>NVP</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>OSD</td>
<td>Oral Solid Dose</td>
</tr>
<tr>
<td>PEPFAR</td>
<td>President’s Emergency Fund for HIV/AIDS Relief</td>
</tr>
<tr>
<td>PhRMA</td>
<td>Pharmaceutical Research and Manufacturers of America</td>
</tr>
<tr>
<td>PI</td>
<td>Protease Inhibitor</td>
</tr>
<tr>
<td>PMA</td>
<td>Pharmaceutical Manufacturer’s Association</td>
</tr>
<tr>
<td>PMTCT</td>
<td>Prevention of Mother to Child Transmission</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>PPPY</td>
<td>Per person per year</td>
</tr>
<tr>
<td>/r</td>
<td>Low-Dose Ritonavir</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>RTV</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>SACU</td>
<td>Southern African Customs Union</td>
</tr>
<tr>
<td>SADC</td>
<td>Southern African Development Community</td>
</tr>
<tr>
<td>SCMS</td>
<td>Supply Chain Management System</td>
</tr>
<tr>
<td>SCP</td>
<td>Structure-Conduct-Performance</td>
</tr>
<tr>
<td>TAC</td>
<td>Treatment Action Campaign</td>
</tr>
<tr>
<td>TFDA</td>
<td>Tanzania Food and Drug Administration</td>
</tr>
<tr>
<td>THRIP</td>
<td>Technology for Human Resources and Industry Programme</td>
</tr>
<tr>
<td>TIC</td>
<td>Tanzania Investment Centre</td>
</tr>
<tr>
<td>TRIPS</td>
<td>Agreement on the Trade-Related Aspects of Intellectual Property</td>
</tr>
<tr>
<td>TPI</td>
<td>Tanzania Pharmaceutical Industries</td>
</tr>
<tr>
<td>UN</td>
<td>United Nations</td>
</tr>
<tr>
<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
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<tr>
<td>UNCTAD</td>
<td>United Nations Centre for Trade and Development</td>
</tr>
<tr>
<td>UNDP</td>
<td>United Nations Development Program</td>
</tr>
<tr>
<td>UNIDO</td>
<td>United Nations Industrial Development Organization</td>
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<tr>
<td>USTR</td>
<td>United States Trade Representative</td>
</tr>
<tr>
<td>VAT</td>
<td>Value Added Tax</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WTO</td>
<td>World Trade Organization</td>
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Chapter 1: Introduction, Literature Review and Methods

Introduction – ARVs, TRIPS and the Issue of Drug Access

Evidence of the use of antiretroviral (ARV) drugs in treating individuals living with the human immunodeficiency virus (HIV) was presented at a crucial period in the HIV/AIDS timeline. In 1996, at the opening of the 11th International Conference on AIDS in Vancouver, Canada, Dr. Peter Piot, head of the United Nations Program on HIV/AIDS (UNAIDS), announced that more than 21 million people were infected with HIV and that nearly 6 million already had died since the virus’ identification in 1984 (Maugh, 1996). It was at this conference that researchers indicated that a triple combination therapy of ARVs, called Highly Active Antiretroviral Therapy (HAART), could effectively reduce the presence of HIV in the bloodstream (Brown, 1996). This finding was the first treatment breakthrough for countries that were experiencing increasingly high infection rates.

HAART, however, ranging in price from US$7,944 to US$20,224 per person per year (pppy) (Floyd & Gilks, 1998) was extremely expensive. This was particularly the case for Sub-Saharan African countries where the annual per capita health expenditure was less than US$29 (World Bank, 2008b) and where the overwhelming burden of HIV/AIDS was, and continues to be, faced. Infection rates in Sub-Saharan Africa have increased dramatically from 5 million individuals in 1990 to 22 million in 2007 and now accounts for up to 67% of the 33 million people living with the virus (UNAIDS, 2008). While estimated HIV prevalence rates among adults aged 15 to 49 years stabilized in the region at 6% in 2007, and even decreased in some countries, HIV incidence continues to climb as a result of both new infections and increased
lifespan due to treatment availability. Unfortunately, the number of new HIV infections each year exceeds the number of people receiving treatment by a ratio of two-and-a-half to one (UNAIDS, 2008).

Recent efforts to lower ARV price and scale-up treatment access in Sub-Saharan Africa saw the cost of HAART decrease from approximately US$10,000 pppy in 2000 to less than US$100 in 2007 (MSF, 2007) and treatment increase from 2% of those clinically in need in 2003 to 28% at the end of 2006 (UNAIDS, 2007). In 2006, the G8 summit supported the call to achieve universal access (defined as 80% treatment coverage) by 2010. Yet, treatment rates throughout Sub-Saharan Africa are not uniform and, in 2007, 72% of HIV-infected individuals in need of treatment were without access to ARVs (UNAIDS, 2007). For example, Botswana and Uganda have reached high treatment coverage rates of 85% and 56%, respectively. South Africa’s treatment program, by comparison, with one of the largest HIV/AIDS populations and treatment programs in the world, lies below the regional average, at 21% (UNAIDS, 2008).

Inequities in treatment rates are due not to one single factor but a mix of causes, including income gaps and government failures (Reich, 2000) as well as the negative externalities resulting from global markets (Cohen-Kohler, Forman, & Lipkus, 2008). With other notable barriers to treatment access, such as health care provision, political commitment, poverty, tariffs and taxes, drug access remains complex for many developing countries (Matthews, 2004). Yet, of all these factors, one of the most prominent concerns over ARV access in developing countries is the World Trade Organization’s (WTO) Agreement on the Trade-Related Aspects of Intellectual Property (herein referred to as TRIPS) and the impact its patent terms have on ARV prices.
Outline of the Dissertation

Chapter 1 of this research introduces the challenges faced by Sub-Saharan African countries to access affordable ARV treatment for the region’s large HIV-infected population. This prominently includes the role of the World Trade Organization’s (WTO) Agreement on the Trade-Related Aspects of Intellectual Property (TRIPS) and generates two lines of inquiry for this research. First, a review of the literature on the protection of intellectual property (IP) and the transfer of pharmaceutical technology under the TRIPS Agreement finds that research centres on economic theory in developed and rich developing economies. It does not provide an in-depth understanding of the implications this relationship has for developing and least-developed countries (LDCs) in Sub-Saharan Africa, particularly with respect to ARV technology and manufacturing. Second, there is a dearth of research on the domestic production of essential medicines in developing countries. In particular, few assessments have been conducted on new ARV manufacturing initiatives in Sub-Saharan African countries and these firms’ ability to manufacture ARVs cheaply. A comparative case study is then proposed to address both of these research gaps. Methods for data collection and analysis are also outlined.

The subsequent chapters address these two lines of inquiry through an alternative format thesis. Chapter 2, 3 and 4 presents studies suitable as stand-alone journal articles. Prompted by gaps in the literature and guided by the research questions presented in Chapter 1, diverging case studies in Chapter 2 and 3 assess: 1. the domestic conditions that affect the type of technology transfer arrangement a developing country drug firm will enter to manufacture ARVs and 2. the factors influencing the firms’ affordable ARV pricing. Chapter 2 analyzes a case study of an imitator technology transfer arrangement at the drug firm Tanzania Pharmaceutical Industries (TPI) in
Tanzania. Chapter 3 analyzes a case study of voluntary licensing arrangements at Aspen Pharmacare, a drug manufacturer in South Africa.

The results of the case studies in Chapter 2 and 3 provoke a multi-country analysis of ARV manufacturing initiatives across developing countries, found in Chapter 4. Here, the association between the transfer of technology and two variables, patent compliance and domestic firm ownership (private or state-owned), are quantitatively tested. Lastly, Chapter 5 identifies the unique contribution of this research to the literature and discusses the implications of the comparative case study findings. This chapter ends with a discussion of the limitations of this dissertation and recommends areas for future research.

**Background of TRIPS and its Drug Access Provisions**

The World Trade Organization (WTO) is an international forum that sets the rules of trade between its 153 member countries. Its overarching goal is to keep trade between countries open and free. It was developed in 1994 out of the eighth negotiating round (the Uruguay Round from 1986 to 1994) of the multilateral General Agreements on Tariffs and Trade (GATT). Whereas GATT remains the WTO’s umbrella treaty for trade of goods among countries, two agreements deal with the trade in intellectual property (IP) and services, the TRIPS Agreement and the General Agreement on Trade in Services, respectively (WTO, 2007).

The TRIPS Agreement came into effect in 1996 as a multilateral treaty that, for the first time, linked international trade liberalization with the protection of intellectual property (IP). IP includes trademarks, copyrights, and patents. Under Article 33, the Agreement harmonizes the
protection and enforcement of both pharmaceutical product and process patents for 20 years after their filing date (generally around the time of discovery). This provides patent holders market exclusivity for the duration of the patent. These right holders are then able to set their drug prices as high as the market will bear, which is argued by many to be too expensive.

The TRIPS Agreement also addresses the transfer of technology and development of technological capabilities that result from IP protection. Article 7 states,

[the] protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations. (WTO, 1994, p. 323)

Also, Article 66.2 of the TRIPS Agreement and the WTO’s Decision of the General Council of 30 August 2003 (on the implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health) encourage developed countries to provide industry incentives for pharmaceutical technology transfer and capacity building in developing countries (WTO, 1994).

Under the TRIPS Agreement, the modes through which technology is transferred are not specified and interpretation is left to the member state. Competing views exist on what constitutes the transfer of technology or how this will occur. In the research-based pharmaceutical industry, the transfer of technology is most commonly exchanged through
voluntary licensing rights occurs through foreign direct investment (FDI). FDI is any investment made by a foreign company in a manufacturing base and subsequent production capacity of another country. Here, the foreign company retains ownership and control. A voluntary license, however, is a formal contract between the patent holder and another party, which transfers the right to exploit a patent and manufacture the product when it would otherwise be illegal. The terms of each licence are generally confidential and can include a royalty fee as well as other stipulations and restrictions. Among developing countries, the term technology transfer is often viewed more comprehensively than by the research-based pharmaceutical industry. It includes assistance though capacity building and skill development in order to enable self-sufficiency of domestic institutions, in addition to the formal exchange of rights.

With pharmaceuticals, the power to determine what constitutes technology transfer is generally conferred on the patent holder. This has generated controversy among developing countries over the full utilization of Articles 7 and 66.2 under the TRIPS Agreement. In return for patent protection that is compliant with the TRIPS Agreement (hereafter called TRIPS compliance), developing countries anticipate knowledge of patented technologies to be diffused in their home country. The research-based industry often instead provides development assistance to build general infrastructure and regulatory capacity. As a result, there is a disparity among parties on what activities comprise the transfer of technology. This disparity then makes it difficult to ensure that the terms of technology transfer “are given effect and translated in to practice” (UNCTAD, 2002, p. x). As a result, in the late 1990s the concern over the assurance of both the transfer of technology and ARV access became major platforms for developing countries at the

The implementation of the TRIPS Agreement gained significant media attention, because it occurred at an important intersection on the HIV/AIDS timeline: the exponential rise of HIV prevalence and the development of ARVs effective first-line treatment of the virus, HAART. Appendix A covers WHO classifications for first- and second-line treatment regimens, which are followed within this research. Generally, WHO (2003, 2006a) guidelines first outlined initial treatment recommendations for patients as well as secondary treatment options when first-line treatment fails or resistance to treatment occurs. In developing countries, the most commonly procured first-line HAART has been 3TC+d4T+NVP, either as single products or in a fixed-dose combination (FDC). With ARVs available for patient treatment, the drugs’ patent protected status led to prices that were out of reach for the developing world. In 2000, the lowest priced originator’s product (i.e. those produced by patent holders) for first-line triple therapy cost US$10,439 per person per year (pppy) (MSF, 2007). The price was far beyond the financial capacity of many Sub-Saharan African countries, whose total per capita health expenditure at the time averaged $US29 per year (World Bank, 2008b).

The TRIPS Agreement was a source of concern for AIDS activists, non-government organizations (NGOs) (such as Médecins sans frontières (MSF) and Oxfam), international

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1 In resource-limited settings, WHO (2003) recommends as the preferred first-line treatment option a combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), such as stavudine (d4T) or zidovudine (AZT) with lamivudine (3TC), along with a non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine (NVP) or efavirenz (EFV).

2 Fixed-dose combinations have two or more active pharmacological products in the same pill, capsule, tablet or solution. They are highly desirable, because they significantly reduce the number of pills a patient must take, which leads to greater compliance and appropriate use.
organizations, academic groups, as well as developing country members, who felt that they were
strong armed into the Agreement by the political interests and pressure of developed countries,
most prominently the United States. In response, advocates called for the use of flexibilities and
safeguards within the TRIPS Agreement to ensure affordable prices and increase treatment
access.

TRIPS flexibilities include the utilization of a developing country’s transition period to
implement patents as well as the issuance of compulsory licences, both of which are discussed
here. TRIPS transition periods exist to allow developing countries and least-developed countries
(LDCs) time to adapt their legislation and implement both pharmaceutical process and product
patents\(^3\) to their requisite obligations. As there is no WTO definition of developing country, its
members are required to announce themselves (WTO, 2008a). This research classifies
developing countries according to the World Bank (2008) grouping of low- and middle-income
countries. There are 107 member developing countries with a per capita Gross National Income
(GNI) of US$11,455 or less (World Bank, 2008). WTO (2007) recognizes LDCs by their United
Nations (UN) designation. Of the 49 designated LDCs, 32 are members of the WTO. Appendix
B is a list of these developing countries and LDCs discussed in this research.

The TRIPS transition periods enable developing countries time to develop the appropriate
infrastructure to review patent applications as well as to ensure patent enforcement under this
new legislative requirement. During these transition periods, the country is obliged to provide a

\(^3\) There are two types of pharmaceutical patents: product and process. Pharmaceutical product patents protect the
final drug form (often there can be a number of patents for one drug). Pharmaceutical process patents protect the
methods or operations undertaken to produce a product. Therefore, if a country protects only process patents and not
pharmaceutical products, then any drug can be manufactured by any firm, so long as it can discover an alternative
process to produce the final drug (and not infringe upon the protected process patent).
mailbox system. This system allows applications for patents to be filed, but only examined once the transition period ends. At that time, if the invention is deemed patentable, a patent is granted for the remainder of its term from the filing date. As the transition period was explicitly provided for under the TRIPS Agreement, this manufacture can be done theoretically without fear of repercussions over IP infringement by developed countries and the research-based pharmaceutical industry, in the form of lawsuits and trade sanctions.

Essentially, there are three transition periods under the TRIPS Agreement. Appendix C provides an in-depth discussion of these transition periods as well as examples of countries that have used them. First, developing and LDCs were not obliged to patent pharmaceutical processes or products for drugs that were in development, or on the market, at the time the TRIPS Agreement came into force. Only drugs for which a patent application was filed from January 1, 1995 onward were included under TRIPS patent obligations. Table 1 is a list of pertinent ARVs, their drug class, and whether they fall under the pre- or post-1995 implementation of the TRIPS Agreement. Second, the TRIPS Agreement gave developing countries until January 1, 2000 to apply TRIPS standards to both product and process patents. In addition, developing countries that had not legislated product patents prior to the TRIPS Agreement (regardless of whether or not they had process patents in place) were given until January 1, 2005 for their introduction. Third, although LDCs were initially required to amend their patent legislation by January 1, 2006, pursuant to the Doha Declaration this deadline was extended to 2016.

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4 The mailbox provision in Article 70.8 of TRIPS is for filing patent applications for pharmaceutical products during the member country's transition period.

5 Under the amendments to India’s Patent Act passed in 2006, however, if locally produced generic versions of the patented product are already on the domestic market and a substantial investment has been made, generic manufacturers can continue production without patent infringement suits, as long as a royalty fee is paid to the patent holder until expiration. Important to drug access, the transition period also allows the generic production of products that are patented in TRIPS-compliant countries.
Table 1: ARVs, by Treatment-Line, Drug Class, and Pre-TRIPS Patent Status

<table>
<thead>
<tr>
<th>ARV Line</th>
<th>ARV Class</th>
<th>Generic Name</th>
<th>Abbreviated Name</th>
<th>Pre-TRIPS Patent†</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-Line*</td>
<td>NRTI</td>
<td>Stavudine</td>
<td>d4T</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zidovudine</td>
<td>AZT</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abacavir</td>
<td>ABC</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lamivudine</td>
<td>3TC</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Didanosine</td>
<td>ddl</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emtricitabine</td>
<td>FTC</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tenofovir‡</td>
<td>TDF</td>
<td>No</td>
</tr>
<tr>
<td>Combination NRTI</td>
<td>Lamivudine+zidovudine</td>
<td>3TC+AZT</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>Nevirapine</td>
<td>NVP</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Efavirenz</td>
<td>EFV</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Combination NRTIs+NNRTI</td>
<td>Tenofovir+emtricitabine</td>
<td>TDF+FTC</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zidovudine+lamivudine+Abacavir</td>
<td>AZT+3TC+ABC</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tenofovir+emtricitabine+efavirenz</td>
<td>TDF+FTC+EFC</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Second- and Third Line</td>
<td>PI</td>
<td>Indinavir</td>
<td>IDV</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nelfinavir</td>
<td>NFV</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ritonavir</td>
<td>RTV</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Saquinavir</td>
<td>SQV</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atazanavir</td>
<td>ATV</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Darunavir</td>
<td>DRV</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amprenavir</td>
<td>APV</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lopinavir</td>
<td>LPV</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tripravir</td>
<td>TPV</td>
<td>No</td>
</tr>
<tr>
<td>Combination PI</td>
<td>Lopinavir low-dose boosted ritonavir</td>
<td>LPV/r</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Note. NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor

* First-line regimes include two NRTIs combined with a NNRTI. Second line regimens include two NRTIs combined with a PI that is boosted with a low-dose of ritonavir. NRTIs not used in first-line treatment can be part of the second line regimen. See Appendix A for a further description of treatment regimens.
† ARVs that were either on the market or had already been patented (in countries with domestic patent laws) prior to implementation of the TRIPS Agreement. Essentially, pre-TRIPS ARVs are not subject to the terms of patent protection under the agreement and can be manufactured in developing countries.
‡ Tenofovir is a nucleotide reverse transcriptase inhibitor (NtRTI). It is classified with NRTIs as the mode of action is essentially the same. One major difference, however, is that in first-line treatment an NtRTI is generally less toxic than an NRTI.

For countries already compliant with TRIPS patent protection standards, the TRIPS transition periods are not available. In these cases, compulsory licensing is a safeguard that can be implemented to allow generic ARV manufacture within the country. Compulsory licenses are provided for under Article 31 of the TRIPS Agreement, which states “the law of a Member allows for other use of the subject matter of a patent without the authorization of the right holder” (WTO, 1994, p. 333). This provision enables national governments to grant licenses to make and sell drugs without the permission of the patent holder. A compulsory license can be implemented in cases where the patent holder refuses to grant a voluntary license on reasonable commercial terms or “in the case of a national emergency” (WTO, 1994, p. 333) with adequate remuneration being paid to the right holder. This remuneration generally takes the form of a royalty rate and is suggested to average from 0% to 6%, based on previous examples in Japan and Canada and as proposed by the United Nations Development Program (UNDP) (Love, 2005).  

Although at the time of implementation of the TRIPS Agreement no developing countries had implemented a compulsory license, this strategy was not new to the developed world. For example, Canada was known for its use of compulsory licensing from 1969 to 1987; Section 41 of the Canadian Patent Act authorized unrestricted compulsory licensing on patented medicines (Chien, 2003; Matthews, 1996; Thompson, 1984). The Canadian Generic Pharmaceutical Association attributes the successful growth of the country’s generic drug industry to this unrestricted compulsory licensing (Cohen, 2004).

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6 This royalty rate is not fixed. Issuing compulsory licenses for ARVs, Malaysia set a royalty of 4%, Mozambique 2%, Zambia 2.5%, and Indonesia 0.5% (Love, 2005).
Even though compulsory licensing provisions have been used in developed countries, developing countries feared economic repercussions from the United States Trade Representative (USTR). It left them cautious in using this broadly defined term in the context of HIV/AIDS. After international pressure by activists, advocates, and developing countries to clarify compulsory licensing terms, the Declaration on TRIPS and Public Health was adopted in November 2001 at the WTO Ministerial Conference in Doha, Qatar. The Doha Declaration was developed to promote public health and access to essential medicines within the TRIPS Agreement and states:

> We agree that the TRIPS Agreement does not and should not prevent members from taking measures to protect public health…[Each Member has] the freedom to determine the grounds upon which such licences are granted…[and] the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency. (WTO, 2001, p. 1)

The political context of the timing of this declaration is important. Around this time, developing countries members were growing increasingly unhappy with the TRIPS Agreement and the inflexibility of its supposed flexibilities. One of the most vocal developing countries was Brazil, which had been threatened with trade sanctions by the United States Trade Representative (USTR) over its use of TRIPS provisions. Pessimism grew after 39 pharmaceutical manufacturers brought the government of the Republic of South Africa (hereafter called South Africa) to court, claiming that compulsory licensing provisions infringed patents and violated the
TRIPS Agreement. After much pressure from health activists, institutions, and political leaders as well as attention of the international media, the industry withdrew its case in April 2001. From this action, momentum rose among activists and developing countries to push for the protection of public health. Concern also grew among developed country member states that developing countries and activists would stall trade talks within the WTO negotiation rounds. With the terrorist attacks of September 11, 2001 and the anthrax dispersion scares in the United States, the country was prepared to abrogate patent protection for domestic production of an antibiotic, ciproflaxin (Sell, 2003, p.160). A result of all these influencing forces, the Doha Declaration of 2001 was a mechanism intended to provide an increase in confidence to developing countries to utilize these mechanisms without concern of retaliation.

Within the safeguards to use compulsory licensing, the Doha Declaration left one issue unresolved: the lack of pharmaceutical manufacturing capacity in developing countries. Article 31(f) of the TRIPS Agreement requires that products made under a compulsory license be “predominantly for the supply of the domestic market” (WTO, 1994, p. 333). That means that compulsory licenses can only apply to countries that can use them domestically, or, essentially, countries that have a domestic pharmaceutical base. This left no recourse for countries without this capacity to produce generic medicines for their population in times of health crises, referred to in Paragraph 6 of the Doha Declaration. While Article 7 of the TRIPS Agreement contends that enforcement of intellectual property enables the transfer and dissemination of technology, there is no obligation on the part of pharmaceutical firms to enter these arrangements, regardless of public health needs (WTO, 1994). The Doha Declaration called for expedited resolution of this issue.
This issue was addressed by the 30 August Decision of the General Council in 2003, during the WTO Cancún Round of trade negotiations. The Ministerial Decision waives exporting member countries’ TRIPS obligations under Paragraph 6 and allows them to export generic drugs under compulsory license to an importing developing country member that lacks manufacturing capacity. Important for domestic capacity, the Decision also encourages developed countries to provide industry incentives for pharmaceutical technology transfer and capacity building in developing countries (WTO, 2003a).

**Statement of the Issue**

In the context of the TRIPS Agreement, its provisions, and the challenge of ARV access in developing counties, Sub-Saharan African countries with large HIV/AIDS populations have a number of strategies at their disposal to increase the supply of affordable medicines, including negotiating voluntary licenses with patent holders, the use of TRIPS transition periods, and, issuing compulsory licenses. The adoption of the latter two strategies requires an appropriate legislative framework, the commitment of the government, and willingness of the local manufacturer. In 2001, a firm in South Africa, Aspen Pharmacare (hereafter called Aspen), was the first in the world to receive a voluntary license for ARVs, and by September 2004 Cosmos Ltd. in Kenya had followed suit. Also by this time, Zimbabwe, Mozambique, and Zambia each issued compulsory licenses for ARVs, based on public health concerns of HIV/AIDS in their respective countries. Other countries, such as Tanzania, Ethiopia and Uganda, utilized their TRIPS transition period to manufacture generic ARVs.
In addition, each of these countries has used technology transfer arrangements to gain assistance in developing the technological know-how to manufacture the ARVs. These arrangements rely on external aid through a technology supplier. At the time of this research, no comprehensive empirical analysis could be found of these technology transfer events. As such, it is not well understood what factors lead to the development of these transfer arrangements and, in particular, the role that IP protection plays. Also, the ability of these initiatives to produce affordable ARVs has not been well examined. Given the scare evidence from the field, this research aims to contribute a framework that identifies and assesses the domestic conditions that affect the development of ARV technology transfer arrangements and their affordable ARV production. This framework can then be used to inform developing countries of the important factors to consider when forming and implementing technology transfer arrangements for public health purposes to lower treatment costs. It can then be used to benchmark other transfer arrangements.

**Research Questions**

With the increasing number of ARV manufacture and technology transfer initiatives in Sub-Saharan Africa, this dissertation addresses two critical issues that can be posed as general theoretical questions:

1. Does the protection of pharmaceutical patents lead to the transfer of ARV technology to developing countries as expressed under Article 7 of the TRIPS Agreement?
2. Are Sub-Saharan African countries able to increase affordable treatment access through local generic manufacturing initiatives?
In order to address these issues, two specific research questions are posed. They are examined through case studies of current initiatives South Africa and Tanzania:

1. At the macro-level, what domestic conditions lead to technology transfer arrangements for the production of patented ARVs?

2. At the micro-level, what domestic conditions influence the affordability of locally manufactured ARVs?

To appropriately contextualize these questions the terms technology transfer, technology transfer arrangements and affordability are defined and discussed in the literature review.

**Literature Review**

The requirement of pharmaceutical patents protection under Article 33 of the TRIPS Agreement generates two lines of inquiry as they pertain to ARVs in developing countries. The first line of inquiry addresses drug access and the ability of domestic generic ARV manufacturers to increase drug access, particularly affordability. The second line of inquiry focuses on the transfer of technology to developing countries to meet the objective of affordable access, and the role IP plays in their development. The following section reviews and discusses the relevant concepts as well as the literature encompassing these issues. It also points to the current gaps in the literature that drove the development of the research questions.
I. TRIPS and ARV Access

A. ARV Access – Concept and Definitions

For the last half century, the term *access* has been ubiquitous in the health literature and advocacy community. Yet, this loaded term was only substantially defined and developed in the 1980s, through the work of Penchansky and Thomas (1981). Previous literature describes components of this definition individually or in small groups related to access (Bice, Eichhorn & Fox, 1972; Donebidian, 1973; Fein, 1972; Freeborn & Greenlick, 1973; Simon, et al., 1979). Yet, Penchansky and Thomas (1981) were the first to conceptualize a taxonomic definition of access to the health care system. They created measurable indicators for each of these components, and tested them for validity. In recent years, WHO more prominently developed equitable access frameworks and measures specific to drug access in developing countries. Table 2 summarizes the conceptualization of the often used term, access.

Penchansky and Thomas (1981) describe five dimensions important to access: 1. availability, 2. accessibility, 3. acceptability, 4. accommodation and 5. affordability. *Availability* refers to the adequacy of the health human resource supply, services, and infrastructure. *Accessibility* indicates the relationship between the location of the patient and to these services (distance, time and cost). The manner in which resources arrange to treat patients (such as a clinic’s hours of operation) and patients’ ability to adjust to these factors denotes *accommodation*. Both patients and health care providers’ attitudes expectations of personal and practice characteristics (e.g., age, sex, gender, and ethnicity) signify *acceptability*. Finally, *affordability* marks the patient’s or health insurer’s ability to pay for the necessary treatment and services (Penchansky & Thomas, 1981).
The concept of *access* developed by Penchansky and Thomas, however, was predominantly directed toward access to health care services in developed countries. Since the 1970s, the WHO has compiled data to estimate the extent of the access burden on developing countries. By the 1990s, the lack of access to essential drugs, vaccines, and health commodities in developing countries was pronounced and its significance to the global community heightened.

**Table 2: Concepts and Dimensions of “Access” Definitions**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Scope</th>
<th>Concept</th>
<th>Dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penchansky and Thomas</td>
<td>1981</td>
<td>• Access to Care</td>
<td>• Degree of fit between patients and the health care system</td>
<td>• Accessibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Availability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Acceptability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Accommodation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Affordability</td>
</tr>
<tr>
<td>WHO and MSH</td>
<td>2000</td>
<td>• Health Commodities (Essential Medicines, Vaccines, etc.)</td>
<td>• Framework of the relationships between factors influencing access</td>
<td>• Geographical Accessibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Physical Availability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Acceptability (Satisfaction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Affordability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Quality of products and services</td>
</tr>
<tr>
<td>WHO</td>
<td>2004</td>
<td>• Essential Medicines</td>
<td>• Collective Action Framework for Improving Equitable access</td>
<td>• Rational Selection and Use Reliable health systems and Supply</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Sustainable Financing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Affordable pricing</td>
</tr>
</tbody>
</table>

At the beginning of WHO’s Essential Medicines Programme\(^7\) in 1975, an estimated one-half of the world’s population lacked access to essential medicines. While the proportion of individuals

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\(^7\) The WHO Essential Medicines Programme arose from the World Health Assembly in 1975, where a report by the WHO Director-General outlined potential policies on what were considered basic essential medicines as a guideline to increase access to priority treatments in respective countries. In 1977, this led to the first Essential Medicines List,
without access decreased substantially to one-third by 1999, the absolute number remained the same: an astounding 1.7 billion people did not have regular access to medicines (WHO, 2004a). Rising HIV prevalence rates and the announcement of HAART effectiveness at the International AIDS Conference in 1996, along with an increase in media attention, further underscored the issue of drug access.

Despite the work of Penchansky and Thomas and others to conceptualize and measure access, WHO and MSH believed that access was not clearly defined with an appropriate framework and reliable measures (WHO-MSH, 2000). These organizations found it difficult to measure changes in access over time or make country comparisons. In 2000, WHO and MSH met to derive an appropriate framework for discussing and measuring access. This work was based on Penchansky and Thomas (1981) and refined the term access for medical commodities, such as essential medicines, vaccines, and medical devices. Here, developing countries were the focus. Access was defined in terms of geographic accessibility, physical availability, acceptability (patient comfort and satisfaction), affordability, and quality of products and services. In addition, the WHO-MSH framework emphasized that good quality products and services are an essential component of access that cuts across all dimensions except accommodation.

Although the WHO-MSH framework was practical for quantifying and measuring access, it omitted the important role that coherent and supportive policies play in medicine access in developing countries. General Comment 14 of the International Covenant on Economic, Social and Cultural Rights obliges countries to ensure access to essential medicines under an

\[\text{which aimed to be a model for developing countries governments to address priority public health treatment needs. ARVs were added to the list in 2002 (WHO, 2007b).}\]
individual’s right to the “highest attainable standard of health” (UNCESCR, 2000, p. 1). To provide health services and essential drugs that are of good quality and accessible physically, economically as well as geographically, a government must commit to support the appropriate institutions and mechanisms. For example, a multi-sector strategy for HIV/AIDS over both the medium and long-term that coordinates both policy and resources is crucial to realize drug access at the patient level.

Modifying previous access definitions, the WHO World Medicines Strategy 2000-2003 focussed further on improving equitable access to essential medicines for health priority. These priorities were specific to HIV/AIDS, malaria, tuberculosis, and childhood illnesses, where the burden of illness generally falls on developing countries. This brought the concept of access into a new light and developed a collective action framework for countries, to work together to break down access barriers in developing countries, seen in Figure 1 (WHO, 2004).

Figure 1: WHO’s (2004) Collective Action Framework to Improve Access to Essential Medicines
This model framed enabling factors for access to essential medicines and placed emphasis on the role developing country governments play in ensuring access. These enabling factors included a drug’s rational selection (safety and cost-effectiveness, based on a national essential drugs list and treatment guidelines), sustainable financing through equitable funding mechanism (government revenues or social health insurance), reliable private/public health and supply systems, as well as affordable pricing for governments, health care professionals, and patients. In recent years, the WHO Model List of Essential Medicines has been one of the most important public health tools to increase access to medicines and promote their rational selection and use. This list also helped gain international acceptance for the concept of essential medicines as a powerful way to promote health equity (Wilson, Esmail, & Cohen, 2004).

In context of the multiple factors affecting drug access, the TRIPS Agreement predominantly concerns one component: affordability. WHO (2004b, p. 3) states that, “with the potential cost of providing a full range of treatments for prevailing common diseases, medicine prices and financing are inescapable factors in access to essential medicines”. By patenting essential medicines, such as ARVs, pharmaceutical companies can price drugs out of the reach of many individuals. This is particularly true in developing countries, where financial resources are extremely limited. In 2001, the average per capita health expenditure in high-income countries was $US2,764, compared with US$66 in low- and middle-income countries and $US29 in Sub-Saharan African countries. Similarly in 2000, while developed countries spent approximately 7% to 20% of health expenditure on pharmaceuticals, this percentage rose to 66% (de Joncheere, 2001) and even 80% (Ford, 2004) in developing countries. Kaplan (2004) recommends that, to
determine what constitutes affordable pricing, “country-specific case-by-case basis”
consideration should account for epidemiological factors, such as prevalence and urgency,
alternative treatments, effectiveness of treatment, purchasing power of the population, and the
capacity of government to subsidize drug costs in some form. Strategies implemented to increase
affordability will improve the cost-effectiveness of therapy and free resources to either treat
greater numbers of patients or improve other access components. Affordability, as it pertains to
the domestic production of essential medicines, such as ARVs, will be discussed in the section A
National Issue: Local Manufacture and ARV Affordability.

B. Barriers to Affordability – Patents and Drug Prices
The TRIPS Agreement focuses on protection of IP and harmonizes its member countries policies
with a 20 year patent protection period. Multinational patent holding pharmaceutical companies
claim that patents provide so called rent for the high costs and risk of new product research and
development (R&D) and encourage further investments. This rent is essentially a reward to the
patent holder in the form of royalties on product sales paid by users. Critics counter that this
reward, and the resulting high drug prices, are not justified, particularly in developing countries
where purchasing power is small and little R&D takes place to treat diseases predominantly
affecting these countries. To give context to the issue of IP and understand how the TRIPS
Agreement affects the affordability of ARVs in developing countries, Appendix D discusses
intended outcome of IP protection, and innovation, and how this affects drugs for diseases in
developing countries. Here, the affect patents have on the affordability of drugs prices for
patients and governments in developing countries are addressed.
Around the time of AZT’s market entry in the late 1980s, the annual cost of treatment for this drug alone was reported to be US$10,000 per patient per year (pppy) (Sabatier, et al., 1989). With the announcement of HAART as an effective treatment for HIV/AIDS patients in 1996, concern simultaneously grew over its affordability to patients. This was the case for those who carried the burden of illness Sub-Saharan African countries. With the most limited resources of any other global region and the highest HIV/AIDS prevalence rates, treatment was unaffordable for these patented products. In 1997, the price for a variety of triple therapies of HAART ranged from US$7,944 to US$20,224 pppy if the second-line booster ritonavir was added (Floyd & Gilks, 1998). As a result of patents protecting these new life-saving medicines, there was no generic competition for these products, and prices were set freely on the market.

In a controversial article, Attaran (2004) claims that patents are not the barrier to access in the developing world, but that other factors, such as poverty, have greater significance. Drug tariffs, sales taxes and a lack of sufficient international financial aid to fund ARV treatment enhance these barriers (Matthews, 2004). Attaran’s (2004) study found that patents for essential medicines are uncommon in poor countries, and, as a result, cannot explain the limited access to medicines. This view has been vehemently contested (Love, 2004; Goemaere, et al., 2004). Goemaere and colleagues (2004) reflected Attaran’s article with two key points. First, those few key patents that do exist on essential medicines in developing countries make up a large proportion of developing countries’ health budgets, such as the three new ARVs that accounted for 63% of Brazil’s total AIDS program cost in 2003. Second, patent holding drug firms do not file their patents in countries for which there is neither a “market” nor the manufacturing capacity to produce the drug, but patents are enforced in developing countries that might meet...
these criteria. Referencing their previous research (Goemaere et al., 2002), they note that, South Africa, one of the few developing countries with manufacturing potential at the time of Attaran’s (2004) analysis, had more than 95% of ARVs under patent. Unless developing countries like South Africa use the flexibilities within the TRIPS Agreement, they must purchase these drugs from the right holders and wait until patent expiry before generics can be produced.

Currently, LDCs that do not have ARV patents, but lack the manufacturing capacity for generic production, can import freely from countries that also do not protect the ARV patents, but can manufacture ARVs. For example, India, exercising its TRIPS 2005 transition period, has been the major manufacturer and supplier of generic first-line ARVs to developing countries. This scenario changes, however, with some second-line and later generation ARVs. Since India amended patent legislation to the TRIPS Agreement after 2005, many ARVs are facing patent review under the mailbox provision the country was required to put in place. If the AR is deemed patentable and is not currently being produced in India, exclusive rights must be awarded to the patent holder. If this occurs, LDCs without manufacturing capacity also become dependent on the patent holders for these drugs. Though these ARVs may not be patented in the LDC, it likely does not have the capacity to produce them, and thereby can only import the ARVs from the patent holder (since developing countries’ transition period ended in 2005).

The fear, again, becomes that the patent price will be set too high for developing countries to afford. A new fusion inhibitor, enfuvirtide, produced by Hoffmann-La Roche (hereafter called Roche) is one of the few options available for salvage therapy in treatment experienced HIV-infected individuals. Enfuvirtide is patented and there is no generic substitute on the market.
Brazil’s National AIDS Programme, with an increasing number of treatment experienced patients, introduced enfuvirtide into its treatment plan in 2005 and procured the drug at a price of US$17,301 pppy in 2006 (Nunn, et al., 2007). Although only procured in small volumes, Nunn and colleagues (2007) found that patented ARVs amounted to nearly 80% of the 2005 Brazilian ARV budget of US$414 million for its total 175,000 patients. This more than doubled the budget of US$193 million in 2004. Although speculative, given only a small increase in new patients (8%), this dramatic rise in cost could be attributed to unexplained increases in procurement volume (up to 50%) as well as patients switching to newer and more expensive treatments (Nunn, et al., 2007). Treatment cost increases have grave implications for other developing countries and LDCs that have much larger numbers of HIV-infected individuals as well as much smaller per capita treatment budgets. For example, Tanzania requires a large amount of donor aid for its treatment program, which aimed to treat 423,000 HIV-infected individuals in 2008 with a drug budget of approximately US$237 million. If treatment costs increase in Tanzania as a result of switching to newer therapies, it remains unclear whether donor funding will also increase to make up this difference.

As discussed, there are a variety of components in WHO’s access framework and, admittedly as Attaran (2004) suggests, patents are not the only barrier to increased ARV access; however, patents do increase the price of ARVs that generic competition in the market would otherwise lower. Evidence of this came when the first Brazilian generic ARVs came on the market in June 2000, reducing the cost of therapy drastically from US$10,439 to US$2,767 pppy (MSF, 2007). Also, a report by MSF (2006) at the XVI International AIDS Conference found that the cost of treating 58 patients on patented second-line ARV treatment at its program in Khayelitsha, South
Africa, was the same as treating 550 patients with generic first-line ARVs (MSF, 2006). Without competition, patents tend to make drugs more unaffordable to the developing world. It is not until the patent term expires and generics are able to penetrate the market that ARVs are sold at a fraction of their former cost.

C. Government-Level Financing, the Global Fund, and PEPFAR

Unaffordable drugs and limited treatment availability in developing country markets is not only a failure of the market, but one of public policy. Orbinski (2003) suggests that, when the market is ineffective in providing public goods, the government has a duty to create the capacity to ensure access. This is evident with the development of universal ARV access programs in many developing countries, most notably Brazil in 1996. At the national level, Cohen (2003) notes that, in 1999, Brazil confronted massive stress on public sector health budgets after designating approximately one-third of its federal drug budget to supply ARVs to citizens at no charge. In 2001, it was estimated that Brazil spent US$232 million on ARVs alone (Galvão, 2002) rising to US$414 million in 2005 (Nunn, et al., 2007). Currently, 83% of the HIV-infected population in Brazil receives ARV therapy (UNAIDS, 2008).

Even with financing at the government level, Ford (2004) underscores that price, again, is the dominant variable that limits access to drugs in developing countries. The cost of essential medicines can amount to 80% of health expenditure in some countries. Most developing countries do not have the means to commit that high a percentage of finances to treat one illness. As mentioned, the lack of accessible treatments for HIV/AIDS and malaria are a result not only of individual inability to pay, but government inability as well (Ford, 2004). These governments
often prioritize drug treatment plans poorly further inhibiting drug access. Although various strategies may exist at the national level to potentially increase the affordability of drugs, it is uncertain whether they affect a government’s commitment to spend on behalf of its vulnerable citizens.

Noting these constraints at the national level, international organizations, donor countries, multilateral agencies, and NGOs roles in assisting with HAART have increased substantially. With the rise in HIV/AIDS in the developing world, UNAIDS was established by the United Nations Economic and Social Council in 1994. It was one of the first financers of HIV/AIDS programming and currently supports an expanded response, engaging a variety of sectors for treatment, prevention, support, and care. In 2000, cooperation between WHO, UNAIDS, the UN Population Fund, the World Bank and seven patent holding pharmaceutical firms (Abbott Laboratories, Boehringer Ingelheim [BI], Bristol-Myers Squibb [BMS], Gilead Sciences, GlaxoSmithKline [GSK], Hoffman-La Roche [Roche], and Merck & Co., Ltd. [Merck]) formed the Accelerating Access Initiative (AAI). This collaboration of organizations worked with developing country governments and stakeholders to broaden access to affordable and good quality ARVs through the implementation of national HIV/AIDS treatment plans and ARV price reductions from individual drug firms. When AAI began in 2000, fewer than 10,000 HIV-infected individuals in Africa were receiving treatment. This number rose to 75,000 in 2003 and 424,000 in 2006 (IFPMA, 2006).

AAI has been criticized by activist organizations, such as the AIDS Coalition to Unleash Power (ACT UP). ACT UP claims that AAI offers minimal progress in terms of price reductions and
limits competition in developing countries from generic drug firms. The terms of the agreements between the pharmaceutical companies and the developing countries ministries of health remain confidential; however, ARV discounts are often restricted to particular ARVs, quantities, and distribution sectors. In addition, these agreements can be tied to a commitment from developing countries governments to increase IP protection (ACT UP, 2002).

In addition to collaboration of international organizations and patent holding drug firms to improve ARV access in Africa, financial resources devoted to HIV/AIDS programs increased substantially. Financial resources devoted to HIV/AIDS treatment in low- and middle-income countries increased from US$300 million in 1996 to an estimated $10 billion in 2007 (Whiteside, 2008). This is mostly from two initiatives: the Global Fund to Fight HIV/AIDS, Malaria and Tuberculosis (hereafter called the Global Fund) and the President’s Emergency Fund for HIV/AIDS Relief (PEPFAR) of the George W. Bush Administration. Since it began in 2001 and through 2008, the Global Fund attracted US$4.7 billion in financing (Global Fund, 2008). In May 2003, PEPFAR was approved by the United States Congress and pledged US$15 million to combat HIV/AIDS over 5 years, the largest commitment by any nation to combat a single disease. Roughly half of this budget was directed to treatment and the remaining to care and prevention (Dietrich, 2007).

In December 2003, WHO and UNAIDS launched the “3 by 5” Initiative aimed to treat 3 million HIV-infected individuals by 2005. While the “3 by 5” Initiative failed to reach its target, its efforts tripled treatment numbers to 1.3 million, with assistance from the Global Fund and PEPFAR. By March 2008, PEPFAR supported treatment for approximately 1.68 million
individuals through programs in its 12 focus countries Sub-Saharan Africa (PEPFAR, 2008). Additionally, in July 2008, the reauthorized PEPFAR pledged US$48 billion to its projects (know as PEPFAR II). In the period 2009-2013, PEPFAR II expects to treat approximately 3 million individuals. However, with the change in United States government from the Bush Administration to the Obama Administration in January 2009, and the struggling global economy, uncertainty remains about the amount of resources that PEPFAR II will devote to ARV treatment in Sub-Saharan African.

PEPFAR is not without controversy. Some of these issues were explored thoroughly in the work of Dietrich (2007). Discrepancy remains over PEPFAR’s treatment numbers because it consolidates its figures on direct financing with those of the Global Fund (to which PEPFAR contributes) as well as any other indirect treatment funding that may arise out of PEPFAR’s “general system strengthening” (Dietrich, 2007, p. 281). Also, approval to purchase generic ARVs was slow to materialize. At the commencement of PEPFAR, funds were only available to purchase ARVs from their patent holders, as a means to both respect IP and ensure drug quality. This policy was criticized for a number of reasons. First, at the time, many Indian ARV generic drugs were tested and approved internationally under the WHO Prequalification Programme and were purchased by UN agencies and other donors. Second, because patents were not a concern for generic manufacturers, they were able to combine these drugs into triple FDCs where mostly single drugs were only available from patent holders. FDCs generally simplify treatment and keep adherence rates high. Third, generic drugs were significantly cheaper than

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8 The Prequalification Programme began in 2001 and is a service provided by the World Health Organization (WHO) to facilitate access to medicines that meet unified standards of quality, safety, and efficacy for HIV/AIDS, malaria, and tuberculosis. This is done by providing a list of products and their manufacturers that meet specified quality and safety requirements evaluated by WHO or a stringent drug regulatory authority, such as the United States Food and Drug Administration or the European Medicines Agency.
their patent counterparts. Generic drugs allow more people to be treated numbers under the same budget. Finally, the policy of purchasing patent medicines was criticized as a means to support United States pharmaceutical manufacturers by the two groups formed by the pharmaceutical industry to lobby Congress for PEPFAR’s funding approval, the Corporate Council on Africa’s Task Force on AIDS, and the Coalition for AIDS Relief in Africa (Dietrich, 2007).

Although PEFPFAR changed this policy in May 2004 under pressure from a variety of organizations both domestic and international, another restriction was imposed. Any drug purchased under PEPFAR, whether patented or generic, required approval by the FDA, suggesting that its quality assurance was more stringent than WHO prequalification. No generic manufacture was then eligible for PEPFAR funding until it was FDA approved, which first occurred in January 2005, nearly 2 years after PEPFAR implementation. Critics felt that this stipulation was not only redundant but that it was “a political move designed to reassert U.S. independence and to maintain profits for U.S. companies” (Dietrich, 2007, p. 286). Although a number of generic ARVs are approved under PEPFAR, it continues to allocate the majority of its treatment resources to patented medicines. Finally, the bilateral nature of PEPFAR instead of multi-country initiatives under UN programming, such as the Global Fund, came under criticism. It was seen as a competitive and unilateral approach that could adversely affect the desired program objectives as the Bush Administration openly questioned the Global Fund’s management, financial accountability, and effectiveness.
II. TRIPS and the Transfer of Technology

A. Technology Transfer – Concepts and Definitions

Historically, technology transfer has been viewed as “systematic knowledge for the manufacture of a product, [or] for the application of a process” (UN, 1979; UNCTAD, 1985). However, due to the cross-disciplinary nature of technology transfer, the literature, which has grown exponentially since the 1970s, remains disjointed (Zhao & Reisman, 1992). Technology transfer has been addressed over the years in economics, sociology, anthropology, engineering, and management, resulting in varied definitions and uses of the term. Table 3 summarizes the role of the transfer of technology across a number of disciplines. Zhao and Reisman (1992) suggest that technology transfer is used as a mechanism to enhance technological capabilities and competitive advantages at the level of a firm, industry, country, or region, and that it is the “means toward economic progress, social development, quality of life, and even of culture and value systems” (p. 1).

More recently, as demonstrated by the United States National Sciences Board, the concept of technology transfer expanded to incorporate a variety of activities, from the exchange of ideas to contractually structured research collaborations (Lee, 1997). Lee uses the term transfer interchangeably with cooperation and collaboration while also drawing attention to diffusion, knowledge transfer, know-how transfer, and R&D collaboration. Lederman (1994) even describes technology transfer as a “body contact sport” (p. 293) that involves conversations, consultations and coaching. Even though these descriptions are more expansive than the narrow technology transfer definition provided above, both are generally confined to the process of
vertical technology diffusion, from innovation to industry commercialization, seen in licensing arrangements within developed countries, not to developing countries.

Table 3: Role of “Technology Transfer” Across Disciplines

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Role of TT</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociology</td>
<td>• Improve social living</td>
<td>• Rogers (1983), Williams and Gibson (1990)</td>
</tr>
<tr>
<td>Anthropology</td>
<td>• Cultural change and advancement of society</td>
<td>• Foster (1962), Cunningham and Sarayrah (1994)</td>
</tr>
<tr>
<td>Management</td>
<td>• Strengthen competitiveness and gains benefits</td>
<td>• Lake (1979), Barason and Roark (1985), Goel Cohen (2004)</td>
</tr>
</tbody>
</table>

Source: Zhao and Reisman (1992)

Maskus (2004), however, takes the concept a step further, describing technology transfer as a “comprehensive term” (p. 7). The transfer of technology is “any process by which one party gains access to a second party’s information and successfully learns and absorbs it into his production” (Maskus, 2004, p. 9). Here, technology transfer involves the mechanisms for both transporting information across borders and effectively diffusing it into host countries. Technology transfer not only encompasses the complex processes mentioned previously, ranging from innovation to the international marketing of technology, but also expands to include technology absorption through imitation.
Maskus (2004) suggests that technology transfer can be disseminated both through market and non-market mediated mechanisms. Market-mediated mechanisms are those with a formal transaction underlying the transfer of technology that can be seen in the market. This relates the traditional definition of technology transfer and includes modes such as FDI and voluntary licenses. Correa (2003) suggests that licensing can be an important source of pharmaceutical innovation and technical transformation for developing countries. This type of transaction is seen currently in South Africa and Kenya, with voluntary licenses between domestic firms and patent holders. Contrary to licensing, non-market mediated mechanisms often have no formal transaction in the market. They are often in the form of imitation, and there is little or no compensation to the technology holder in formal markets (Maskus, 2004). In pharmaceuticals, imitation is often through reverse engineering of compounds. Recognizing imitation as a mode of technology transfer increases both the number of possible channels and sources through which technology transfer may occur. This mechanism of transfer reflects the technology transfer arrangements currently experienced by LDCs (such as Tanzania, Uganda, and Zambia) manufacturing ARVs locally with the assistance of generic firms and NGOs.

Although the definition of technology transfer provided by Maskus (2004) is quite broad, it re-conceptualizes what was a very narrow focus of what could constitute the transfer of technology. This is important to note. This particular definition broadens the lens through which one views Article 7 of the TRIPS Agreement: “protection and enforcement of intellectual property should contribute to the promotion of technological innovation and the transfer and dissemination of technology” (p. 323). Here, the TRIPS Agreement refers to market-mediated mechanisms and not the broader definition of technology transfer by Makus (2004), Lee (1997) and Lederman
(1994). However, if technology is perceived to be transferred by agents other than the patent holder, they way developing countries also perceive the protection of patents may change. Developing countries commonly seek to increase their level of technology development, and depending on the definition of technology transfer, the channels through which they choose to absorb technology may also vary.

Defining Technology Transfer

Considering these important implications, the definition of technology transfer for the purposes of this research integrates the definitions by Maskus (2004) and UNCTAD (1985). Technology transfer is a process for the transformation of information between a technology supplier and a recipient for the manufacture of ARVs. This information can be disseminated through a variety of modes. The supplier and the recipient may be individuals, groups, organizations or firms. As such, technology transfer can range from the exchange of technical knowledge through formal documentation, such as a license to exploit a patent, or through technical know-how and training of human resources, such as assistance to reverse engineer an imitation of the product. Important, there must be intent to pass on technological information from a supplier for to an unrelated recipient firm. For example, in this research, FDI into subsidiaries in developing countries is not considered transfer of technology. This is because the patent holder remains the only right holder of the information, and the effective monopoly conferred by the patent status stays intact.

Given this information, this research classifies technology transfer arrangements into two forms, distinguished by whether or not the technology supplier is the patent holder. An arrangement where ARV technology is provided by its right holder under a contract to exploit a patent, or a
number of patents, is classified as a voluntary licensing arrangement. Voluntary licenses can be a naked patent, simply authorizing a domestic manufacturer the right to exploit the patent (i.e., make, use and sell what is claimed in the patent document), or they can have more encompassing terms, assisting with knowledge that is exogenous to the patent (i.e., know-how and production assistance). This research does not distinguish between the specific licensing terms and, despite their potential differences, they are all considered voluntary licensing arrangements because the agreement derives from the patent holder. When the supplier is not the patent holder, but a generic firm, pharmaceutical personnel from other countries, or any other type of organization with the knowledge to formulate and manufacture the product, the arrangement is classified as an imitator arrangement. Imitator arrangements rely on individuals and organizations external to the patent holders that have knowledge on the production of the patented ARV. These arrangements commonly include more extensive technology transfer terms than found in voluntary licenses, including know-how transfer, training of personnel, and assistance with production and testing of quality.

**B. Does IP Encourage the Transfer of Technology?**

Described in the Introduction to this Chapter, the TRIPS Agreement includes provisions that address the transfer of technology and development of technological capabilities in developing countries through market mediated mechanisms, such as voluntary licensing and FDI. Articles 7 and 66.2 of the TRIPS Agreement and the 30 August Decision of the General Council encourage developed countries to provide industry incentives to “recognize the desirability of promoting the transfer of technology and capacity building in the pharmaceutical sector in order to overcome the problem identified in paragraph 6 of the Declaration” (WTO, 2003a, p. 1). Additionally,
Article 8.1 of the TRIPS Agreement states that members may adopt measures to protect public health and promote public interest in sectors of vital importance to their technological development. However, it is uncertain what effect these provisions have, especially given the varying understanding of what may constitute the transfer of technology.

Researchers advocating IP protection cite a resulting increase in FDI, technology flow, and R&D resources to local pharmaceutical firms (Rozek, 2000). Yang and Maskus (2001) developed an economic model to analyze the effects of developing country IP enforcement on the extent of technology licensing undertaken by developed country firms. Here, the key assumption was that strengthening patent rights would increase the licensor's share of profits and reduce the costs of enforcing licensing contracts, thereby making licensing more attractive. Govindaraj, Reich, and Cohen (2000) state that patents could expand drug access and encourage technology transfer and R&D investments if firms introduce new products into small developing country markets. Maskus (2000) found that licenses and production rights would require large fees for developing country firms shortly after strengthening patent protection. In the long-term, however, annual growth of 0.5% could be produced through increased trade, FDI and licensing.

However, benefits from IP protection through the transfer of technology tend to concentrate among upper-middle-income countries, such as Brazil, Russia, India and China, which are commonly referred to as BRIC. Investment banking firm Goldman Sachs coined this term to describe these fast growing and emerging markets that, by the year 2050, will together become the most dominant economies globally. The investment community views the interplay between BRIC economies and developed economies, such as the United States and the European Union,
as a critical aspect of globalization and interdependence (Chen, et al., 2007). Maskus (2004) emphasizes that those results similar to BRIC countries might not be experienced by LDCs once IP protection is strengthened domestically. In fact, some suggest that LDCs might even be harmed by the increased market power of IP holders, especially if patented products are marketed at high, monopoly prices (Cohen & Illingworth, 2003; Maskus, 2000). Govindaraj, Reich, and Cohen (2000) state that a stronger patent regime may create significant challenges for vulnerable groups that depend on low-cost generic versions of patented products.

A large body of research also suggests that the enforcement of patents will not encourage the transfer of technology, FDI, or R&D to developing countries that lack the appropriate resources and infrastructure (Correa, 1995; South Centre, 1997; WHO, 2000). In his model of IP enforcement and technology licensing, Helpman (1993) supposes that a decline in the amount of effort devoted to imitation by firms in developing countries would limit technology flows to the developing world. In his model, a strengthening of IP is not in the interest of such countries; it could reduce global innovation and restrict global welfare. These findings are reinforced by Glass and Saggi (1995) who found that the protection of IP can decrease technology transfer. Similarly, LaCroix and Kawaura (1996) examined the introduction of pharmaceutical product patents in Korea and their impact on Korean firms. Utilizing the stock market, LaCroix and Kawaura determined that the country’s wealth losses were large. Kaplan and Laing (2005) cited this study to illustrate that strengthening patents in developing countries cannot only generate economic loss, but also increase political controversy.
Furthermore, many LDCs feel that developed countries have failed to live up to their commitments in the TRIPS Agreement and argued that the transition periods are not sufficient to develop the appropriate capacity (Micalopolous, nd). African countries announced their desire for measures that were concrete and that would encourage investment in LDCs, citing the current provisions on technology transfer as simply “paper promises” without progress beyond the negotiation table. They stressed that these measure should use legal force (Yusuf, 2004, p. 49).

Addressing this concern, the TRIPS Council since 2003 requires that developed country members submit a detailed report every third year (and updates in the intervening years), outlining actions taken or planned with respect to their obligation under Article 66.2 (WTO, 2003b). This includes the special incentives they provide to encourage the transfer of technology as well as information on the applicability and adaptability of the particular technology in the country. In its detailed report in 2005, Switzerland outlined a number of initiatives to assist with program development in water supply and sanitation, health systems, and rural development, as well as research partnerships in biology, methane development and health diagnoses (WTO, 2005). However, there were no initiatives specific to capacity building in the pharmaceutical sector as requested by African countries.

Addressing the need for technology transfer to developing countries, international institutions have formed to assist local capacity building in domestic production. These programs are found in institutions such as the United Nations Industrial Development Organization (UNIDO), United Nations Development Program (UNDP), United Nations Centre for Trade and Development (UNCTAD) as well as in bilateral initiatives from Brazil, Thailand and other developed
countries. For example, the transfer of technology and development of local capacity has been assisted by the European Commission, which in 2003 established a grant for domestic drug manufacturing. The priority area was “technology transfer, leading to local production of affordable key pharmaceuticals and commodities in prevention, treatment and care of HIV/AIDS, malaria and tuberculosis,” the Commission offered to finance proposals of up to $US6 million (European Commission, 2006). In November 2006, a German NGO, Action Medeor, partnered with a Tanzanian manufacturer, Tanzania Pharmaceutical Industries (TPI), and was successfully awarded funds for the construction of a new ARV plant.

While there is plenty of research modelling the economic effect of IP on technology transfer, there is a dearth of research describing in-depth the potential factors influencing the development of technology transfer arrangements, such as the ones financed by the European Commission. Most empirical research measures technology transfer only through licensing and FDI. Due to its economic nature, this literature not only omits Maskus’ (2004) concept of imitation as a channel of technology transfer, but also important policy considerations that may influence the development of technology transfer arrangements. Finally, little research addresses why a country or a firm would enter a particular type of technology transfer arrangement to manufacture ARVs, whether through a voluntary license or other means. This research intends to fill this gap, to understand how these initiatives may or may not be affected by IP as well as what factors influence the affordability of these initiatives.
III. A National Issue: Local Manufacture and ARV Affordability

A. The Great Debate: Make or Buy?

The local manufacture of essential medicines in developing countries has been debated since the 1960s. With 95% of the drugs on the WHO Model List of Essential Medicines no longer patented (Bale, 2001), any able manufacturer can produce and sell these drugs. During the 1960s and 1970s, international organizations, particularly UNIDO and UNCTAD, provided financing to improve developing countries’ manufacturing capacity with the goal of reducing dependence on imported drugs (UNIDO 1980; UNIDO, 1984). This was in response to a popular ideology of the time: dependency theory. Dependency theory asserted that the suppression of economic growth in underdeveloped countries, known as the periphery, enabled the flow of resources to and the growth of advanced economies, the core (Amin, 1976).

To counteract the reliance on developed countries, the concept of import substitution was explored. Import substitution suggested that government-induced industrialization could occur through interventionist economic and industrial policies, including government spending and subsidies on national industries and the imposition of trade barriers to limit imports (Baer, 1972; Chang, 2002). From this perspective, local production was seen to not only reduce foreign dependence but also to reduce drug costs, and a number of other reasons to maintain a basic level of manufacturing capacity. These includes, but were not limited to, national health security, achieving industrial policy goals, minimizing adjustment costs (Mayer, 1977), acquiring learning effects (Arad & Hillman, 1979) or preparation in case the supply of imported drugs decreases (Evenett & Hoekman, 2004).
With development of the WHO Essential Medicines Programme in 1975, the focus shifted. Developing countries were encouraged in their national drug policies in to concentrate primarily on establishing an essential medicines list, effectively regulating drugs, pricing, and creating an internal distribution system with the assistance of international organizations, such as WHO. Additionally, the adoption of the TRIPS Agreement in 1995 placed developing countries and LDCs on a path to harmonize the protection of pharmaceutical patents with those of developed countries. Once ratified domestically, legislation further limits local production efforts by excluding the ability of firms to copy and manufacture patent medicines.

Even though the TRIPS Agreement deters local production as a result of patent protection, developing countries consider it to have public health benefits. With the provisions outlined in the TRIPS Agreement and the Doha Declaration of 2001 that prioritize public health over trade and allow developing countries to manufacture patented medicines in cases of national emergency, attention has focused again on aspects of local pharmaceutical manufacturing and the transfer of essential medicines technology. Drugs are manufactured through voluntary licenses, compulsory licenses or by exercising TRIPS transition periods. These strategies can secure access to low-cost essential medicines.

**Defining Affordability**

The primary opportunity for these local manufacturing initiatives to enhance drug access is through affordability. As such, factors affecting affordability are of interest in this research. For these purposes, affordability is defined as the ability of a domestic firm to manufacture good quality ARVs at a cost that is competitive with imported ARVs (within 15%). The 15% price
range is a guideline by the World Bank, which describes a 10 to 15% domestic preference margin for local manufacturers on government tenders (Kaplan & Laing, 2005). This preference margin is used to account for the Cost, Insurance and Freight (CIF) of the bid price of a foreign manufacturer. Therefore, domestic preference is given if the customs duties and taxes that the importer would have to pay exceed 15% of the CIF price of the drugs (World Bank, 2003).

**Buy-Side: Levers to Increase ARV Affordability**

There are a number of measures developing country governments can utilize to increase the affordability of imported ARVs. A few of these measures discussed here include generic drug competition, negotiation with patent holders and bulk procurement.

**Generic Drug Competition.** Generic drugs have lower prices than patented drugs because generics do not carry the sunk R&D costs of the drug discovery process and subsequent clinical trials required to bring a product to market. With generic drugs, the largest costs are associated with production. This essentially makes generic drugs a commodity-based market where, with increasing competition, products are sold near marginal cost. In this way, generic manufacturing shifts a pharmaceutical product from a high-value, low-volume market to a high-volume, low-value market. Requiring international competitive bidding in government ARV tenders ensures a maximum amount of generic competition from large multinational generic drug firms, such as those in India, reducing prices substantially.

Waiting until after the 2005 transition period to enforce product patents in its domestic legislation, India fostered and expanded its generic drug industry. With efforts from AIDS
advocates and international organisations, such as the William J. Clinton Foundation and MSF, India’s generic firms paved the way for dramatic ARV price reduction and now are the major suppliers for developing countries. When generic ARVs first entered the market through Brazil’s manufacturing initiative, patent holders dropped their prices significantly from over US$10,000 pppy to approximately US$727 for the least expensive HAART (3TC+d4T+NVP) in 2001 (MSF, 2007). That same year, however, an Indian manufacturer Cipla shocked the market introducing of a generic triple FDC of these drugs costing US$350 (MSF, 2007).  

With the increase in the number of Indian manufacturers entering the market (such as Ranbaxy, Strides Arcolab, Matrix, and Aurobindo), prices dropped even further. By 2007, the Clinton HIV/AIDS Initiative (CHAI), which advocates on behalf of developing countries’ national AIDS programs to negotiate prices for ARVs with major generic manufacturers, brokered an agreement with Ranbaxy to offer this FDC at US$99 (MSF, 2007). By April 2008, CHAI negotiated agreements with seven generic manufacturers on ARV formulations, active pharmaceutical ingredients (APIs) and pharmaceutical intermediates (MSF, 2007). For example, CHAI negotiated a price reduction of the newly preferred, alternative first-line treatment tenofovir+emtricitabine+efavirenz (TDF+FTC+EFV): from US$487 pppy in 2007 (MSF, 2007) to US$349 in 2008 (CHAI, 2008).

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9 This had implications not only for price, but also treatment effectiveness. This is because the triple FDC’s ease of use could increase adherence to treatment, given that all three drugs are combined in one pill.

10 CHAI has negotiated ARV prices with six Indian manufacturers (Aurobindo Pharma, Cipla Ltd., Hetero Drugs, Matrix Laboratories, Ranbaxy Laboratories and Strides Arcolab), and one Chinese firm (Zhejiang Huahai Pharmaceutical Co.). The ARVs included in the negotiations are: abacavir (ABC), didanosine (DDI), efavirenz (EFV), emtricitabine (FTC), lamivudine (3TC), lopinavir/ritonavir (LPV/r), nevirapine (NVP), stavudine (d4T), tenofovir (TDF) and zidovudine (AZT).

11 Refer to Appendix A for a discussion of alternative first-line treatment regimens.
In the ARV market, the success of Indian manufacturers has further polarized the *make-or-buy* debate for many developing countries and LDCs. With increasing generic ARV competition from Indian manufacturers and price negotiations by the Clinton Foundation for governments and large procurement agencies, such as the International Dispensary Association (IDA) HIV/AIDS Group, United Nations Children’s Fund (UNICEF) and PEPFAR, low-cost generics drugs are available for import by developing countries that do not protect the specific ARV patent.

**Price negotiations with patent holders.** For ARVs where generic competition is not possible due to domestic patent protection, developing countries can enter negotiations with patent holders. As mentioned, the Accelerating Access Initiative (AAI) and its six participating patent holders aim to negotiate ARV prices with governments to increase ARV affordability (as well as assist with a number of other access components) in developing countries. In addition, Brazil and Thailand have been noteworthy in their own efforts to reduce the prices of patented ARVs. In both countries, compulsory licensing threats initiated significant price reductions from the research-based pharmaceutical industry. Brazil’s bargaining power to reduce patent holders’ ARV prices was modelled by Cohen and Lybecker (2005). In a two-level game theoretic model, they showed that the Brazilian government’s credible threat to issue a compulsory license for Roche’s second-line protease inhibitor, nelfinavir, resulted in Roche offering steep price discounts during negotiations. However, Brazil’s bargaining power is unique among developing countries as it has both the manufacturing capacity to produce generic drugs and a lucrative pharmaceutical market in which to sell them. Price negotiations, along with generic production
of ARVs not patented domestically prior to the TRIPS Agreement (such as first-line drugs d4T, 3TC, and NVP), facilitated a more affordable treatment scale-up for the Brazilian government.

**Bulk procurement.** With implementation of a universal ARV access program, it is possible that a government, as a large producer or purchaser, may ensure low drug prices. Bulk purchasing occurs across developed and developing countries for a variety of medicines, for two reasons. First, the purchaser has monopsony power. This means that the purchaser is the only buyer in the market and, as such, has leverage to negotiate price decreases. Second, bulk purchasing tenders large volume contracts. Large-scale purchases enable a manufacturer to use economies of scale to lower its production costs gives buyers volume discounts. For example, the Eastern Caribbean Drug Service (ECDS) is a pooled procurement service comprising nine ministries of health in small island countries of the Caribbean. In its first procurement cycle Huff-Rouselle and Burnett (1996) found that bulk procurement enabled the ECDS to reduce unit costs for pharmaceuticals more than 50%. This reduction was achieved by pooling demand; combining generic and therapeutic alternative bidding; standardizing drug dosages forms, strengths and sizes of packs; and consolidating transport. A similar rationale could be used, domestically or regionally in Sub-Saharan Africa, where governments have universal ARV rollouts in place and large volumes of ARVs are procured. However, research illustrates that appropriate political set-up and political commitment need to be in place to achieve the benefits of bulk purchasing.

*Make-Side: Drivers of Local ARV Production*

For developing countries considering the domestic production of ARVs over their importation, a number of drivers exist in addition to increasing affordability. Some of these drivers include
public health interests (including national security and sustainability of supply), economic interests and technological development interests.

**Public health interests.** Even with the possible benefits of bulk purchasing and price negotiation, drug access concerns increased when the transition period for developing countries under the TRIPS Agreement ended in 2005. India has a long history of manufacturing and supplying cheap generic medicines. India has supplied not only its domestic market, but also the international market, with its high-volume, low-cost drug production, making drug treatment much more affordable to developing country governments and patients paying out-of-pocket. India’s revision of its patent legislation to comply with the TRIPS Agreement, drastically changes the ARV market. The majority of HIV-infected patients receive generic ARV treatment from India, which costs a fraction the price of patented ARVs. Under the mailbox provision set by the TRIPS Agreement, a number of ARVs, including the important second-line protease inhibitors (PIs) lopinavir/ritonavir and atazanavir, are under review by the Indian Patent Office. Additionally, any new drug discoveries will also go through the patent application process. As the major supplier of generic ARVs to the developing world, it is feared that this new patent regime will lead to unaffordable prices for new patented ARVs around the world.

As a result of the changing market dynamics, LDCs feel that their health security is threatened. Sub-Saharan African members of the WTO, who have until January 2016 to adopt patent legislation, have begun to exercise their transition flexibility. This includes Uganda and Tanzania among others. Other countries, such as Zambia and Zimbabwe have issued compulsory licenses citing national health emergencies due to the HIV/AIDS epidemic. Each are taking steps to
emulate the Indian, Brazilian or Thai experience of generic manufacturing to enable price reduction and ensure the sustainability of supply. As mentioned, however, drug firms in these countries generally do not have the manufacturing capacity to produce ARVs unaided and have entered into technology transfer arrangements with generic manufacturers from Cuba, Brazil, India and Thailand.

**Economic benefits.** In addition to public health benefits, developing countries consider local drug manufacturing it to have substantial economic benefits. With the appropriate industrial and technical infrastructure, it is theorized that developing countries can enhance job creation as well as self-sufficiency, reducing foreign-exchange needs and contributing to industrial development (African Union, 2007; Bennett, Quick, & Velásquez, 1997; MSH, 1997; WHO, 2005a).

**Technological capabilities.** Local production is challenging for developing countries, both technically and financially. Levels of manufacturing capacity have been described by a number of sources (Attridge & Preker; 2005; Kaplan, et al., 2003; Kaplan & Laing, 2005; Rovira, 2006; UNIDO, 1980; WHO, 2005a). Three (or sometimes four) levels of production are delineated in developing countries; the levels are discussed below.

*Primary production* includes the conversion of raw materials and intermediates to active pharmaceutical ingredients (APIs). APIs are the biologically active compounds found in drugs that elicit the intended therapeutic effect. This manufacturing process can take place through chemical synthesis, fermentation or extraction of organic chemicals from biological products. Most prominently, developing countries with API capability are India and China. A sublevel of
primary production, often classified as its own production category, is the manufacture of intermediates. An intermediate is an additional step (through purification or molecular change) that can occur during the conversion of a raw material to an API.

_Secondary production_ involves the processing and formulation of finished dosage forms from APIs. This production level is found in countries such as Brazil and South Africa (although facilities in both countries have some API production as well). Most Sub-Saharan African countries have relatively little manufacturing capacity. Correa (2002) found that they, at most, had only reproductive capabilities to produce finished products from imported ingredients (e.g., Nigeria, Kenya and Tanzania).

_Tertiary production_ packages and labels finished products from primary and secondary sources; for example, manufacturing intravenous solutions or oral liquids. Most LDCs only have tertiary production, or, as in Botswana, Swaziland and Senegal, no pharmaceutical industry at all (Correa, 2002a). Generally, countries first develop the capacity for tertiary production, which can help build the requisite skills and experience for higher levels of production over time (Bennett, Quick, & Velásquez, 1997).

Although it is hoped that investment in local manufacturing within a developing country will stimulate technology transfer from abroad, production predominantly involves only processing and finishing products (Kaplan, et al., 2003). Questions then arise about these countries’ capability to manufacture ARVs that are more technologically sophisticated than other products, and supply them more cheaply than imported products.
B. Research on Local Production

Limited research has been conducted on the viability of local pharmaceutical manufacturers producing low-cost medicines, particularly ARVs. Most of the literature that is available is based on reviews, theoretical modelling or Gray Literature. The effect of international trade and IP on compulsory licensing has had its most public manifestation in Brazil, Thailand and Sub-Saharan Africa, where some developing countries suggest that local production of pharmaceuticals is an important solution to ensure a sustainable supply of affordable ARVs in the region. However, local production efforts in developing countries have resulted in varying “success” rates (Kaplan et al., 2003). India and Brazil, as discussed, both have a notable degree of capacity and have made much advancement in providing low-cost generic ARVs, not only domestically, but internationally. Other initiatives have little evidence to prove their viability.

As mentioned numerous times in this Chapter, Brazil is noted for its universal ARV access program, which has seen decreases in ARV prices with the assistance of local ARV production. Making patent legislation conform to the TRIPS Agreement in 1997, Brazil remained able to produce a number of ARVs that had been patented prior to this year. Because of generic local manufacturing initiatives, the price of ARVs decreased 72.5% from 1996 to 2000, compared with a decrease of only 9.6% for imported products (Oxfam, 2001). Since this time, however, Brazil’s ability to compete internationally on price against growing generic industries has remained in question.

Seminal work on Brazil’s ARV pricing was conducted by Nunn and Colleagues (2007). The study found that, when comparing Brazil’s prices for locally manufactured generic ARVs to the lowest international prices of ARVs meeting international quality standards, domestic generic
prices are on average much higher. Additionally, they note that these prices in Brazil are actually increasing while the prices of those generic drugs elsewhere are decreasing. As such, they estimated that Brazil spent an extra US$110 million from 2001 to 2005 by buying local ARVs rather than importing. As Brazil’s generic industry is highlighted as a model system for generic manufacturing, it has important implications for other developing countries considering production. In addition, Nunn and colleagues (2007) compared Brazil’s ARVs with those having met international quality standards, which Brazil’s products have yet to achieve. Cohen (2000) notes the insufficient implementation of drug manufacturing quality regulations in Brazil, including a lack of bioequivalence testing. Although bioequivalence testing of ARVs became mandatory under the Ministry of Health’s National Drug Policy of 2001, not one Brazilian firm or manufactured ARV has received international quality accreditation. These issues signal to other developing countries the difficulty of maintaining a competitive domestic industry of international quality.

There are a number of manufacturers in Eastern Mediterranean countries that supply the majority of essential medicines (60% to 95%) domestically: Egypt, Islamic Republic of Iran, Jordan, Morocco, Pakistan, Syrian Arab Republic and Tunisia. However, as Kaplan and Laing (2005) reiterate, there is no documented evidence of their product price and quality. Among LDCs, Bangladesh is frequently cited as an example of local production initiatives (Kaplan & Laing, 2005; MSH, 1997; Rovira, 2006). In 1982, Bangladesh introduced its National Drug Policy which heavily favoured domestic production over imports. With this new policy, the country was able to increase the proportion of domestically produced drugs from 30% to 80% of total production value between 1981 and 1990 and reduce its dependence on pharmaceutical imports.
(Rovira, 2006). Reich (1995) notes, however, that the Bangladeshi restrictions on pharmaceutical imports resulted in decreases in FDI and fewer new drugs on the market. Reich did not determine the ability of this initiative to lower drug costs over those imported.

Guimier, Lee and Grupper (2004) undertook theoretical research to develop a simulation model (based on research of pharmaceutical firms in West Africa) to determine whether or not domestic drug production in Sub-Saharan Africa could be sufficiently profitable while providing lower drug prices than those of international sources. To do so, they tested three different types of manufacturing initiatives: 1. production of 13 drugs to treat HIV/AIDS, tuberculosis (TB), and malaria (considered the baseline initiative); 2. production of baseline drugs along with eight ethical drugs (to treat diabetes, hypertension, and gastrointestinal ailments); 3. production of baseline drugs along with two over-the-counter (OTC) drugs. Within each initiative, Guimier, Lee and Grupper modelled for a *greenfield* facility (construction of a new plant) and an *extension* case (product addition to an existing plant). Each initiative and its products were assumed to comply with Good Manufacture Practices (GMPs) of the WHO Prequalification Programme.

Guimier, Lee, and Grupper’s (2004) research found a positive net income at the end of three years for each of the local manufacturing initiatives. However, the baseline initiative (focused on drugs for HIV/AIDS, TB, and malaria) was the least profitable because of their specific procurement requirements. Ethical drug production was the most profitable, ARVs intermediately profitable, and drugs for TB and antibiotics were unprofitable. Guimier, Lee and Grupper conclude that domestic drug production can meet the outlined objective to provide lower cost drugs than can be imported, so long as the financial resources are available and are
invested in extensions cases or greenfield plants that produce a variety of drugs (in addition to those for HIV/AIDS, TB, and malaria). They also caution that the ability of an initiative to provide price reductions is sensitive to active pharmaceutical ingredients (APIs) price and market share.

While the research of Guimier, Lee, and Grupper (2004) provide a promising model for developing countries, more often than not, researchers believe local production to be neither cost-effective nor economically sound in developing countries (Bennett, Quick, & Velasquez, 1997; Foster, 1987; Kaplan, et al., 2003; Kaplan & Laing, 2005; MSH, 1997). Some of the most recent work on evaluating local manufacturing initiatives in developing countries is that of Kaplan and Laing (2005). They developed indices that could be used to determine the conditions under which domestic production can compete internationally. In doing so, they determined that a “critical mass” (p. 26) must be reached, in terms of human and technical resources, and industrial and socioeconomic development in order for a domestic drug industry to be viable. Their findings indicate that, for a domestic industry to be globally competitive, the developing country should meet the following criteria: a GDP greater than US$100 billion, a population greater than 100 million, adequate enrolment in secondary and tertiary education, a fairly good competitiveness index rating, and a net-positive pharmaceutical balance of trade. Most developing countries, and in particular Sub-Saharan African countries, do not meet these conditions. This indicates that manufacturing in the region is not likely to be viable (Kaplan & Laing, 2005).
As profit margins on generic drugs can be low, it is very difficult for small local producers in Sub-Saharan Africa to be as efficient as large-scale manufacturers. As a result, a government may end up imposing import restrictions through taxes and duties to maintain local dominance (Cohen, 2001; Foster, 1987). This comes at the cost of affordability; therefore, local manufacturing is difficult to justify unless domestic drug producers are able to match or better international prices. Yet, most developing countries and LDCs are not in the position of Brazil, India, and Thailand because they neither have the appropriate manufacturing capacity to produce ARVs nor the political commitment to support these initiatives. Even though LDCs can use the 2016 transition period, it is difficult for them to exercise it given their capacity constraints (unless they are given technical and financial assistance). For developing countries that were required to comply with the TRIPS Agreement in 2005, lack of manufacturing capacity makes compulsory licensing threats less credible than those used in Brazil or Thailand. As such, power dynamics during their drug negotiations are presumably very different and may not lead to same price reductions.

Cohen (2004) stresses developing countries considering the manufacture of patented pharmaceuticals face a variety of constraints in addition to issues of manufacturing capacity and negotiations with patent holders. These include, but are not limited to, abiding by stipulations in bilateral trade agreements, ensuring that WTO monitors the procedures, and demonstrating appropriate technological capabilities as well as the necessary administrative infrastructure to absorb the technology. When drugs are produced locally, developing country governments have difficulty assuring that quality pharmaceuticals meet the GMP standards that WHO requires. This may not impede access in the short term, but it may affect the quality of treatment as well as
C. Political Aspects of Technology Transfer and Domestic Drug Production

Economic scholars suggest that, as a source of technological knowledge and development, technology transfer is increasingly significant in a developing country’s industrialization and economic growth (G. Cohen, 2004). However, unlike economic research might suggest, technology transfer is not apolitical (Grace, 2004; Lee, 1997; Maskus, 2004). As international markets for technology transfer are inherently subject to failure, there is strong justification for public intervention (Maskus, 2004). Furthermore, essential medicines are not ordinary commodities that can be left to market forces. Essential medicines, by definition, are those that “satisfy the priority health needs of the population” (WHO, 2002, p. 1) and are selected due to the prevalence of diseases as well as the safety and cost-effectiveness of medicines. Since these medicines are necessary to the health of all individuals (whether to cure, treat, or prevent illness), access to them is viewed by many as a human right (Forman, 2005; Hogerzeil, 2006; Shaley, 2004). Seeking to achieve public health objectives, governments must face the responsibility of ensuring access to essential medicines.

Policy decisions about whether to import essential medicines or to promote their local manufacture, therefore, should be based on a thorough situation analysis and a critical appraisal of the feasibility and economic sustainability of domestic production (Kaplan, et al., 2003;
WHO, 2005a). Investment in local production is efficient only when pharmaceuticals are produced more cheaply than imported (Kaplan, et al., 2003). This often leads to a conflict between industrial policy goals and health policy objectives both within and across countries (Jacobzone, 2000). Policies to promote a domestic drug industry often contrast low-cost public health goals with profit-maximizing industry objectives. Cohen (2001) also notes that political considerations are often put before economic ones. Govindaraj, Reich, and Cohen (2000) caution that a politically strong, domestic pharmaceutical industry can often persuade a government to purchase locally manufactured pharmaceuticals, even if this cost more than importing drugs. Developing countries have often overlooked the economic arguments against public production as powerful interest groups can benefit from the market monopoly (Cohen, 2001). As such, policies promoting the domestic drug industry can, at times, result in inefficient public sector production where slow start-ups and cost inefficiency affect the population’s access to drugs (Govindaraj, Reich, & Cohen, 2000).

Policy makers must then also be aware of the potential ownership implications of domestic pharmaceutical firms. Globally, private firms manufacture the majority of pharmaceuticals (Kaplan, et al., 2003); however, some countries, such as Brazil, China, Egypt, Nepal, Sri Lanka, and Indonesia, some centrally planned economies (Bennett, Quick, & Velásquez, 1997), and Sub-Saharan African countries still have state-owned facilities. Brazil, the most prominent example, has 18 state-owned laboratories. Six of these laboratories manufacture ARVs\(^\text{12}\) (Cassier & Correa, 2007). In 1999, 47% of Brazil’s ARVs were procured from local firms, 92.5% of which were state-owned. This increased to 63% local ARVs in 2001, which amounted to 43% of

\(^{12}\) Far-Manguinhos/FIOCRUZ/Ministry of Health, Fundação para o Remédio Popular/SP, Laboratório Farmacêutico do Estado de Pernambuco, Fundação Ezequiel Dias/MG, Indústria Química do Estado de Goiás, and Instituto Vital Brasil/RJ
expenditure (Galvão, 2002). As mentioned, the case of Brazil and its manufacturing capacity is quite unique among developing countries and may have limited generalizability to other countries.

Currently, the World Bank and WHO discourage the use of state-owned production to increase drug access (Rovira, 2006). This is because infrastructure development often becomes the prime focus for government and leaves insufficient resources for state-owned enterprise management and execution. As such, governments can find them a financial drain (Marton, 1995; UNIDO, 1997). A recent update of WHO’s guidelines for implementing national drug policies suggests that production of medicines and vaccines is best left to the private sector. The role of governments should include increasing the quality of locally produced medicines and building industrial capacity, by strengthening its drug regulatory authority (DRA) and arranging for human resource training in GMP (WHO, 2005a).

When governments consider local production, the most important objective should be delivery of high-quality essential medicines at affordable prices. Particular attention should be paid to the costs, drug quality, and prices with which the locally produced medicines will compete. Long-term contribution to and sustainability of technology transfer programs in developing countries, particularly in Sub-Saharan Africa, depends as much on political and institutional factors as on the technology being promoted (Lee, 1997).

Finally, implementing local manufacturing initiatives under compulsory licenses may deter FDI in local manufacturing, as well as R&D investment in neglected diseases that afflict populations
of developing countries (Chien, 2003; Correa, 2003). These caveats are strengthened by the fact that the United States Trade Representative (USTR) placed Thailand and Brazil on its Special 301 Report after the two countries implemented compulsory licenses for ARVs lopinavir/ritonavir and efavirenz. To exploit generic manufacturing fully, both political commitment and technical capability to produce these drugs are required because a country may face pressure, lawsuits, and threat of trade sanctions from developed countries (Chien, 2003).

**Policy Incentives**

The viability of domestic manufacturing initiatives is influenced by many factors noted in the previous section, such as manufacturing capacity. Also important is the ability of governments to use a variety of policies to influence activity in the market (Bennett, Quick, & Velásquez, 1997). Government policies can actively support, remain neutral, or impede local manufacturing. To encourage local production of essential medicines, it is imperative that policies are developed to improve the prospects for access to low-cost, good quality, effective medicines (MSH, 1997). Such measures may include regulatory and legal provisions, industrial development incentives, economic incentives, and import duties, each of which is discussed below.

**Registration.** Registration requirements in each country promote the availability of safe, effective, good quality essential drugs. Drug regulatory authorities (DRAs), such as the FDA, control the products placed on the domestic market by evaluating each product’s dossier. The registration process in developing countries, however, can often be burdensome or even corrupt and limit a manufacturer’s incentive. Enabling a registration process that is quick, fair, and affordable to local firms is more likely to attract investment (MSH, 1997). DRAs can also
introduce fast track registration times, often through a higher fee, for essential medicines. Kaplan and Laing (2003) recommend fee reduction as an appropriate public policy instrument in developing countries, to promote the registration of generic drugs. They also caution, however, that lower fees may cause substantial delays as low-quality manufacturers may begin to submit applications “haphazardly” (p. 10).

**Good Manufacturing Practices (GMPs).** GMPs are standards adopted by domestic DRAs, and internationally by WHO, that serve as guidelines for industry, to ensure the production of safe and effective medicines. Most countries that have DRAs also have their own GMP standards, which may or may not be align with those of WHO. In a variety of countries, such as Colombia, Ecuador, Nepal, and Venezuela, the ministries of health have arranged training in GMPs for local private producers (Bennett, Quick and Velásquez, 1997). As mentioned, the WHO Prequalification Programme was introduced in 2001 to help developing countries without stringent DRAs assess the quality of ARVs on the international market. The program publishes a list of certified products and manufacturers that meet quality and safety standards to facilitate the public procurement process (WHO, 2004c). Additionally, under PEPFAR, the FDA has a fast-track system for generic ARV approvals. Although these requirements may not initially encourage investment in local production, they do ensure the viability of high-quality local industries and contribute to their regional and global competitiveness.

**Intellectual Property.** The TRIPS Agreement states that the protection of IP, such as through patents, should increase the transfer of technology to developing countries. Put simply, multinational patent holding pharmaceutical firms are more willing to introduce new products in
developing country markets that have adequate patent protection. This may increase access to
drugs as well as provide an impetus to FDI, licensing, technology transfer, and R&D investment
(Cohen & Illingworth, 2003). Compulsory licenses, local working provisions, and other generic
policies can be included in domestic legislation to maintain some degree of flexibility and
safeguard against any detrimental effects of adopting stronger patent protection. Weak patent
protection can also attract home-grown generic industries that reverse engineer of
pharmaceutical products to produce low-cost copies of patented medicines, as seen in India and
China.

a. Compulsory Licensing. As discussed previously, compulsory licensing allows unauthorized
use of patents by third parties, such as developing country governments, sometimes with a small
royalty paid to the patent holder. It is generally agreed that the royalty should be no more than
5% (Love, 2004). Compulsory licensing can be invoked in the interest of public health, national
emergencies, or when voluntary licensing agreements cannot be reached. In 2004, compulsory
licenses for ARVs were issued in Zambia, Mozambique, and Zimbabwe and, in 2007, in
Thailand and Brazil. As mentioned, compulsory licenses remain controversial among WTO
member countries with experiences in Brazil and Thailand resulting in threats of unilateral trade
sanctions by the USTR.

b. Local Working Requirements. With a local working requirement in place, patent rights are
contingent upon patent holders setting up domestic production within an allocated timeframe;
otherwise, they are subject to compulsory licensing. Even though local working provisions are
not specifically in violation of the TRIPS Agreement, given the USTR’s complaint against
Brazil’s local working provision, the political feasibility of including and invoking such a clause is questionable (Cohen, 2001).

c. Generic Policies. Policies that require generic labelling of drugs, generic substitution by pharmacists, and allow differential profit margins on drugs might all encourage investment in a local industry. For example, Brazil both supports local production and decreases its cost by requiring all government contracts to procure generic drugs and all pharmaceutical prescriptions to use generic names (Cohen & Lybecker, 2005). Also, an early working or research exemption, called the Bolar provision\(^\text{13}\) authorizes generic product development during the life of the pharmaceutical patent. This can include access to innovator and product safety data, production tests on patent protected products as well as early generic testing for bioequivalence and stockpiling of the drug prior to patent expiry. Provisions of these types can be found in other countries, such as Canada and Argentina, and allow generic drugs to penetrate the market immediately once the patent life expires. Like compulsory licenses, the Bolar provision is controversial among WTO member countries. In November 1998, the European Community filed a complaint with the Dispute Settlement Body of WTO against Canada’s Patent Act for its authorization of the Bolar provision, which the European Community considered an infringement of the 20 year patent term awarded under the TRIPS Agreement. Although WTO upheld Canada’s patent legislation in 2000, this case highlights the tension among WTO members over the terms of the TRIPS Agreement and the difficultly of implementing to domestic legislation certain measures that may be ambiguous in language.

\(^{13}\) Also known as the Roche-Bolar provision, named after the court case between generic manufacturer Bolar Pharmaceuticals and patent holder Roche Products.
**Economic and Industrial Incentives.** Direct subsidies, access to start-up capital, training support, and tax abatement can all decrease industry start-up costs (MSH, 1997). Incentives for R&D may or may not be useful, depending on the level of production desired by the home government. India places limits on the share of the domestic industry foreign companies can own. Additionally, a country may require the repatriation of profits by foreign-owned local firms to deter multinational firms and increase the market advantage of local manufacturers. Local subsidiaries, joint ventures, minority/majority ownership shares with international firms, and licensing agreements can encourage the transfer of technology and technical skills to developing countries and strengthen developing country production capabilities (Bennett, Quick, & Velásquez, 1997). Depending on the production level and strength of the local economy and market, providing incentives for one or a number of these venture types may be a desirable form of local production support. Many local production facilities in developing countries must import the raw materials, which incur a large percentage of production costs; therefore, it is imperative that local firms have access to foreign exchange. As only 5% of developing country pharmaceutical products are exported (MSH, 1997), legislative incentives to promote exports are unlikely to influence investment decisions.

**Import Duties.** Depending on the desired level of production, duties may be lowered, removed, or increased on specific imports. An equal playing field for local producers and importers can be created through equal tax treatment of raw materials and finished products. Also, reducing taxes on production equipment and packaging can further encourage local production, while charging duty to foreign manufacturers on their imported products can explicitly give preference to locally manufactured products.
As discussed, there are a variety of means through which a developing country may encourage the development and growth of pharmaceutical firms locally. It is important to understand how these policies may impact the development of technology transfer arrangements, positively or negatively, as well as the affordability of locally produced medicines. The interaction of these factors in the developing country context is not well understood and, as such, requires further investigation. This is particularly true in the case of ARVs where, faced with acute and long-term treatment needs, developing countries are looking to local manufacturing as an alternative to provide access to affordable ARVs.

**Significance of the Study**

In the context of the HIV/AIDS epidemic in highly affected developing countries, it is possible that a variety of strategies may lower ARV prices and increase access to patented medicines (Chien, 2003; Matthews, 2004). Pursuant to provisions within the TRIPS Agreement, the first cases of local ARV manufacturing in Sub-Saharan Africa developed through technology transfer arrangements. As controversially stated in Article 7 of the TRIPS Agreement, the protection of intellectual property should result in an increase in technology flow between nations. However, in-depth research has yet to analyze this statement within the public health lens of ARV access, where over 70% of HIV-infected Sub-Saharan Africans, in clinical need of ARVs, remain without access to treatment (UNAIDS, 2008). No empirical research has been conducted on diverging ARV technology transfer types; therefore, it is not well understood what domestic conditions lead to the development of these arrangements.
In addition, the recent resurgence of local ARV manufacturing initiatives has been sparked by fears in both developing countries and LDCs, that the current import supply cannot meet countries’ ARV needs and that the cost of procurement will grossly exceed government and donor-assisted budgets. Yet, little country-level evidence has been used to assess these initiatives and the conditions that will affect local ARV affordability.

These manufacturing events issue a call for a multi-disciplinary comparative case study to address current questions surrounding ARV production in Sub-Saharan African countries. This research contributes to the sparse literature a framework to assess the domestic conditions that affect the development and implementation of ARV technology transfer arrangements and local production efforts. The results of this study will be useful to policy makers, researchers, and institutions involved with ARV procurement and technology transfer. This research can inform governments on the appropriate policies and incentives to put into place to attract the desired production efforts and type of transfer arrangement, whether from a patent holder in a voluntary licensing arrangement, or from another source (such as a generic firm or multilateral aid agency) in an imitation arrangement. This research also can be used to not only inform developing countries of the important opportunities, but the significant constraints, to low-cost ARV production. For researchers, these case studies assist to develop further theoretical propositions and provide a framework to benchmark future research in the field of technology transfer, ARV manufacturing, and ARV affordability in developing countries.
Conceptual Framework

Research studying technology transfer arrangements and the affordability of locally manufactured ARVs is quite complex with many possible influencing factors. As little empirical research has been conducted in this field, the research of this dissertation is not set firmly within one particular school, but borrows concepts of a number of different theories to guide the research process in an interdisciplinary approach. This research draws loosely on frameworks and important concepts emerging from policy analysis, strategic management, and industrial organization. These theoretical approaches were consolidated into an integrated framework to address the complexity of policies involving the pharmaceutical industry, its market characteristics, as well as international interests in developing countries. An interdisciplinary framework also enables flexibility in the research to allow salient themes to emerge, including an exploration of these themes. The results of the analysis could then situate within this framework or develop in a new context.

General Framework – Policy Analysis

Policy analysis provides the overall framework that guided this study. Anderson (1975) defines policy as a course of action taken purposefully by an individual, or individuals, in order to deal with a problem or matter of concern. This action can take place at the national, regional, or international level as well as at the level of the firm or organization. Policy analysis has varying definitions made by varying scholars. Heclo (1972) notes that policy analysis has many different forms emanating from a large variety of theories, and it can vary from description to prescription. In doing so, policy analysis draws on concepts from a number of disciplines: economics, political science, sociology, public administration, and history. Policy analysis
emerged as a sub-discipline in the late 1960s. At that time it was predominantly used in research in the United States. Although policy analysis is an established research and academic discipline in developed countries (Fischer, 2003; Parsons, 1995), its application to developing countries has been limited, and the health sector, in particular, appears to have been neglected until recently (Walt & Gilson, 1994).

Traditionally, health policy analysis focused on the content of specific policies, rarely taking into account the context of why these policy decisions were made or the actors and processes that were involved in their design and implementation. In response, scholars developed new approaches to health policy analysis specifically for developing countries (Barker, 1996; Reich, 1995; Walt, 1994). This new paradigm integrated politics, process, and power into the study of health policy.

Walt and Gilson (1994) suggested that an inclusive policy analysis model could make the difference between effective and ineffective policy choice and implementation (Walt & Gilson, 1994). This model is based on the understanding that policy is a product of, and constructed through, political and social processes. The roles of political institutions and public bureaucracies in policy making are important aspects of this analysis, but it also acknowledges and considers the influence of non-state actors, including private sector and civil society organizations14 as well as international agencies in developing countries.

Research in this field is applied and multi-disciplinary. It has a broad social science base, is

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14 Civil Society is defined as both informal and formal groups and/or organizations that act independent of the government and the market. These groups are outside of public and private sectors and can include voluntary organizations, community groups, charities, and non-government organizations.
problem focused, and seeks to strengthen policy making (Parsons, 1995; Gilson & Raphaely, 2008).

Walt and Gilson (1994) argue that their policy analysis technique provides a comprehensive framework for analyzing health reform, as opposed to approaches that concentrate on the technical features or content of a policy. In addition to context, the analytic model comprises the concepts of policy context and process as well as how state and non-state actors influence policy. Figure 1 illustrates the relations of each of the model’s concepts. Key to analysis, Walt and Gilson emphasize that framework must be viewed as a dynamic process as “the policy environment is continuously shifting, transforming relations between groups and between institutions” (1994, p. 366). The authors refer to Warwick (1979), who poignantly terms his work a transactional analysis instead of policy analysis, to reflect this dynamism as well as the complexity of the interactions.

**Figure 2: General Conceptual Framework – Policy Analysis**

![Diagram](image)

Adapted from Walt and Gilson (1994).
Within Walt and Gilson’s policy analysis model *context* encompasses political, economic and social factors. Whitehead (1970) suggests the context of policy making comprises the socio-structural determinants of a country, such as social class, self-interest of politically powerful sectors, economic ideologies, historical traditions (e.g., the experience of war), as well as the formal properties of political institutions. The policy *process* is best summarized by Grindle and Thomas (1991). It focuses on actors, agenda setting, decision making, and the implementation of reforms. Process is the way in which policies are initiated, developed, or formulated (Clarke, 2005). It illustrates “how issues get on to the policy agenda, how they fare once there” (Walt & Gilson, 1994, p. 355). Finally, *actors* are both state and non-state and can be an individual, a group of individuals, or an organization. These actors can be at the international, national, or sub-national level (Walt & Gilson, 1994). Gulhati (1990) describes how political variables influence national policy makers, such as foreign donors and investors, the size of the civil services, and the characteristics of a country’s political leaders.

Walt and Gilson (1994) caution that the model simplifies an extremely complex set of interrelationships, which gives the impression that each can be considered separately. Although this model may provide a simplistic overview of complex relations, actors at the centre are influenced by the context in which they live and work, which in turn affects both the process of policy making and its content. These relations shape policy and its implementation. All levels of policy making, from international to sub-national, have made use of Walt and Gilson’s framework (Beyer 1998; Birungi, et al., 2001; Crichton, 2008; Gilson, 1998; Green, 2000;

In this research, the conceptual framework of Walt and Gilson also guided both the data collection and analysis to ensure that the research questions appropriately addressed all of the necessary elements inside and outside the policy sphere. Given the complex system in which technology transfer and local manufacturing initiatives take place, it is important to ensure that all aspects of policies, their context, content, process, and the actors are understood and considered. As well, the interaction of all these concepts was kept in mind throughout the process of this research. This framework assisted to guide the data collection providing a comprehensive lens through which to view the cases.

This research remained open to all possible actors involved who might affect the technology transfer and local manufacturing process. Some of these actors were anticipated to include government officials and policy makers (particularly in the ministries of health and trade and industry), international organizations (including the Global Fund, PEPFAR, WHO), and civil society organizations in each respective country, such as Action Medeor in Tanzania and Treatment Action Campaign (TAC) in South Africa. This research focused on the central actor, the pharmaceutical industry (both domestic and international), the relationships between these firms, as well as the other actors involved. As domestic firms are directly involved with local production initiatives, transfer of technology and ARV affordability, it was important to integrate Walt and Gilson’s conceptual framework with frameworks that specifically address the vantage point of pharmaceutical firms. As a result, to answer the macro- and micro-level research
questions, portions of other conceptual frameworks were borrowed: from the fields of strategic management and industrial organization.

**Macro-level Framework – Strategic Management**

Strategic management researchers assess firms by the industries, business, and political environments in which firms are involved. The concept of *strategy* came about in the 1960s. Using strategy, firms set goals, meet changed circumstances, new technology, competitors, and deal with new social, financial, or political environments (Lamb, 1984). Strategy embodies the joint selection of the market where a firm competes and the policies that define how it will compete. Strategy is not necessarily a single decision, but a collection of resource allocating decisions and implementing actions (Dobbin & Baum, 2000). As a result, strategic management theorists draw not only on multiple paradigms, but on multiple disciplines, including economics, psychology, and sociology (Dobbin & Baum, 2000). This research utilizes strategic management concepts for their practical applications. For example, Rumelt, Schendel, and Teece (1991) state that strategic management, as a field of inquiry is firmly grounded in practice and that:

> The field has not, like political science, grown from ancient roots in philosophy, nor does it, like parts of economics, attract scholars because of the elegance of its theoretical underpinnings. Rather, like medicine or engineering, it exists because it is worthwhile to codify, teach, and expand what is known about the skilled performance of roles and tasks that are a necessary part of our civilization. (p. 2)

Practical in nature, strategic management builds theory to explain and predict a firm’s success and failure. Is concerned with creating efficient organizations by studying their “creation,
success and survival, as well as with understanding their failure, its costs, and its lessons”
(Rumelt, Schendel, & Teece, 1991, p.2)

This strategic management approach grounded the work of Goel Cohen (2004) in Technology
Transfer: Strategic Management in Developing Countries. Whereas previous research examined
the financial and economic aspects of technology transfer (Glass & Saggi, 1995; Helpman, 1993;
Yang & Maskus, 2001), Cohen suggests that they do not sufficiently understand the technology
transfer process as a whole. He reflects on the lack of a consistent theoretical framework to
understand the process behind the transfer of technology to developing countries. He calls for a
model of technology transfer with a new interdisciplinary approach, based on both practical and
theoretical elements, strategic management.

The framework developed by Goel Cohen (2004), and adapted from Buckley and Casson (1976),
informed my macro-level research question. This framework defines four factors that affect the
development of technology transfer arrangements to developing country firms: 1.
international/region-specific factors; 2. nation-specific factors; 3. industry-specific factors, and 4.
firm-specific factors. The first two encompass external elements pertaining to the process of
technology transfer, such as government regulations, international relations and agreements,
policy-based constraints, strategic advantages, and facilities provided by international
institutions. The characteristics of a technology, the type of transaction, and the mode of transfer
are industry-specific factors that are internal elements of technology transfer. Finally, firm-
specific factors affect the two-way transfer between supplier and recipient. This framework,
then, not only considers recipient skills, technological capabilities, and the institutional support, but also supplier strategy and experience in technology transfer.

Goel Cohen (2004) suggests that multinational corporations (in the case of this research, patent holders), as the main technology suppliers, tend to dominate the process of technology transfer. Also, their goals are generally removed from those of the recipient firm and the interests of the developing countries. During the technology transfer process, domestic governments tend to maintain a more passive role in the process. Cohen illustrates the relationships between the key players in the transfer of technology, at both the international and national levels. He demonstrates that policy making for the transfer of technology depends on the developing country government’s relationship and agreements with the UN, its related departments, and the suppliers of the technology.

Goel Cohen (2004) conceived new models for technology transfer, compartmentalized into micro-level and macro-level frameworks. His micro-level framework (Figure 3) conceptualizes the relationship between the developing country, the technology supplier, and the developing country firm, but omits the relationship that these institutions have with international organizations. Similarly, his macro-level framework (Figure 4) includes the relationships of the developing country and technology supplier with international institutions, but omits the role of the developing country firm. This macro-level framework suggests that technology transfer is affected only in a one-way, indirect manner from international institutions to developing countries and technology suppliers.
Figure 3: Cohen’s (2004) Micro Conceptual Framework for Technology Transfer

Figure 4: Cohen’s (2004) Macro Conceptual Framework for Technology Transfer
This research, however, argues that the model neglects to identify the reciprocity of this relationship given that the policies of international institutions derive from pressure and influence by developed and developing country interests. In addition, international institutions are narrowly defined as UN-related organizations. Given the importance of other international institutions in shaping technology transfer and local ARV manufacturing initiatives, NGOs (such as MSF and the Clinton Foundation) as well as bilateral and multilateral agencies, (such as the WTO, Global Fund, PEPFAR and the European Union) were included into the research framework.

For the purposes of this research, Goel Cohen’s two levels were integrated and adopted as one framework in Figure 5. Here, the interaction of governments and firms with international organizations is two-way reflecting dynamic and highly political relationships. Also incorporated within the new model are the four characterises, specified by Buckley and Casson (1976) and Cohen (2004) that influence technology transfer arrangements. Finally, in this model, all elements described do not act in isolation; instead, they interact within a political, social, and economic environment where context, content, process and actors also come into play, as illustrated by Walt and Gilson (1994) in the general policy analysis framework. All these relationships must be understood for an appropriate assessment of any technology transfer arrangement.

Therefore, to answer the macro-level research question of this dissertation, Walt and Gilson’s (1994) policy analysis framework provided the overall lens through which to view the case and collect and analyze the data. Then, technology transfer framework (Figure 5) helped to identify
the key actors involved and conceptualize how these actors interacted at the international, national, and firm levels. During data collection the model in Figure 5 also assisted to target documents for analysis and formulate questions for interviews in order to understand the factors affecting the development of technology transfer arrangements.
Micro-Level Framework – Structure-Conduct-Performance Paradigm (SCP)

Adapted by strategic management theorists, the structure-conduct-performance (SCP) paradigm is rooted in industrial organization and was developed by Bain (1956, 1968), Clodius and Mueller (1961), and Slater (1968) among others. The SCP model balances formal structures of
economic theory and empirical observations of organizational experience in imperfect markets (Hai, 2003). The adapted model used for this research is seen in Figure 6.

The basic tenets of SCP model are this: the structure of the market affects the conduct of the firm in the market which, in turn, affects the market’s performance. Structure is the stable dimensions of an industry which create the context for competition to occur (Bain, 1972). Crucial to structure is the number and size of firms, their product differentiation, and the characteristics of demand for the product (Bain, 1968). One of the most important components of structure is the barriers a firm encounters to entering the market (Bain, 1956). These include the features in the market that influence both competition and price (Hai, 2003). Conduct relates to the behaviour of the firm and its decisions about key factors, such as pricing, quality, advertising, R&D, and choice of technology. According to Stern and colleagues (1996), market performance is a multi-dimensional concept and is defined broadly. Within strategic management, it can be seen as profitability of the market (allocative efficiency), cost-minimization (technical efficiency), or innovativeness (Porter, 1981). Performance, here, is assessed by its social efficiency.

Performance can mean reducing a company’s profits to a purely competitive level that would lower prices, and thereby increase social efficiency. Performance can be measured by indicators such as price, cost, and volume of output (Bressler & King, 1979). As a whole, the SCP model suggests that, as the number of firms in the market increases, their market power decreases (structure), firms begin to set prices more competitively (conduct), and the price of the product moves downward toward marginal cost (performance). Generally, greater market power relates to lower social efficiency and vice versa.
Figure 6: Micro-level Conceptual Framework—Factors Affecting ARV Affordability

Adapted from Bain (1959), Scherer and Ross (1990), and Harrison (2004)

Direct mechanism  
Indirect mechanism
The work of SCP scholars was later modified to include the role of government (Scherer, 1970). Procassini (2000) suggests that the SCP model is generally applied to a domestic industry, but it can also be applied in more than one country or to a global industry. Therefore, the outcomes of this SCP model are applicable not only to firms entering the market, but to public policy makers at both the national and international level. Wills (1974) and Kotler and Zaltman (1971) suggest that a government has two main functions: first, to provide goods and services of public interest and, second, to regulate the efficiency of private businesses to supply these goods and services. Policy makers in ministries of health as well as trade and industry need to balance the health security of their countries with the interests of their domestic industry.

In the pharmaceutical industry, government was incorporated into the model as a means to identify the driving force behind strategies used by industry to secure greater IP enforcement and strategies used by governments to maintain a degree of equitable access (Harrison, 2004; Scherer and Ross, 1990). This is because Scherer and Ross (1990) and Harrison (2004) suggest that policy, using legislation or regulation, causes changes in market structure and market conduct and, as such, defines the criteria for market performance. Therefore, governments must determine not only consumers want, but need, and must ensure proper product planning, distribution, and pricing to affect the desired result (Hai, 2003). Often influenced by the goals of the administration in office or international relations, the structure of the market can change quickly. As a result, the relationship of governments in developing countries to their domestic industries is both dynamic and critical.
Although the SCP model was adapted to include the influence of government policy on market dynamics, this research felt that one factor was missing: the role of key stakeholder groups, such as civil society organizations, international organizations, and pharmaceutical industry groups. These stakeholders often influence public policy through political pressure, lobbying and international treaties. As seen in Figure 6, stakeholder groups react to market performance and, based on their position, push government to make appropriate policy changes within market structure or conduct to achieve the desired outcome (such as policies to reduce the cost of medicines on the market).

McWilliams and Smart (1993) caution scholars who adapt the SCP paradigm of industrial organization into the study of strategic management. They feel this adaptation is pervasive and gives little consideration to competing paradigms in economics. Due to the interdisciplinary nature of this research, however, the intended use of this model is not explicitly concerned with the SCP model’s strict theoretical underpinning. Quite simply, this model was used as a guide to frame domestic industry in order to collect and analyze data. This model helped to consider the important factors that influence the environment of domestically manufactured ARVs and find the salient features that influence the firm’s performance with respect to affordability.

Another limitation to this model in Figure 6 is its endogeneity. There is a dynamic relation between many of these factors. Although market structure influences the way a firm behaves, the way a firm behaves and the market performs also affects the structure of the market (often seen through changes in regulations). For example, a government’s introduction of pharmaceutical patents impacts the structure of the market by limiting the number of firms manufacturing the
product. As a result of the limited competition, the firm keeps its prices high. This leads to high profit, but low affordability. Given this performance, the government may then intervene and change policies to elicit a different response, such as allowing the entry of generic drug manufacturers through compulsory licenses. Also, policy makers armed with knowledge of market entry barriers can create incentives to encourage market entry, in the form of subsidies, tax rebates, or market exclusivity. This has important implications for this research and reminded the researcher throughout data collection and analysis of the cyclical relationship many of these factors have with one another. Within the data collection and analysis, the research was then cautious in attributing cause-and-effect relationship and rested more broadly on the interplay of these factors and their important elements. To assist this process and to answer the micro-level research questions of the dissertation, the SCP model was integrated with Walt and Gilson’s (1994) general policy analysis framework. This ensured the social, political, and economic dynamics as well as their context, their processes, and their influencing actors were given appropriate consideration understanding how they affect the dynamics of ARV manufacturers and their market, and thus the affordability of locally produced ARVs.

**Concepts in Research Analysis**

**Technology Transfer Definitions**

To assess the broad notion of technology transfer in the literature and defined in this dissertation, this research focused specifically at its conduit, technology transfer arrangements. This research defined technology transfer arrangements as the relationship between the technology supplier and the technology recipient. This term is shaped by the status of the technology supplier: either
a patent holder (a voluntary licensing arrangement) or an unauthorized supplier (an imitation arrangement).

Within the macro-level research question, the technology transfer arrangement type is the outcome, and factors that explain the development of these technology transfer arrangements are of interest. Using the adapted model of Cohen (2004) and Buckley and Casson (1976), detailed in the conceptual framework, these factors are categorized as international, nation-specific, industry-specific, and firm specific:

1. **International/region-specific factors**
   
   a. International agreements – the content and number of bilateral, regional, and multilateral trade and investment agreements. Generally, each aims to promote free trade or investment between countries. Regional agreements are found in the East African Community (EAC, includes Tanzania, Kenya, Uganda, Rwanda, and Burundi), the Southern African Customs Union (SACU) between South Africa, Namibia, Botswana, Lesotho and Swaziland and the Southern African Development Community (SADC) between 14 member countries. Multilateral agreements include the TRIPS Agreement, the European Union–Africa, Caribbean, Pacific Partnership Agreement as well as the European Union’s Trade, Development and Co-operation Agreement (TDCA) with South Africa. Bilateral trade agreements include the United States–SACU Free Trade Agreement and the United States–South Africa Trade and Investment Framework Agreement.
b. Civil society and international/bilateral organizations – the presence of organizations (such as voluntary, non-government, and activist organizations) within the country and their strategy for lobbying government and pharmaceutical firms at the national or international level. They include international organizations such as WHO, UNAIDS, UNIDO, and the Global Fund; bilateral organizations such as PEPFAR; non-government organizations, such as MSF, CHAI, Action Medeor (in Tanzania); and TAC (in South Africa).

2. Nation-specific factors/Government policies

a. Government regulations

i. Intellectual property legislation – the terms and conditions of pharmaceutical patents.

ii. Industrial policy – the strength of industry-friendly policies. Industry-friendly policies can include government subsidies or tax relief on investments as well as exemption from import duties for raw materials and machinery.

iii. Health policy – the strength of universal ARV access as a health policy objective. This includes treatment targets, available resources, and ARV tender regulations. This may include preference for domestic manufacturers.

iv. Science and technology policy – the development of R&D policies for innovation, education, and the training of human resources.

b. Strategy– national goals for health security, self-sufficiency, employment rates, foreign exchange, or access to essential medicines.
c. Civil society and bilateral/international organizations – As mentioned, the presence of organizations within the country and their strategy for lobbying government and pharmaceutical firms at the national or international level.

3. **Industry-specific factors**
   a. Characteristics of technology – ability to support the technology within the country.
   b. Mode of transfer – the way in which pharmaceutical technology is commonly delivered: data, license, personnel, published material, reverse engineering, interpersonal communication, collaborative agreements, etc.

4. **Firm-specific factors**
   a. Supplier firm
      i. Strategy – the firm’s objectives and terms of the transfer agreement, such as licensing fees, royalties, restricted markets, and quality assurance testing requirements.
      ii. Experience in technology transfer – the number of previous transfer experiences with firms in developing countries as well as their role in the transfer.
      iii. Ownership – whether the firm is private, state-owned, or mixed.
   b. Recipient firm
      i. Technological capabilities – the number of products and its production base in ascending order of complexity: packaging of finished products only, development from intermediates or formulated from active pharmaceutical ingredients (APIs), innovative capabilities, and a strong R&D base.
      ii. Ownership – whether the firm is private, state-owned, or mixed.
iii. Institutional support – the commitment and services available to the recipient firm within the developing country environment. For example, the ease of drug registration, GMP guidelines, and training available to personnel.

iv. Experience in technology transfer – the number of transfer experiences the firm has, with both developed and developing country firms, as well as their role in the transfer.

v. Strategy – the amount of competition within the market and firm’s objectives, such as providing public and/or private markets, pricing schemes, long-term production and innovation goals.

This guide assisted data collection through key-informant interviews, documents and observations (as described in Methods). Use of the guide in data analysis enables these and other important factors to emerge from the research.

**Affordability Definitions**

The concept of access is most generally used to in the essential medicines literature when discussing the implications of the TRIPS Agreement and the potential outcome of domestic drug production. However, for the purpose of this research, access is understood by the factors affecting one of its components, affordability. Affordability is the primary means for local production to impact drug access. As mentioned, this research defines affordability as the ability of a firm to manufacture good quality ARVs in a sustainable manner, at a cost that is competitive (within a 15% range), if not lower than imported ARVs, within a public or donor-financed tender.
Affordability is the outcome within the micro-level research question. This research aims to understand the factors that influence the ability of domestic firms to price ARVs affordably. As described in the modified SCP framework (Figure 6), the conditions affecting market performance are market structure, market conduct, and government policies. The conditions are described as follows:

1. **Market Structure**
   a. Size – amount of market (potentially) held by the firm, number of patients treated.
   b. Entry barriers – deterrents to entering the market, such as IP, pricing policies, quality standards.
   c. Cost structure – expenses that a firm must take into account when manufacturing a product or providing a service, such as materials, machinery, and overhead.

2. **Market Conduct**
   a. Product pricing – the price of the product on the national market. For ARVs procured under national treatment plans, international competitive tenders are preferred by most governments and their donors. Depending on the IP status of the products within the country, competition may be restricted to the patent holder only. If this is the case, direct negotiations are likely.
   b. Research and innovation – R&D investment by the firm as well as the domestic government.
c. Firm investment—resources invested into the development of the firm, such as plant modifications, and hiring and training of human resources.

d. Cost reduction—strategies and ability of the firm to minimize development and production costs.

3. Government Policies (as in above guide):

a. Government regulations

   i. Intellectual property legislation—the terms and conditions of pharmaceutical patents.

   ii. Industrial policy—the strength of industry-friendly policies. Industry-friendly policies can include government subsidies or tax relief on investments as well as exemption from import duties for raw materials and machinery.

   iii. Health policy—the strength of universal ARV access as a health policy objective. This includes treatment targets, available resources, and ARV tender regulations. This may include preference for domestic manufacturers.

   iv. Science and technology policy—the development of R&D policies for innovation, education, and the training of human resources.

b. Strategy—national goals for health security, self-sufficiency, employment rates, foreign exchange, or access to essential medicines.
c. Civil society and bilateral/international organizations – As mentioned, the presence of organizations within the country and their strategy for lobbying government and pharmaceutical firms at the national or international level.

Within both the macro- and micro-level research questions, the above definitions assisted data collection and analysis. Currently, there is a dearth of literature surrounding both these research questions. The conditions at each of the levels comprise the appropriate framework to view these multi-factored questions while allowing all relevant themes to emerge from the data.

**Research Design**

**Comparative Case Study**

The case study method was utilized to answer the research questions. A small-\(n\) comparative case study was undertaken of voluntary licensing and imitation arrangements in South Africa and Tanzania, respectively. Case studies are the best method to analyze the complex technology transfer arrangements and local manufacturing initiatives in these countries. Small-\(n\) studies enabled the collection and analysis of rich, in-depth data necessary for these cases, which had not been analyzed previously. The possible factors influencing the development of technology transfer arrangements as well as the affordability of local production were many and varied. As a result, this research needed to examine the entire context of these initiatives. This included the analysis of public policies, industry and market factors, international relations, firm strategy as well as other factors, which all take place within a large socio-political environment. The case study is the only method that enabled all this data to be captured and analyzed within the larger environment.
The results of this small-\(n\) study were also tested by comparing them with secondary data from other developing countries across a large-\(n\) multi-country sample. Information was also used to identify any false-positive variables that may otherwise be assumed to contribute to technology transfer arrangements or affordability of ARVs produced in local manufacturing initiatives.

Yin (1994) states that it is essential in any case study to clearly define the case and unit of analysis in order to determine the limits of the data collection. These two small-\(n\) studies were: (a) voluntary licensing arrangements in South Africa and (b) an imitation arrangement in Tanzania. Both arrangements were for the production of first-line ARVs. In the South African case, the voluntary licensing arrangements from patent holders GlaxoSmithKline (GSK) and Boehringer Ingelheim (BI) to the local manufacturer Aspen Pharmacare (Aspen) were examined. In Tanzania, the imitation arrangement to Tanzania Pharmaceutical Industries (TPI) by the former manager of Thailand’s Government Pharmaceutical Organization (GPO) and the international organization Action Medeo was examined. Important details of the country environments surrounding ARV treatment and production will be discussed in Chapters 2 and 3. Within each case, the unit of analysis at the macro-level is the factors influencing formation of the arrangement and, at the micro-level, the conditions influencing the affordability of domestically produced ARVs. The timeframe of data collection began with the enforcement of the TRIPS Agreement in 1995 and ceased at the end of field research in 2008.

This research was conducted through institutional affiliations with the School of Pharmacy at Muhimbili University College of Health Sciences (MUCHS) in Tanzania, and the Health
Economics HIV/AIDS Research Division (HEARD) at the University of KwaZulu-Natal in South Africa. These affiliations ensured that ethical considerations in each country were appropriately addressed and helped to identify the necessary material and contact valuable key-informants for interview.

**Justification and Selection of the Cases**

As previous research in the field of domestic drug production in developing countries cautions that these initiatives are not economically viable, the resurgence of local manufacturing, specifically for ARVs, prompts interest in these initiatives. The TRIPS Agreement also raises concerns about drug affordability and flow of technology. The cases in Tanzania and South Africa provide unique insight into the first instances of ARV technology transfer and production in Sub-Saharan Africa under this international agreement. Research on these cases is of great interest in light of that fact that TRIPS provisions for domestic production and transfer of technology (under Articles 31 and 7 as well as the Doha Declaration and 30 August Decision) may not have been used if not for the international attention the HIV/AIDS pandemic and related drug access gap received. As such, the public health nature of ARV production and the international pressure placed on both governments and pharmaceutical firms to attend rollout treatment provide a rare opportunity to explore these landmark cases.

Guided by these unique circumstances, the piecemeal technology transfer literature, and sparse research on local ARV manufacturing, case studies in Tanzania and South Africa enable research to identify the factors that guided the formation of technology transfer arrangements and the subsequent affordability of ARVs. The two cases investigated in this study share a common
feature: transfer of technology for the local production of ARVs. When selecting cases, it was important that they provide a broad basis for comparison. As a result, the two cases were purposefully selected to feature different types of technology transfer arrangements: one voluntary licensing and the other imitation. The variation in this variable allowed the research to explore similarities and differences in the formation of the transfer arrangements and the affordability of their locally manufactured ARVs in each country.

Technology transfer arrangements in South Africa and Tanzania were selected for this study. At the time of selection in April 2006, few arrangements existed in Sub-Saharan Africa to produce ARVs, at least ones announced publicly.\textsuperscript{15} Table 4 provides selected indicators for these countries. These included Mozambique, Zambia, Zimbabwe, Kenya, South Africa and Tanzania.

South Africa, the case of a voluntary licensing arrangement, has been at the forefront of international debate on access to patented ARVs. It was the first country in the world granted a license for generic ARV manufacturing. This circumstance alone makes the South African case one of great interest. The potential impact this arrangement had on drug access and on subsequent transfer arrangements in the region needed exploration. The South African case is of also interest considering the high prevalence of HIV/AIDS, 18.1\%, and its strong manufacturing capacity relative to other African nations.

At the time of selection only one other country, Kenya, was known to have a firm with a voluntary licensing arrangement, agreed to in 2004. However, the case in South Africa was more

\textsuperscript{15} After April 2006, ARV manufacturing initiatives were found in Uganda, Ethiopia, Democratic Republic of Congo, and Senegal.
interesting due to the precedent it may have set for developing countries, such as Kenya, to follow. This is because the voluntary licenses in South Africa followed two contentious court cases that brought much international attention to the issue of drug access.\(^{16}\) Questions surround whether the issuance of these voluntary licenses in South Africa is, in fact, a misnomer seeing as they resulted from coercion and threats of compulsory licensing. For the purpose of this research, Aspen’s arrangement is viewed as voluntary licensing, since private negotiations did take place between the firms before and after the second court case. Furthermore, due to South Africa’s strong investment climate and manufacturing industry, it is in South Africa’s interest, and the interest of developed countries, for South Africa to remain TRIPS-compliant. South Africa, thereby, faces the most pressure of any African WTO member country. The case of South Africa, therefore, has great implications for other developing countries with pharmaceutical industries.

To contrast the case of South Africa, a most different case was sought. This was found in the imitation arrangement in Tanzania. Unlike South Africa, as an LDC Tanzania was able to exercise a clause in the TRIPS Agreement allowing the country until 2016 to implement patent regulations without violating the agreement. By comparison, Tanzania has remained in the background of any international attention on local ARV production. Also, Tanzania has little manufacturing capacity.

\(^{16}\) First, 39 manufacturers brought the South African Government to the Pretoria High Court, claiming the infringement of IP in Section 15c of the Medicines and Related Substances Control Act of 1997, which (by their interpretation) gave the South African government too much flexibility in issuing compulsory licenses. Second, the South African activist organization TAC and some South African physicians brought both GSK and BI before the South African Competition Commission for excessive pricing of its ARVs. Prior to adjudication, GSK and BI agreed to negotiate voluntary licenses with local manufacturer Aspen Pharmacare as well as other domestic producers.
Two other LDCs, Zambia, Mozambique and one developing country, Zimbabwe, had each announced the production of patented ARVs under compulsory licenses and imitation transfer arrangements; yet, Tanzania’s was the only known arrangement where manufacturing was taking place at the time of data collection in 2007. Although Zambia and Mozambique would provide interesting accounts of the constraining or limiting factors of technology transfer arrangements, it would have been more difficult to assess the factors affecting affordability, because the product had not yet been brought to market. Additionally, developing country Zimbabwe would have made for an interesting case, given its political unrest and economic crises. Zimbabwe was not selected for two reasons. First, the high rates of inflation and trade sanctions by many developed countries (while interesting for a single case study) made Zimbabwe’s situation difficult to generalize to other developing countries. Second, and more practically, the instability of the country made it difficult to gain access to appropriate resources for the necessary data collection.
Table 4: Selected Country Indicators

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Kenya</th>
<th>Tanzania</th>
<th>South Africa</th>
<th>Zambia</th>
<th>Mozambique</th>
<th>Zimbabwe</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDP (US$) /capita (2002)</td>
<td>$388</td>
<td>$267</td>
<td>$2,376</td>
<td>$342</td>
<td>$186</td>
<td>$1,385</td>
</tr>
<tr>
<td>HIV Prevalence (2003)</td>
<td>7.5%</td>
<td>6.4-11.9%</td>
<td>17.8-24.3%</td>
<td>13.5-20%</td>
<td>9.4-15.7%</td>
<td>21.7-27.8%</td>
</tr>
<tr>
<td>Human Development Index (2002)</td>
<td>0.488</td>
<td>0.401</td>
<td>0.666</td>
<td>0.386</td>
<td>0.356</td>
<td>0.491</td>
</tr>
<tr>
<td>Pharmaceutical Firms</td>
<td>33 Registered</td>
<td>Few Subsidiaries</td>
<td>98 Registered</td>
<td>Unknown</td>
<td>Few Subsidiaries</td>
<td>Unknown</td>
</tr>
<tr>
<td>Coface Country Ratings</td>
<td>C</td>
<td>B</td>
<td>A3</td>
<td>C</td>
<td>B</td>
<td>D</td>
</tr>
<tr>
<td>Production Means</td>
<td>Voluntary License</td>
<td>TRIPS 2016 transition period</td>
<td>Voluntary License</td>
<td>Compulsory License</td>
<td>Compulsory License</td>
<td>Compulsory License</td>
</tr>
<tr>
<td>Transfer Arrangement</td>
<td>Licensed</td>
<td>Imitation</td>
<td>Licensed</td>
<td>Imitation</td>
<td>Imitation</td>
<td>Imitation</td>
</tr>
<tr>
<td>ARVs Produced</td>
<td>Lamivudine, zidovudine, nevirapine</td>
<td>Lamivudine, stavudine, nevirapine</td>
<td>Lamivudine, zidovudine, nevirapine</td>
<td>Lamivudine, stavudine, nevirapine</td>
<td>Lamivudine, stavudine, nevirapine</td>
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<td>GSK, BI</td>
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Data Collection and Analysis

Through document analysis, key-informant interviews and observation policy makers, pharmaceutical industry leaders, academics and involved organizations, this study answered the research questions. These techniques enabled the identification of key conditions influencing technology transfer arrangements as well as the affordability of ARVs manufactured in the country.

A structured, focused comparison method emphasizes controlled collection of similar data across carefully selected units (George & Bennett, 2004). Purposive sampling of documents, key-informant interviews and event driven observation were used to collect data. The purposive sample comprised particular data, settings, actors, and events selected deliberately to provide important information that could not be derived by any other sampling method (Maxwell, 1996). Purposive sampling also assured that those interviewed and observed had specific knowledge on the events leading to technology transfer arrangements and local manufacturing initiatives. Sampling aimed to achieve representativeness of the settings for each respective case study. Appendix E contains the information letter and consent form signed by each informant. Appendix F lists the semi-structured interview questions. These multiple sources of evidence allowed for triangulation and increased the validity of the study.

Data Collection Techniques

Documents

Document collection began with publicly accessible documents and reports from international organizations, such as the World Bank, WHO, WTO, and a variety of NGOs. Government
policies on pharmaceuticals, industry and technology, local pharmaceutical industry documents, as well as documents relating to local manufacturing and technology transfer agreements were then collected. Key-informants were crucial to locating some of the documents of interest. Following is a non-exhaustive list of collected documents:

- Patent legislation
- Health legislation
- National drug policies
- Science and technology policies
- Industrial policies
- National AIDS plans
- ARV tender documents
- Bilateral/multilateral/international trade agreements
- Submissions to government by interest groups
- Local pharmaceutical industry assessments
- Annual reports of drug firms
- Newspaper articles, industry newswires, and press releases

From these documents, data on involved actors, policy contexts, content, and processes related to the development of transfer arrangements and domestic production affordability were identified.

Key-Informant Interviews

Concurrent with document analysis, key-informant interviews were conducted using a multi-stream snowball sampling technique (Miles & Huberman, 1994). To maximize sample variation, key-informants included representatives from government (ministries of health, trade and industry, science and technology); recipient and supplier pharmaceutical firms; members of civil society organizations, NGOs, international organizations; and academic researchers. Multiple
iterations of snowball sampling achieved an accurate representation of the case study context and helped to avoid potential bias or systematic error that can result from a shift in one direction over a set of replications (King, Keohane, & Verba, 1994).

For key-informant interviews, the sample size was undetermined; data collection ceased when thematic data saturation occurred (Ezzy, 2002). Saturation is the point in data collection when newly collected evidence produces no new information or themes. Based on the principle of consensus theory (where expert informants tend to agree with each other), samples as small as four can generate accurate information with high confidence intervals (Romney, Batchedler & Weller, 1986). Guest, Bunce, & Johnson (2006) determined that six interviews are sufficient to identify basic themes and elements of metathemes. Kuzel (1992) states that 12 to 20 interviews are required when trying to achieve maximum variation of a sample. In Tanzania 24 interviews were conducted and 17 were conducted in South Africa. The breakdown of interviews is as follows:

In Tanzania a total of 24 interviews were conducted among the following groups:


2. International, bilateral organizations and NGOs – 4 interviews at WHO, PEPFAR, UNIDO, and Action Medeor.

3. Pharmaceutical industry – 11 interviews at Tanzania Pharmaceutical Industries, local drug firms and subsidiaries, local distributors, and technology suppliers.
A total of 17 interviews were conducted in South Africa among the following groups:

1. Government representatives and agencies – 7 interviews at the Competition Commission, Department of Science and Technology (DST), Technology and Human Resources for Industry Programme (THRIP), and the Department of Trade and Industry (DTI).

2. International organizations, civil society organizations and academics – 6 interviews at WHO, UNIDO, the HIV/AIDS Network (HIVAN), Nelson Mandela School of Medicine (University of KwaZulu-Natal), and TAC.

3. Pharmaceutical industry – 4 interviews at Aspen, GSK, BI, and Bristol Myers Squibb (BMS).

The purpose of these key-informant interviews was to retrieve more in-depth information than was available in documents alone. At the beginning of each interview, the informant signed a consent form (Appendix E). This form reminded the informant of the purpose of the interview, its confidentiality, and that at any point the interview could be terminated. These interviews were semi-structured and lasted for approximately one an hour. Depending on the level of consent by key-informants, some interviews were audio-recorded, while in others notes were written. Those audio-recorded were transcribed by the researcher for analysis.

The semi-structured interview is presented in Appendix F. This guide contains a small number of open-ended questions, used to stimulate the free-flow of information where new directions and developments throughout the interview prompted new questions. Each informant was given a general explanation of the research and the interview progressed from informal conversation to a tighter structure, beginning with broad questions and leading to more explicit questions.
Informants were encouraged to use the expressions and jargon common in their environments in order to familiarize the researcher with the appropriate terminology, which proved to be valuable part of the data.

As demonstrated by Sorrell and Redmond (1995), key-informant responses prompted deeper inquiry by the researcher to guide the data collection. Questions and their order changed as data collection and interview coding progressed. Control was maintained, but left flexibility for informants. After completing each interview, the informant was asked to identify someone he/she felt was a valuable informant. With these referrals, new key-informants were selected to interview. Additionally, interviewees were asked for any valuable sources for document analysis.

**Observation**

Researchers deMunck and Sobo (1988) contend that participant observation enables rich and detailed description. DeWalt and DeWalt (2002) suggest that it may also increase validity of the research as it improves the quality of data collection through increased contextual understanding. When in the field both in Tanzania and South Africa, observation was used as a stream of evidence to gain an in-depth understanding of the activities undertaken by those involved in the formation of technology transfer arrangements and local ARV manufacturing initiatives. The number of field activities observed depended on availability and were used primarily to support document and interview analysis. In Tanzania, one week was spent observing interactions between technology suppliers and recipients at the local manufacturing firm, TPI. Additionally, a High Level Meeting on Intellectual Property Rights by government was attended. In South
Africa, the South African AIDS conference was attended where researchers, organizations and industry representatives presented on information related to the research questions.

The type of observation utilized was that of the observer as a participant. Here the researcher’s activities are known to the group being studied, and the emphasis of the research is on “collecting data, rather than participating in the activity being observed” (Kawulich, 2005, p. 7).

As suggested by Kawulich (2005), the observation objectives in this research were known to the participants and they had sufficient understanding of the research topic.

Field notes were used as the data collection technique. Record was kept of the date, time, and location of each event. Notes were taken on all information relevant to the research objectives, using the semi-structured interview questions as a guideline (Appendix F). To keep research findings objective, as suggested by Angrosino and dePerez (2000), structured observation was employed. It was noted what was observed, who was observed, and when and where that sample was observed (Johnson & Sackett, 1998). This maintained objective results by minimizing researcher bias, easing replication and maximizing efficiency.

Analysis of Documents and Key-Informant Interviews and Field Notes

Content analysis was used to identify, both systematically and objectively, special themes and subthemes throughout the data collection process (Corbin & Strauss, 1998). It began with documents and included the key-informant interviews and field notes.
Open coding was used first to identify concepts in the data and discover their properties (Corbin & Strauss, 1998). Open coding scans documents, transcribed interviews and field notes for words, concepts, ideas, or meanings that related to the research questions. Additionally, the researcher remained open to unanticipated results that may emerge (Berg, 2001). The data were coded until thematic saturation occurred.

Once open coding was complete, the data were grouped into categories where relationships among the data began to emerge (Berg, 2001). These categories were grounded in the data from which they emerged, and their development was derived from inductive reference (Berg, 2001; Corbin & Strauss, 1998; Fontana & Frey, 2003). The categories created included common classes, which are often used terms in everyday society (e.g., year, private/public, and national/regional/international). These classes identified characteristics potentially related to patterns in the data. Theoretical classes, which emerged in the course of the analysis, revealed overarching patterns or key linkages (Berg, 2001). After the material was coded, analysis of the various concepts and categories was accomplished more thoroughly (Berg, 2001).

To increase validity of the study, after analyzing of the data, negative case testing was conducted to verify the findings. Negative case testing is searching the data for any indications that the findings may be incorrect, contradictory, or could lead to a different interpretation than the original (Berg, 2001). Finally, to maintain reliability of the findings, two coders analyzed interview transcripts (the researcher and supervisor) for a preliminary coding comparison to establish interrater reliability and standardize results.
Quantitative Analysis

One portion of this research, discussed in Chapter 4, tested variables that emerged from the case study data over a number of ARV manufacturing initiatives across developing countries. A discussion of methods, validity, and limitations of this portion of the research can be found in Chapter 4.

Validity and Limitations of Research Methods

In qualitative research, the concept of validity is debated and no common definition exists. Winter (2000) defines validity as whether the means of measurement are accurate and whether what researchers measure is what they intended. In this research, measures were taken throughout the study to increase the validity of the qualitative findings; however, some limitations remained. Creswell (1998) and Yin (1994) suggest that in case studies there are four types of validity: construct validity, internal validity, external validity, and reliability.

Construct Validity

Construct validity relates to the accuracy of the research findings. In order to increase construct validity in this research, multiple sources of data collection were used to ensure correspondence between the research questions, concepts defined and methods to identify them. Convergence of sources of qualitative data, or triangulation, occurred through the use of document analysis, key-informant interviews, and observation for analysis.

Accessing certain documents within the case studies was quite difficult. As this research centred on technology transfer agreements between technology suppliers and domestic recipient firms
and the subsequent production of ARVs, there were a number of data not made available by key-informants. Much information within the pharmaceutical industry generally remained undisclosed. This included the confidential terms of agreements between firms, data on production costs and profit margins, sourcing of APIs, and even government ARV tender selection processes. This limitation of the research was known prior to entering the field. Even though data were lacking, the research questions had enough importance to developing and LDCs to be worth pursuing with the information that was available.

In case study research and particularly relating to the macro-level research question, an “objective truth” may not exist. Therefore, it was necessary to understand a variety of key-informant perspectives. The small sample size of the case studies’ key-informant interviews could be considered a limitation. A small number of in-depth interviews were conducted across a variety of key informants, 24 in Tanzania and 17 in South Africa. This included pharmaceutical industry representatives from technology suppliers, recipients, and other domestic firms, as well as representatives from government ministries in addition to international and civil society organizations involved in treatment access issues within the countries. This was undertaken to achieve maximum variation and greater representation of the sample. As the area of research touches many aspects of policy, industry, and civil society, the information provided by each of informant was necessary to describe the appropriate context of each case. Providing a spectrum of viewpoints on to the transfer of technology and local manufacturing initiatives was crucial to determine all the important and influential conditions. Even though the sample sizes meet the minimum requirements suggested by Kuzel (1992), Romney and colleagues (1986), and Guest
and colleagues (2006) and each case study did reach saturation of data, this was done with the assistance of document analysis and observation.

The validity of the results was threatened by key-informant availability, which was limited for a variety of reasons within each case. First, due to financial constraints the number of key informant interviews that could be performed was limited by the amount of time spent in each country. Second, given the specificity of the research topic, there were a limited number of informants who could provide a substantial understanding of the case. While this was evident in both case studies, it was particularly noticeable in Tanzania.

In Tanzania a variety of key institutions (such as the Commission on Science and Technology) had limited, if any, knowledge of the fact that ARV production was occurring within the country. This limited the amount of information available that was specific to the case study. However, it simultaneously led to important implications of coherence and effective communication across ministries and among stakeholders in the case study. Additionally, the flexibility of the snowball sampling technique used made the best of this limitation. Key-informants currently at the appropriate institutions at the time of data collection that did have understanding of the case were able to refer other key-informants that were involved.

An obvious limitation of the South African case study was the inability to secure an interview in the Department of Health (DoH). This was a challenge to achieve for two reasons. First, during data collection, there was a strike across all ministries. Although some policy makers remained in office, the death of a civilian during a protest outside a government office limited access for
non-government officials. Second, DoH policy makers are extremely reluctant to discuss its HIV/AIDS policies with researchers and the public, after DoH garnished much criticism over its poor HIV/AIDS leadership both domestically and internationally. This was compounded by the small window of time within which the researcher was in the country to press representatives in person to consent to an interview. Two key-informants suggested that the researcher’s affiliation with the University of Toronto should not be disclosed when approaching DoH. This was in reference to the negative perception Toronto may have gained among government staff after DoH faced sharp criticism, and AIDS activists called for the resignation of the then Minister of Health at the International AIDS Conference in Toronto in 2006. Although this large limitation could not be overcome by documents alone, the perspectives of academic researchers were used to gather information on the position of DoH, as were documents containing interviews with DoH representatives in newspapers or other research studies.

Finally, Maxwell (1996) identifies the selection of data that fits the researcher's existing theory or preconceptions as a major validity threat. It is impossible to eliminate researcher preconceptions, theories and values; however, being aware of these biases aided the researcher to remain objective during data collection and analysis in order to increase the validity of data interpretation. Threats to validity were limited by using an additional coder to standardize the interview notes and transcripts. In addition, discrepant evidence and negative cases were sought in the data to attempt to falsify the proposed conclusion. The latter was accomplished by examining both supporting, and discrepant data to assess whether it is more plausible to retain or modify the conclusion, as suggested by Maxwell (1996). Finally, another threat to validity is the influence of the researcher on the setting. As informant answers are a function of the interviewer
and the interview situation, it is understood that reactivity by the researcher was unavoidable during interviews (Maxwell, 1996). This was minimized, though, by omitting researcher vocalizations of opinions or thoughts on interview subject matter, as well as by avoiding leading questions and expressions.

**Internal Validity**

To improve *internal validity* of the qualitative research (the extent to which inferred relationships among variables are true) negative case testing was conducted after analysis of the data to verify the findings. At times, within certain firms and organizations, one representative was appointed to speak on behalf of the entire organization, or a group of representatives were interviewed simultaneously because of their individual preferences. On the one hand, this provided conformity in the perceptions of the institution. For the purposes of this research, the perspective of the institution (its position, policies, etc.) was desired for analysis. On the other hand, with informants simply providing the party line, many underlying factors may have been omitted. This compromised the validity for two reasons: first, it became difficult to recruit and access other members of the institutions for interviews to increase the sample size. Second, key-informants were less likely to provide information that they felt was confidential or that departed from the general institutional response.

In each country case, there was a limit on the number of potential documents and informants that were available. This was affected by bureaucratic obstacles, unavailability of informants, or unwillingness to disclose information, the last of which was most noticeable in terms of
accessing documents specific to the terms and conditions of the technology transfer arrangements. Some of these limitations were addressed by key-informant interviews.

Finally, it is possible that key-informants avoided discussing the true realities and their perceptions of events by representing their institutions during their interviews. One method used to overcome this problem was to suggest private interviews in a neutral location and assure confidentiality in the consent form. The challenge of confidentiality was evident in Tanzania, where all but two informants within government refused to be audio-recorded or quoted. Informants only consented to note-taking. In one interview, the informant was hesitant to sign the confidentiality agreement. Though the lack of transcribed material proved a limitation to data analysis, it was outweighed by the key-informants position to provide the necessary information that was scarce among stakeholders. As assurance of confidentiality may not be enough incentive for some informants, this validity threat was overcome through multiple sources of analysis, such as other key-informant interviews, documents, and observation.

**Reliability**

*Reliability* is often referred to as the dependability and consistency of research (Golafshani, 2003). Reliability in this research is strengthened by not only the measures described above to increase validity, but the use of multiple coders to analyze transcripts. Both the researcher and the researcher’s supervisor coded 5 transcripts independently and compared to ensure interrater reliability of results.
Retrieving uniform information across both cases was difficult. This is important, as diverging amounts and types of information limit the ability to compare the case studies and their findings. This inconsistency was identified and mitigated as best as possible by using multiple data sources (documents, interviews and participant observation). As the contexts of Tanzania and South Africa are widely different, the documents available, the events observed, and the interviews conducted were not entirely consistent. This was evident in the number of key-informant interviews required to reach saturation of data. For example, 24 interviews were conducted across key-informants in Tanzania, whereas in South Africa 17 interviews were conducted. In Tanzania many informants had a limited understanding of local ARV manufacturing and technology transfer events, and a large number of interviews were required to achieve data saturation. These interviews were also required to supplement the limited number of documents available. In South Africa, however, informants had a much better understanding of events, and fewer interviews were necessary to reach data saturation. Much more research has been conducted within the field of local manufacturing in South Africa, which was evident as a number of key-informants were themselves researchers. This information was supplemented with a larger number of documents in the South African case.

External Validity

Finally, Yin (1994) suggests that when using single or multiple case studies, the findings can only be abstracted to theory when external validity exists. External validity is the degree to which findings can be generalized to other situations. As a researcher’s goal is to expand theory, not simply to enumerate frequency (Yin, 1994), performing multiple case studies in this research increased generalizability (Morse, 1997). In this research, the theoretical framework derived is a
means to infer local constructs and provides insight into the factors that have not been described previously. In addition, to support these findings a multi-country analysis was conducted across 25 developing countries to test these findings. External validity is discussed more thoroughly in the Limitations section of Chapter 5.

**Ethical Considerations**

Even though the comparative case study represents a composite picture rather than one of individuals, ethics still remained a priority in key-informant interviews and observation (Creswell, 1998). A dissertation proposal was submitted, reviewed and approved by the Health Sciences I Research Ethics Board at the University of Toronto as well as the review boards at the Muhimbili University College of Health Sciences, Tanzania, and the University of KwaZulu-Natal, South Africa. These review boards ensured that the appropriate research considerations were addressed and followed within each country of analysis.

Any researcher deception about the nature of the study was mitigated by presenting general information about the study (such as its purpose) to key-informants prior to interviews and observation. An information letter, stating the purpose of the study, and a letter of consent (Appendix E) were presented to, and signed by, each informant prior to each interview. Therefore, these details were known and consented to by the participant with the completion of a consent form prior to the interview. Any risk to the individuals being interviewed or observed was minimal because their information was kept strictly confidential (if desired) and coded on a Master Code List. Informants could choose the level of confidentiality, as indicated in Appendix E. This included key-informant preference to not be audio-recorded or quoted directly. Although
no informants withdrew from the study, there was no risk should any have chosen to cease participation. Additionally, there was no payment for participation in the study.

The Master Code List, the audio-recorded interviews and interview transcripts were accessible only to the researcher and the researcher’s supervisor. Digital versions of the recordings and the transcripts were stored on a password protected hard drive. The audio-recorded interviews will be destroyed 2 years after transcription. For purposes of verification, the transcripts will be kept for 6 years from the completion date of the study, after which, they will be destroyed.

**Summary Chapter 1 and Introduction to Chapter 2**

In this dissertation, Chapter 1 presented the role that World Trade Organization’s (WTO) Agreement on the Trade-Related Aspects of Intellectual Property (TRIPS) plays in decreasing access to affordable ARV treatment in Sub-Saharan Africa. A review of the literature on the TRIPS Agreement, the transfer of technology, and local drug manufacturing in developing countries identified a gap in understanding the impact of intellectual property (IP) on the transfer of ARV technology across Sub-Saharan Africa and their firms’ ability to manufacture ARVs cheaply. A research design was proposed using a comparative case study of diverging types of technology transfer arrangements: an imitator arrangement and a voluntary license arrangement. Methods for data collection and analysis were outlined.

Chapter 2 analyzes the first case of the comparative analysis: an imitator arrangement. The case is focused in Tanzania, where the domestic firm Tanzania Pharmaceutical Industries (TPI) is manufacturing ARVs with the assistance of an international NGO and a European Commission
grant. This case study aims to understand both domestic conditions affecting the development of this technology transfer arrangement and the factors influencing the affordable pricing the firm’s ARVs in the Tanzanian public sector.
Chapter 2: Access Granted? Domestic Conditions Affecting the Transfer of Technology and Affordable ARV Manufacture in Tanzania

Introduction

Approximately 22 of the 33 million people infected with HIV live in Sub-Saharan Africa. Although antiretroviral (ARV) drug treatment coverage has increased substantially in the region, from 2% for those in clinical need in 2003 to 28% by the end of 2006, 72% of HIV-infected individuals in need of treatment remain without access (UNAIDS, 2007). One of the primary factors inhibiting treatment access is the affordability of ARVs. The World Trade Organization’s Agreement on the Trade-Related Aspects of Intellectual Property (TRIPS) harmonizes a 20-year pharmaceutical patent protection period across its 153 member countries. Drug access advocates cite that patent protection results in monopolistic prices that developing countries simply cannot afford (MSF, 2007).

As a means of increasing a sustainable supply of affordable ARVs, Sub-Saharan African countries with large HIV-infected populations have been adopting provisions of the TRIPS Agreement to facilitate local ARV manufacturing. These provisions evolved under the Doha Declaration on TRIPS and Public Health of 2001, which states that patents should not prevent the protection of health in member countries. TRIPS provisions include the issuance of voluntary licenses by patent holders, compulsory licenses by developing country governments, and the use of transition periods until 2005 and 2016 to incorporate pharmaceutical patents into domestic legislation for developing countries and least-developed countries (LDC), respectively. Theoretically, during a period, domestic firms may manufacture drugs that are under patent in
other countries without facing repercussions. This gives an advantage these countries to enter the generic ARV market prior to patent expiry and potentially reduce price.

The manufacture of essential medicines in developing countries has been debated since the 1960s. Framed in the context of the “make-or-buy” dilemma, developing country government officials must decide whether to produce essential medicines for their populations locally or import them. As the major opportunity for local production to impact drug access is through affordability, domestic manufacturing is only efficient if drugs are produced more cheaply than they can be imported. Some theoretical research presents a case for affordable drug production in developing countries (Grace, 2004; Guimier; Lee and Grupper, 2004), while others contend that it makes little sense economically, as initiatives are most often not reliable and do not reduce prices (Bennett, Quick, & Velasquez, 1997; Kaplan & Laing, 2005; MSH, 1997). Despite this research, many developing countries contend that local manufacturing brings benefits in addition to price. The African Union (2007) argues that domestic drug production develops the appropriate industrial and technical infrastructure that can enhance long-term health security, self-sufficiency, employment, foreign exchange, in addition to access to essential medicines.

In light of the TRIPS Agreement, its aforementioned provisions, and the need for increased ARV access, a number of Sub-Saharan Africa countries have begun to manufacture ARVs locally. Since many of these countries lack the pharmaceutical manufacturing capacity to produce ARVs unaided, local firms utilize technology transfer agreements. In exchange for a 20-year patent protection period, the TRIPS Agreement addresses the transfer of technology and development of technological capabilities. Article 7 of the TRIPS Agreement states,
[the] protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations. (WTO, 1994, p. 323)

Article 66.2 of the TRIPS Agreement and the Decision of the General Council of 30 August 2003 further encourage developed countries to provide incentives for the research-based pharmaceutical industry to transfer technology and build capacity in LDCs (WTO, 2003a,b). Technology transfer under the TRIPS Agreement most often alludes to foreign direct investment (FDI) and voluntary licenses; however, technology transfer is also viewed to include the exchange of information through the provision of know-how, and assistance with technical expertise (Maskus, 2004; UCTAD, 1985). For purposes of this research, the broad technology transfer definition is used and patented information can be disseminated by the right holders (voluntary licensing arrangements), or by generic firms, skilled personnel, NGOs, and international organizations (imitation arrangements).

This chapter examines a case of ARV manufacturing in the United Republic of Tanzania (hereafter called Tanzania) under an imitation technology transfer arrangement. To address the need for treatment scale-up, local manufacturer Tanzania Pharmaceutical Industries (TPI)
entered this agreement to produce a triple fixed-dose combination (FDC)\textsuperscript{17} of first-line ARVs lamivudine, stavudine, and nevirapine (3TC+d4T+NVP), named TT-Vir. The arrangement began in October 2005 between TPI and a former member of the Research & Development Institute of the Government Pharmaceutical Organization (GPO) of the Ministry of Health, Thailand. In November 2006, the arrangement formally partnered with a German non-government organization (NGO), Action Medeor, to construct a new ARV manufacturing facility financed by a US$6 million grant from the European Commission.

For this case study, the collection and analysis of rich qualitative data was conducted through documents, observations, and key-informant interviews across government, international organizations, and industry. The case study identified the domestic conditions that affect both the development of the technology transfer arrangement as well as the ability of TPI to produce affordable ARVs: the domestic policy environment, the market for ARVs, as well as TPI’s manufacturing capacity and financial structure. The relationship between these conditions and their impact on the development of TPI’s technology transfer arrangement and its ARV affordability are modelled in Figure 7. Portions of Buckley and Casson’s (1976) model of the multinational enterprise as modified by Goel Cohen (2004), for the transfer of technology to developing countries, and the structure-conduct-performance model of Scherer (1990), adapted to the pharmaceutical industry by Harrison (2004) were utilized in the formation of the framework for this study.

\textsuperscript{17} Fixed-dose combinations have two or more active pharmacological products in the same pill, capsule, tablet or solution. They are highly desirable because they significantly reduce the number of pills a patient must take, which leads to greater compliance and appropriate use.
With the Tanzanian patent system not yet compliant to the TRIPS Agreement, TPI was able to manufacture generic ARVs without patent holder consent. The country’s weak intellectual property (IP) system and TPI’s poorly financed state-ownership dissuaded both patent holders and generic manufacturers from transferring their technology. These domestic conditions were
perceived favourably, however, by Action Medeor as well as the development aid agency, the European Commission. Here, an imitation arrangement aimed to fill both public health objectives and development goals in Tanzania as well as the mandate of these aid organizations. As a result, this case study highlights the important role international institutions play to facilitate the technology transfer arrangement in LDCs, supplying both the technology and financial assistance.

Research by Losse, Schneider, and Spennemann (2007) argues a case for drug manufacturing in Tanzania’s donor market, which they suggest is large enough to accommodate Tanzanian manufacturers. However, they question manufacturers’ ability to compete in the international markets against large-scale generic drug firms. This research argues that TPI cannot compete in the ARV market either domestically or regionally.

From TPI’s technology transfer arrangement, the affordability of generic ARVs produced at TPI is influenced by the country’s ARV market characteristics as well as the manufacturing capacity of the firm. In Tanzania, the ARV market is constrained by donor-financed tenders that restrict competitive bidding to generic manufacturers with internationally accredited products, which TPI has not yet achieved. Without access to these large-volume tenders and without the capacity to manufacture active pharmaceutical ingredients (APIs), the main driver of ARV cost, TPI cannot meet the necessary economies of scale to reduce price. As a result of these conditions, it difficult for TPI to manufacture first-line ARVs more affordably than they can be imported from international generic manufacturers in countries, such as India.
This chapter is presented in six sections. First, a background of Tanzania’s HIV/AIDS strategy, the local pharmaceutical industry, as well as TPI’s technology transfer arrangement will be described. The subsequent sections outline four domestic conditions critical to analysis: the Tanzania’s policy environment, TPI’s structure and manufacturing capacity, and characteristics of the ARV market. A discussion then presents how these factors, particularly the level of IP protection, led to the current technology transfer arrangement and whether a local manufacturing initiative of this type can produce affordable ARVs. The final section considers implications of these conditions for other developing countries.

**Background**

Tanzania, an LDC in the East African Community (EAC), has a Gross National Income (GNI) per capita of US$400 and is ranked 159th of 177 countries on the Human Development Index (UNDP, 2008). Table 5 displays a number of socio-demographic, health, and pharmaceutical industry indicators. Since emerging from a socialist economy in the mid-1980s, Tanzania has rapidly privatized to encourage both local and foreign direct investment through the Mini-Tiger Plan (MTP) 2020. With the MTP, investment-friendly policies have been implemented to encourage industry growth. In 2007, GDP rose an estimated 7.1%, higher than experienced in Tanzania’s largest EAC neighbours, Kenya (6.9%) and Uganda (6.5%) (World Bank, 2008).
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<td>Until 2016</td>
</tr>
<tr>
<td>Domestic Firm</td>
<td>Tanzania Pharmaceutical Industries</td>
</tr>
<tr>
<td>Domestic Firm Ownership</td>
<td>40% Government, 60% Private</td>
</tr>
<tr>
<td>ARVs Produced</td>
<td>lamivudine (3TC), stavudine (d4T), nevirapine (NVP) and fixed-dose combination (FDC) 3TC+d4T+NVP</td>
</tr>
<tr>
<td>Year ARV Production Announced</td>
<td>2005</td>
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<td>Production Means</td>
<td>Imitation</td>
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<th>III. Technology Transfer Arrangement</th>
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<tr>
<td>Type of Arrangement</td>
<td>Imitation arrangement</td>
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<tr>
<td>Donor</td>
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<td>Value of Donor Grant</td>
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Note. ARV = Antiretroviral drug, GNI = Gross National Income, HDI = Human Development Index, TRIPS = Agreement on the Trade-Related Aspects of Intellectual Property Sources: World Bank (2008b); WHO (2005c); UN (2007); MOHSW (2003); TFDA (2007).

In 2004-2005, Tanzania’s pharmaceutical market was valued at approximately US$110 million (TFDA, 2007). Tanzania’s market value is similar to that of Kenya and Uganda, but lags far behind South Africa’s US$2.6 billion industry (IFC, 2008). Currently, there are eight licensed pharmaceutical firms in Tanzania, which produce 30% of the drugs purchased in the private sector and by the public distributor, the Medical Stores Department (MSD). With only 30% of its
pharmaceuticals manufactured locally, the market in Tanzania is dominated by foreign manufacturers. As the second largest manufacturer in the country, TPI sold drugs valued at US$6.7 million in 2004-2005. By value, 60% was tendered by MSD, 37% sold to the private sector, and 3% exported (TFDA, 2007).

Faced with an HIV prevalence rate of approximately 6.2%, Tanzania carries a heavy burden in providing HIV services and treatment to its 1.4 million HIV-infected citizens (UNAIDS, 2008). Within the Ministry of Health and Social Welfare’s (MoHSW) HIV/AIDS Care and Treatment Plan 2003-2008, a US$238 million 5-year budget aimed to treat 423,000 HIV-infected individuals with ARVs (MoHSW, 2003). Having treated approximately 64,000 individuals in 2006, Tanzania required a mass treatment scale-up to tackle its 2008 objective.

To contribute to this need for ARVs, TPI entered a technology transfer arrangement for the production of the first-line treatment 3TC+d4T+NVP. Beginning in October 2005, the FDC was approved by the Tanzania Food and Drug Authority (TFDA) and launched in December. In November 2006, a 48-month grant was awarded by the European Commission to Action Medeor in order to assist TPI. Action Medeor is a German medical aid organization authorized as a pharmaceutical manufacturer and central procurement agency, under the German Medicines Act. It provides generic drugs to developing countries at cost or by donation. With an office in Tanzania, Action Medeor also aims to share pharmaceutical expertise and assist to building local capacity. The European Commission grant was valued at approximately US$6 million for the construction of a new ARV plant that meets international quality standards through the WHO
Prequalification Programme.\textsuperscript{18} The grant originated from a call for proposals, focused on the priority area “technology transfer, leading to local production of affordable key pharmaceuticals and commodities in prevention, treatment and care of HIV/AIDS, malaria and tuberculosis” (European Commission, 2006, p. 1).

**Policy Environment of ARV Production and Transfer of Technology**

Investment in the transfer of technology and the establishment of a local pharmaceutical industry relies on a conducive and coordinated policy environment. In Tanzania, a coherent multi-sector strategy for the pharmaceutical industry does not exist. Although drug policy encourages manufacture and regulation, pharmaceutical patent enforcement is weak, and investment in science and technology is stagnant. This provides little incentive for industry to invest in local manufacturing.

Emerging from a strong socialist orientation beginning with Tanzanian independence in 1961 and lasting until the mid-1980s, the government turned to economic liberalization in order to drive growth. From 1989 until 2005, growth in Tanzania fluctuated considerably, between 1\% and 7\% of GDP annually (World Bank, 2006). Elected in 2005, the Fourth Phase of government under President Kikwete set out to modernize Tanzania’s “backward and dependent economy” through the implementation of Tanzania’s Medium-Term Plan (MTP) (Parliament of Tanzania, 2005, p. 6). The MTP was inspired by the experiences of East Asian countries and aimed to increase capital intensive technology with a private investment led economic growth model.

\textsuperscript{18} The Prequalification Programme began in 2001 and is a service provided by the World Health Organization (WHO) to facilitate access to medicines that meet unified standards of quality, safety, and efficacy for HIV/AIDS, malaria, and tuberculosis. This is done by providing a list of products and their manufacturers that meet specified quality and safety requirements evaluated by WHO or a stringent drug regulatory authority, such as the United States Food and Drug Administration or the European Medicines Agency.
Since 2005, growth in Tanzania has remained steady between 6.5% and 7.1% (World Bank, 2008b). In 2006, the World Bank ranked Tanzania one of the top 10 reformers in the world. Although reform has been a priority of the Kikwete Administration, Tanzania ranks only 14th of 48 Sub-Saharan African countries on the 2008 Ibrahim Index of African Governance, falling behind South Africa and Kenya and only slightly ahead of Uganda (Mo Ibrahim Foundation, 2008). This index measures a country’s ability to provide sustainable economic opportunities to investors and includes measures such as the country’s macroeconomic stability, financial integrity, and wealth creation. According to the 2008-2009 Global Competitiveness Report, Tanzania also ranks poorly in its ability to compete globally, placing 113th of 134 countries (Porter & Schwab, 2008). Tanzania has not been able to transition from a factor-driven economy (highly sensitive to commodity price trends, fluctuations in exchange rates and global economic cycles) toward an investment-driven economy (producing standard products and services efficiently) (Porter & Schwab, 2008).

**Attracting Investment**

To enhance its status as a global player and attract investment, Tanzania’s major catalyst is the Tanzania Investment Centre (TIC). TIC assists domestic firms with investments of a minimum US$100,000 and foreign firms with investments of a minimum $US1 million. In line with the MTP, the TIC focuses on the target sectors of agri-business, mineral extraction and infrastructure, with no direct focus on the health sector or, more specifically, the pharmaceutical industry. Although TIC houses representatives of many government ministries to facilitate “one-stop shop” investments, MoHSW is not represented. This reflects the lack of government priority on health sector investment. Instead, the greatest pharmaceutical industry incentives derive from
the fiscal incentives that apply across all industries. For example, the Investment Act of 1997 exempts imported raw material, packaging material, and machinery from duty and value added tax (VAT). For TPI, this reduces the costs of imported machinery, APIs, and overall cost of capital goods, thereby, increasing competitiveness.

The National Science and Technology Policy (1996) emphasizes “rapid socio-economic development and subsequent realization of self-reliance” within the country (Ministry of Science, Technology and Higher Education, 1996, p.4). Here, investment in research and development (R&D) is crucial to enhance both human research capacity and research infrastructure that facilitate the adaptation of foreign technology (Ministry of Planning, Economy and Empowerment, 2006b). This includes the scientific and technological know-how to manufacture low-cost drugs to address national health problems. Despite the emphasis, total domestic R&D allocation is estimated at 0.01% of GDP annually, failing to meet the policy goal of 1% of GDP by 2000. By comparison, EAC member Uganda spent 0.82% of GDP from 2000-2005. Although the low spending is highlighted as a shortcoming in Tanzania’s Macroeconomic Policy Framework for the Plan/Budget 2006/7-2008/9, a new target has yet to be fixed. Limited public investment in science and technology may indicate the government’s dependence on private sector investment in technology; however, little R&D has occurred within Tanzania, either private or public, keeping the country at a competitive disadvantage globally (GCR, 2008).

To assist investments in new technology in Tanzania, the Commission for Science and Technology (COSTECH) Act of 1986 instated the Commission and the Centre for Development and Transfer of Technology. Under Article 15(2) of the Act, the Centre is to “play a major role in
the unpackaging of imported technology including the assessment of the suitability of the technology”, maintaining a registry of imported technology and transfer agreements, and assisting in negotiating and monitoring these contracts (COSTECH, 2001, p. 12). COSTECH, however, has had limited practical use since economic liberalization, with priority placed at TIC to attract private investment. Informants at COSTECH note that the separation of roles has left COSTECH relatively powerless in the technology investment and selection process. Neither COSTECH nor TIC was informed of TPI’s technology transfer arrangement, reinforcing COSTECH’s waning involvement with imported technologies and TIC’s narrow focus on large private investments.

**Promoting Domestic Drug Production**

MoHSW is the only ministry in the Tanzanian government that explicitly promotes the local pharmaceutical industry. Both the National Drug Policy of 1991 and the Pharmaceutical Master Plan (PMP) 1992-2000, under review at the time of data collection in 2007, promote local medicines production to achieve Tanzanian self-reliance and sustainability. Production goals extend from increasing capacity in drug formulation to producing raw and intermediate materials for drugs where there is a national comparative advantage (MoHSW, 1993). Further, Minister of Health and Social Welfare, Professor David Mwakyusa, supported and witnessed the official signing of TPI’s technology transfer agreement with Action Medeor and the European Commission.

To foster general drug industry development in Tanzania, local manufacturers are assisted by MSD during the tender process and by TFDA during registration and inspection. Modelling
Egypt, where 98% of national pharmaceutical needs are met by local industry, the PMP is committed to increase MSD’s procurement of locally manufactured drugs from 30% to 60% of market share by 2010 (TFDA, 2007). MSD also grants a set of restricted tenders for local industry and 15% price equalization for domestic firms during open tenders (TFDA, 2007). This price equalization provides local manufacturers with a price advantage over imported products to adjust for the cost of shipping, duty, and other associated costs.

The ARV tender process has been under scrutiny and informants commented on the lack of transparency and possible corruption. Corruption is difficult to measure objectively and claims are often based on surveys of perceptions in a number of institutions. Transparency International, which publishes the Corruption Perception Index on which the Ibrahim Index is based, defines corruption as the “misuse of entrusted power for private gain” (Transparency International, 2008). On the issue of controlling of public sector corruption, Tanzania ranks 12th of 48 Sub-Saharan African countries, ahead of EAC neighbours Kenya, Uganda, and Rwanda, but behind South Africa, Botswana, and Namibia (Mo Ibrahim Foundation, 2008). Although corruption is often difficult to identify, preferential treatment can influence both regulators and public tender officers. Specific concerns surrounding the tender process is further discussed in the section on Market Structure. Generally, however, Govindaraj, Reich, and Cohen (2000) caution that a politically strong domestic pharmaceutical industry can often persuade a government to purchase locally manufactured pharmaceuticals, even if they cost much more than imported drugs.

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19 Corruption can be either against the rule (a bribe paid for a service the briber is prohibited from imparting), or according to the rule (a bribe paid for preferential treatment for something the receiver is required to do by law), such as preferentially awarding an ARV contract (Transparency International, 2008).
TFDA also strongly supports and works very closely with local drug manufacturers. Since 2003, TFDA has assisted domestic firms to phase in national Good Manufacturing Practice (GMP) standards and consults on the appropriate requirements during the construction of new manufacturing facilities. In conjunction with MSD, TFDA holds forums to provide constructive feedback to local industry on issues extending from quality to packaging. TFDA also provides preferential fees for domestic industry. Importers are required to pay 2% of the Free on Board (FOB) value as a service charge to the TFDA. In addition, local manufacturers queue separately for drug registration and are granted reduced registration and inspection fees. Local industry is charged approximately US$500 to register a new drug and US$350 to register a generic drug (compared with US$1000 and US$750, respectively, for foreign drugs). Lower fees are a common policy tool in developing countries to encourage generic drug registration and favour local manufacturers. Kaplan and Laing (2003) reiterate that differential registration pricing is a violation of Article III:4 of the Global Agreement on Tariffs and Trade (GATT), which requires that domestic and imported products be treated similarly in international regulations. However, differential pricing is not uncommon in developing countries and WTO has yet to take any active measures against Tanzania.

**IP Flexibility**

The level of patent protection in Tanzania domestic legislation is an important determinant for the local manufacture of ARVs. Patents on pharmaceutical products under the TRIPS Agreement are granted for a minimum of 20 years. Tanzania, as an LDC, has until 2016 to comply with these terms. If domestic patent legislation permits, under this transition period Tanzanian firms can manufacture generic versions of patented medicines without prejudice by patent holders or
TRIPS-compliant countries. Articles 7(1) and 8 of the 1987 Tanzanian Patent Act make patents available for both pharmaceutical processes and products. Five first-line ARVs have been patented in Tanzania, lamivudine (3TC), zidovudine (AZT), lamivudine+zidovudine (3TC+AZT), nevirapine (NVP), and abacavir (ABC) (Attaran, 2004). Two of these, 3TC and NVP are included in the FDC treatment manufactured by TPI. Contrary to the TRIPS Agreement, Article 38(1) of the Tanzanian Patent Act grants patents for only 10 years. Therefore, the manufacture of these ARVs neither contravenes the Act (as the patents on 3TC and NVP expired by the year 2001) nor the TRIPS Agreement. In addition, informants broadly assume that these patents were not enforced by government or industry. This is common in Sub-Saharan African where patent holders have waived their IP rights for many first-line ARVs, with the exception of South Africa (Chien, 2007).

Within this context, Tanzania has a comparative advantage over other developing countries for local drug production, given that its current legislative framework allows generic ARV manufacturing without repercussion from patent holders or TRIPS-compliant countries, such as the United States. Tanzanian firms can manufacture ARVs without negotiating voluntary licenses, as experienced in Kenya and South Africa, or government invoking a compulsory license, as occurred in Thailand and Brazil, under Paragraph 6 of the Doha Declaration and Section 61 of the Tanzanian Patent Act. This limits the delays and legal entanglements preventing locally produced ARVs from entering the market. For example, royalty free voluntary licenses were only issued in Kenya after threats of compulsory licenses by the Kenyan Ministry of Health, and in South Africa after a case was brought by civil society before the South African Competition Commission for excessive ARV pricing. In Thailand and Brazil, compulsory
licenses were issued after a number of rounds of price negotiations with the patent holders. In each of these countries, patents have been heavily enforced by their right holders, and the countries have faced pressure to remain TRIPS-compliant. Coercion ensued from the United States Trade Representative (USTR), which threatened trade sanctions against South Africa, Thailand, and Brazil for what it considered an infringement of ARV patents. Tanzania’s ability to use its 2016 TRIPS deadline avoids many negotiation costs, delays, and procedures required by WTO as well as possible trade sanctions from developed countries, specifically the United USTR.

Although Tanzania can be interpreted as exercising the 2016 transition period, this TRIPS flexibility has not been explicitly incorporated into a legislative framework. Recently, TFDA circulated a concept paper recommending government to amend the Tanzania Patent Act to include this provision. Actively incorporating the transition period into the Patent Act would require support from multiple ministries. In contrast to the position of the MoHSW, steps have been taken in other ministries to increase IP protection. The Ministry of Trade and Industries (MoTI) and Ministry of Science and Technology (MoST) through COSTECH and the Business Registration and Licensing Agency (BRELA), launched an initiative to put greater emphasis on IP and its enforcement as part of the country’s growth model. This included the launch of the Intellectual Property Advisory Services and Information Centre, which hopes to increase innovation and technology development within the country.

The poor consensus on IP policies among ministries highlights the difficulty to reconcile health policy and industrial policy goals common within government (Jacobzone, 2000). This is
particularly the case in LDCs, such as Tanzania, where support for economic growth and investment often outweighs support for health care access. The relative strength of the MTP’s economic growth model and its supporting institutions, TIC, COSTECH, and BRELA, compared with the strength of MoHSW and TFDA makes the revision of the Patent Act to exclude pharmaceuticals from patent protection until 2016 seem unlikely.

Attempts to incorporate flexibilities in domestic legislation not only require support in the domestic political arena, but the ability to withstand pressure internationally to strengthen IP, as experienced in South Africa, Brazil, and Thailand (Shadlen, 2007). Even though countries such as Tanzania have not faced repercussions for using their 2016 transition periods, any act to legislate these and other flexibilities might face scrutiny. As such, even if it is within the power of government to facilitate these amendments under the TRIPS Agreement, bilateral aid agencies and trade partners can exert pressure to strengthen IP reform. This pressure could occur both directly, through trade agreements and financial aid conditions, and indirectly, through assistance to support industries or government bodies under a particular ideological framework that emphasizes IP protection.

**Financial Structure of Tanzania Pharmaceutical Industries (TPI)**

Financing to bolster an LDC drug manufacturing industry, is difficult to obtain from government or private investors, whether domestic or foreign. Key aspects influencing the development of the imitation arrangement entered by TPI include the firm’s ownership and its access to financing.
State-Ownership

As in many developing countries, the dominant pharmaceutical firms in Tanzania were state-owned from their inception. Under an initiative to spark industrial development within the country, TPI began in 1977 under an agreement between the state-owned National Development Corporation and a private Finnish firm, Oreon. The Tanzanian government terminated the management contract with Oreon in 1983, and TPI fell under the state’s umbrella organization, National Chemical Industries. As centrally planned economy, TPI informants noted that government policies, unconducive to business, led to the cessation of operations and the facility’s closure in 1994. Partial privatization occurred in 1997, bringing TPI to its current form of ownership: 60% of shares held Tanzanian entrepreneurs and 40% by government.

TPI’s difficulty attracting investors has been compounded by the belief that pharmaceutical production should rest within the private sector. WHO advises that private sector manufacturing is preferred, allowing governments concentrate more on regulatory mechanisms (African Union, 2007). This is because infrastructure development often becomes the prime focus for government and leaves insufficient resources for state-owned enterprise management and execution. Currently at TPI, a representative of each the Ministry of Finance and MoTI sits on the Board of Directors, giving the state partial power in the decision making and strategic direction of the firm; however, TPI informants maintained that government is not involved in the day-to-day management of the firm. Interestingly, even with a vested interest in the generic firm’s success, MoIT has pursued an increase in IP protection that would negatively impact TPI’s growth in the generic industry. The drug industry in Tanzania is also not a priority within the overall strategy of MoTI’s industrial policy. Government support for the generic industry derives from MoHSW.
At the launch of TPI’s artemisin-based antimalarial drug in 2003, the Minister of Health and Social Welfare requested that TPI, using Thai technology, begin manufacturing of ARVs. Although MoHSW did not assist in the development of ARVs, the viability of the ARV market depends on its commitment to rollout ARVs as well as TPI’s relationship with semi-autonomous bodies under MoHSW, TFDA and MSD. In addition, Losse and colleagues (2007) caution an undesirable dependency that could result from TPI’s government sponsored loans, such as those granted by Tanzanian pension funds.

The perception of state-owned pharmaceutical firms, such as TPI, varied across informants. Informants from patent holders, distributors, and private generic manufacturers as well as procurement financers in developed countries with deregulated pharmaceutical industries, such as the Bush Administration’s President’s Emergency Plan for HIV/AIDS Relief (PEPFAR), generally view state-ownership negatively. Informants pointed to a lack of transparency, corruption, poor management, and bureaucracy in state-owned that create inefficiencies within the industry. IFC (2008) cautions that, though political stability has increased within Sub-Saharan Africa, a major barrier to investment in the region remains corruption, whether in the public or private sector. In fact, the Global Competitiveness Report 2008/2009 named corruption as one of the most problematic factors for doing business in Tanzania (Porter & Schwab, 2008). This may deter private investors who believe that a government share in TPI increases bureaucratic procedures and reduces transparency.

By contrast, informants form Action Medeor, state-owned pharmaceutical firms, and development agencies, such as the European Commission, were willing to support a government
sponsored industry. Within its grant application to the European Commission, Action Medeor emphasized the sustainability of the technology transfer initiative given TPI’s status as an enterprise with government shareholders that support the project as part of its responsibility and operations. An informant at the European Commission acknowledged that state involvement and support could have enhanced TPI’s grant application as it assured the country’s commitment to address HIV/AIDS and improve sustainability of supply. In addition, the technology supplier originated from a Thai state-owned enterprise, GPO, and has maintained a strong preference for government involvement in the pharmaceutical industry. This informant affirmed that the pharmaceutical industry should focus on public health objectives instead of profits, making government the appropriate body to oversee ARV manufacturing.

**Access to Finances**

TPI’s ability to finance its current and future operations is limited, and its poor access to large amounts of financial capital has hampered its mission to become “a centre of excellence” within the African Region. At the point of partial privatization in 1997, informants noted that TPI was in a state of “utter disrepair”. Since that time, most investments in restructuring have been financed through small loans from financial institutions, development agencies and investments by public pension funds. In 1999, TPI was granted US$400,000 by the United States Agency for International Development (USAID) through its Social Action Trust Fund to finance the first phase of its rehabilitation. In 2001, TPI entered a joint venture with Tanzania’s Public Service Pension Fund, which contributed US$2.6 million as equity and a shareholder’s loan. This enabled TPI to upgrade its facility, purchase new equipment, implement quality control measures that meet GMP standards of TFDA, and recruit human resources.
In 2001 and 2002, TPI used external funds, the rehabilitation program loan and a working-capital loan from Barclay’s Bank to further modernize. This, along with arrears from previous years, created large debt and high cumulative losses (Losse, Schneider, & Spennermann, 2007), which deceased in 2003 as TPI became more profitable, experiencing a US$4.5 million turnover. In 2004, the National Social Security Fund purchased approximately US$4 million of preferred TPI shares (Losse, Schneider, & Spennermann, 2007). In 2004/2005, sales amounted to US$6.7 million, and US$1 million of internally generated funds were utilized to renovate TPI’s drug plant and create a separate ARV unit. This ARV facility is complies with TFDA GMP standards, but has yet to be assessed by an international body, such as the WHO Prequalification Programme.

Although production at TPI is stable for standard formulations (such as antibiotics) that require only local drug regulatory authority (DRA) approval for procurement, TPI does not have the international accreditation needed for the ARV market. Meeting GMP and WHO prequalification standards generally requires a large investment in upgrading or building new facilities as well as financing for the lengthy application process. In these cases, informants suggested that greenfield projects (i.e. new construction projects) are desired, avoiding difficult renovations of existing facilities to meet international standards. Yet, greenfield projects require a large sum of start-up capital. In East Africa, where health sector investments are considered risky, start-up capital is more difficult to access than working capital (Losse, Schneider, & Spennermann, 2007).
Even though MSD provides letters of credit for local manufacturers to enhance their standing in bank loan applications, the weak investment climate in Tanzania makes receiving loans extremely difficult. The International Finance Corporation (IFC, 2008) notes the challenge faced by Sub-Saharan African entrepreneurs to secure needed capital from financial institutions to expand or initiate new ventures. For example, fewer than 25% of individuals in developing countries have access to formal financial services, compared with 90% in developed countries (IFC, 2006).

**European Commission Grant**

TPI’s difficulty in financing was partially relieved by the US$6 million grant from the European Commission. This grant was directed to the construction of greenfield WHO GMP-compliant ARV facility. The grant also covered human resource training and capacity building, both at TPI, and with local DRAs in the region. Under the terms of this grant, TPI is to finance approximately 10% of the awarded amount, or approximately US$600,000. At the time of writing, TPI had yet to secure financing for this matching amount and construction of the facility had not begun. Informants were sceptical that TPI could meet the project’s objectives with the amount of financing approved. The motives for, and implications of, the grant’s short-term funding are explored in the Discussion. One industry informant challenged the grant noting that upwards of US$40 million is required to develop an internationally approved ARV facility. A similar ARV manufacturing initiative is occurring in Uganda under a joint venture between the Indian generic manufacturer Cipla and the Ugandan firm Quality Chemicals. For this venture, Quality Chemicals generated $38 million internally for the greenfield construction of an internationally certified facility (Barney, 2007). This underscores the importance of domestic financing in
attracting the transfer of technology. Although some pharmaceutical firms might be willing to transfer technology, they may be less likely to invest in substantial start-up costs, particularly for first-line ARVs, for which many generics already exist on the open market.

The European Commission grant only covers costs associated with the construction of a WHO prequalified ARV manufacturing facility and not product development, including formulation, initial production and quality assurance testing. Development costs are high, particularly if these products must achieve international quality standards. WHO prequalification of products can take between 12 and 24 months and can cost a firm up to US$200,000. ARV product dossiers must include clinical data and bioequivalence studies for the FDC, 3TC+d4T+NVP, and each individual pharmaceutical product. This requires not only the appropriate facility and equipment, but also the necessary trained human resources. The total development cost of a single oral dose was estimated by industry informants to be from US$800,000 to US$1 million, excluding any required plant modifications and labour costs. These costs increase if a more technologically complex second-line ARV is developed. All costs are inevitably passed on in the final price of the ARV.

**ARV Manufacturing Capacity in Tanzania and at TPI**

ARV manufacturing capacity is the ability of a local firm to develop a number of quality ARVs and produce them at a competitive price. Manufacturing capacity at TPI is reflected by its development capability and production costs. Because the international market for first-line ARVs is highly competitive, the firm’s success relies not only on its ability to develop WHO
prequalified ARVs, but also on the firm’s cost reduction through economies of scale. TPI’s ability to do so affects final ARV prices, and subsequently their affordability in the public sector.

**Drug Development Skill**

Within Sub-Saharan Africa, 37 countries have some level of pharmaceutical production, with 34 countries able to formulate pharmaceutical products (IFC, 2008). The majority of this production constitutes non-complex, high volume, essential products: generally analgesics, antibiotics, antimalarials, and vitamins. Assessing its current level of pharmaceutical manufacturing complexity, TPI, like many Sub-Saharan African and LDC manufacturers, only has limited capability to formulate and package bulk pharmaceuticals (Kaplan and Laing, 2006; Rovira, 2006; WHO, 2005a). TPI primarily produces antibiotics, analgesics, and antimalarials. Since privatization, and with technical assistance from its technology transfer arrangement, TPI’s production line expanded to include artemisinin-based antimalarials and now 3TC+d4T+NVP and its single ARV products. Technology suppliers pointed to the market demand for domestic manufacturers, such as TPI, to develop off-patent drugs treating opportunistic infections related to HIV/AIDS. For example, the antibacterial cotrimoxazole and antifungal agent fluconazole are more easily formulated than ARVs and the raw materials and formulation processes are less expensive. In addition, their procurement often does not require WHO prequalification or international competitive bidding, making contracts easier for a domestic manufacturer to obtain. TPI has not shown interest in producing these medicines; it has focussed instead on ARVs, where the market is risky but substantially more lucrative if a tender is won.
A country’s skill to develop a range of products and build a local pharmaceutical industry is arguably linked to the country’s average education level; secondary education supplies the basis for technical and maintenance expertise while tertiary education fosters talent for scientific innovation (Kaplan & Laing, 2005). Compared with the Sub-Saharan African average of 27%, Tanzania has the lowest secondary school enrolment rate at just 9% in 2000 (Utz & Aubert, 2008) and ranked last of 134 countries in the 2008-2009 Global Competitiveness Report (Porter & Schwab, 2008). Similarly, Tanzania’s tertiary enrolment rate ranked 130th among 134 countries (Porter & Schwab, 2008) with enrolment rates of 1.5% in 2000-2005 (World Bank, 2008b). Of those that attend tertiary institutions, only 24% study science, engineering, or manufacturing (UNDP, 2008). The country’s inadequately educated workforce is the largest barrier to business ventures in Tanzania, second only to the country’s poor infrastructure (Porter & Schwab, 2008).

Compounding low education enrolment, emigration of health professionals is a concern in the region. In Tanzania, 10% to 15% of graduating doctors emigrate or leave medical practice in order to increase their incomes (IFC, 2008). Also, while 14 to 20 pharmacists graduate annually (Ministry of Planning, Economy and Empowerment, 2006b), only 365 pharmacists and technicians (or 1 per 100,000 inhabitants) have remained in the country (WHO, 2006b). This vast shortage of both dispensing and industrial pharmacists, as well as other science-related graduates, has inhibited TPI’s capability to develop and adapt new technologies. Although TPI recruited one ARV manager from abroad, industry and government informants reported that retaining foreign skilled workers, and their associated cost, is difficult to manage. These challenges make it difficult for TPI to expand, or even sustain, product lines.
Currently, the majority of first-line ARV treatment regimens in Tanzania consist of 3TC+d4T+NVP; however, the 2006 WHO guidelines shifted treatment preference to a better tolerated regimen of tenofovir, emtricitabine and efavirenz. If Tanzania’s National AIDS Control Program (NACP) adopts this treatment plan, TPI needs to be able to adapt to the changing market demand. Without appropriate human resources to adapt or transfer the relevant technology, TPI’s sustainability in the ARV market is limited. Developing the alternate first-line ARVs recommended by WHO has greater costs than the regimen already being produced. These development costs will become difficult to bear, considering that the level of competition in the market necessitates low prices.

**Drug Production Costs**

Typical in most developing countries, a major hurdle in minimizing production costs is sourcing APIs to formulate ARVs. TPI’s lack of vertical integration and Tanzania’s weak infrastructure limit lower production costs. Integrating all phases of manufacturing, from raw material production to the final dosage, creates cost reduction through both in-house manufacturing and scale. API development requires a high degree of technological sophistication and production requires large volumes to substantially impact cost reduction, as they often contribute from 65% to 90% of the manufacturers’ cost (Pinheiro, Autunes, Fortunak, 2008).

Without the technology to manufacture APIs, firms must import them from producing countries, such as India and China. TPI currently procure APIs from China’s MChem under a 5-year fixed-cost agreement. As a result of these costs, TPI’s fight for ARV market share has been strained as integrated generic firms, such as those in India, are able to achieve greater economies.
of scale along with lower labour and overhead costs. To compete, TPI would need to be assured an expanded regional market to generate the large volumes necessary to reduce the contracted API price. Without WHO prequalification, this seems unlikely. IFC (2008) emphasizes the comparative disadvantage of small firms to achieve WHO prequalification compared with large-scale manufacturers, given the latter’s greater knowledge base and technical and financial resources to submit product dossiers.

As a result, production scale is one of the most notable disadvantages for an LDC manufacturer. For example, IFC (2008) found that the production cost of simple analgesic tablets in Tanzania is 25% higher than in India and 15% higher than in South Africa. This is partially a result of TPI’s low production capacity. IFC (2008) claims that the conversion-cost scale efficiencies are around 1.0 to 1.5 billion tablets in blister packaging per year. The estimated capacity of Tanzanian firms is 500 million tablets per year, compared with the 1.2 billion of South African and Indian firms (IFC, 2008). TPI’s manufacturing plant planned under the European Commission grant is designed to manufacture 100 million units per year, placing TPI at a large scale disadvantage to its international competitors. In addition, whereas it is often assumed that local production offsets much of the cost of importing, freight costs comprise only 4% of the 25% production cost difference between Tanzanian manufacturers and Indian generic manufacturers (IFC, 2008).

Although there is no tax in Tanzania on imported APIs or intermediates (giving local manufacturers slight advantage over final product importers that pay 2% of FOB value), there may be taxes on packaging material. Therefore, the total tax rate paid by local manufacturers can be subsequently higher than generic product importers (IFC, 2008). Similarly, exporting to
countries within Sub-Saharan Africa can often be more difficult and expensive than importing from Asia. Both exports face the same import tariffs and, even where there are trade agreements among regional countries, Sub-Saharan African countries generally do not include pharmaceuticals (IFC, 2008).

In addition to scale, TPI must also ensure that its overhead costs remain predictable because it operates within a country where the greatest challenge to business is the country’s inadequate infrastructure (Porter & Schwab, 2008). Tanzania’s unpredictable electricity supply is of poor quality, ranking the country 122nd of 134 countries globally, ahead of Uganda, but behind all other EAC members. TPI faced significant challenges with the supply and cost of both electricity and water from 2005 through 2006, when a severe drought swept the country and resulted in a loss of TPI’s power 3 days a week. In these confines, labour schedules were changed to night shifts or shifts that were run on power from external generators, which can be extremely costly. Finally, labour costs in Tanzania poorly relate to worker productivity, compared with other countries with generic manufacturing initiatives, such as India, China, Kenya, and South Africa (Porter & Schwab, 2008). This challenges TPI’s capacity and cost containment strategy and its ability to compete on ARV price in tenders.

**Tanzania’s ARV Market Structure**

The ARV market is unique in LDCs, such as Tanzania, as it remains regulated by donor financing. This influences the ability of locally produced ARVs to compete. Donors create barriers for manufacturers through tender requirements, such as international quality standards and competitive bidding.
**ARV Market Size**

In 2003, only 3.8% of total health care expenditure in Tanzania was accounted for by social security or private insurance schemes, compared with 7.5% in Kenyan and nearly 50% in South Africa (IFC, 2008). Most Tanzanians rely on the public system or out-of-pocket spending. With the majority of Tanzania’s HIV-infected population unable to afford ARV treatment, the country’s ARV market size increased exponentially in 2003 when MoHSW committed to treat 432,000 Tanzanians by the end of 2008. Increasing drug expenditure from $US6.6 million in 2003 to $US42.1 million in 2005 and $US98.7 million in 2008, MoHSW opened a market to attract local industry (MoHSW, 2003). MoHSW’s universal access program and system of public tenders limits the private market for first-line ARVs. These tenders are highly sought by manufacturers as they procure large volumes of ARVs over a set period. Approximately 80% of tenders are for 3TC+d4T+NVP (Losse, Schneider, and Spennemann, 2007), the FDC produced by TPI.

**Tender Requirements**

For domestic firms with basic manufacturing capabilities, the barriers to enter the ARV market are notable. Unlike with other drugs procured in the public sector, donors influence the conditions of the ARV market. IFC (2008) estimates that the donor market in Sub-Saharan Africa ranges from US$750 million to US$1 billion and is primarily targeted toward the treatment of HIV, malaria, and tuberculosis. The Global Fund for HIV/AIDS, Tuberculosis and Malaria (Global Fund) has played a large role, financing 21% of HIV/AIDS programming in Tanzania, part of which includes public sector ARV procurement through MSD (MoHSW, 2003). Additional donors include the Canadian International Development Agency, Swedish
International Development Agency, Norwegian Agency for Development Cooperation, and PEPFAR. Generally, these donors finance ARV procurement through the public sector.

Compared with other Sub-Saharan African countries, donors have directed some of the largest health financing to the Tanzanian government, suggesting confidence in the country’s governance. From 1997 until 2002, 90% of total external funding was channelled through Tanzania’s public sector. By comparison, EAC neighbours Kenya and Uganda received substantially less public sector financing: 60% and 45%, respectively (IFC, 2008). Of note, PEPFAR is the only donor that finances private entities, not MSD, to procure ARVs in Tanzania. Private sector agencies and NGOs are most often involved in procurement and distribution when concerns persist about government corruption, inadequate capacity, and incompetence in managing international aid (IFC, 2008). An informant at PEPFAR in Tanzania remained sceptical of the capacity for governance within the country’s tender system and highlighted the greater efficiency and scale managed by private sector implementers, such as John Snow Inc. (JSI) and Supply Chain Management System (SCMS).  

Others, however, suggest different reasons for the involvement of the private sector. Developing country informants suggested that PEPFAR intentionally targets funds to support American private entities to procure and distribute ARVs throughout Sub-Saharan Africa. This creates unilateral programming that overlaps and conflicts with the initiatives of the multilateral Global Fund.

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20 Private procurement and distribution agencies are often used in Sub-Saharan Africa to finance ARV procurement under PEPFAR. SCMS, a joint initiative between John Snow Inc. and Management Science for Health (MSH) and funded by PEPFAR, unites 16 private sector, non-government, and faith-based organizations across 17 countries to procure and supply low-cost essential medicines.
Regardless of whether donor funding is channelled via the public or private sector, the most important precondition for market entry is compliance with international quality standards. Manufacturers and their products must be approved by the WHO Prequalification Programme, or the United States Food and Drug Administration (FDA) under PEPFAR. TPI has not been granted either certification. This disqualifies the firm from competing in donor-financed ARV tenders (Appendix G details the Global Fund’s quality assurance policy). As such, a lack of international accreditation reduces its possible market. Only with these international standards met can TPI increase its ability to compete not only nationally, but regionally.

**Domestic ARV Competition**

As recommended by WHO, first-line ARVs are procured through international competitive tenders at MSD’s Tender Board. For a competitive bid price to be offered, WHO states that at least five bidders are necessary. Currently, WHO lists six generic manufacturers that produce prequalified 3TC+d4T+NVP regimens\(^{21}\) (WHO, 2008c). Whereas competition benefits affordability by pushing prices down to marginal cost, it inhibits the success of new manufacturers. It is difficult for domestic manufacturers to match the price and quality of longstanding large-scale firms.

In January 2007, TPI estimated to manufacture 3TC+d4T+NVP for approximately US$20 per month, or US$240 per person per year (pppy). This price was without WHO prequalification or FDA approval. By comparison, in a 2005 Global Fund tender, Cipla’s prequalified FDC was purchased for US$123 pppy. With increased international competition, this price dropped to

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\(^{21}\) There are six manufacturers of the most commonly procured regimen, 3TC+d4T+NVP, of which some produce combination and others the single products: Cipla, Emcure, Hetero, Ranbaxy, and Strides and Aspen Pharmacare. All of these manufacturers are Indian firms, except the South African firm Aspen Pharmacare.
US$92 pppy in a 2007 tender (GPRM, 2008a). Even though contracted prices can vary, based on volume and negotiations with the assistance of organizations, such as the William J. Clinton Foundation, this price differential between TPI and its international competitors is vast. Even with the 15% equalization factor offered to local manufacturers in MSD tenders, intense competition exists in the market between domestic firms and large multinational generic firms, such as Cipla. These large manufacturers have the economies of scale to reduce prices significantly. Local industry informants charged that these large firms use predatory prices (where drugs are purposefully priced below their manufacturing costs in specific markets) to keep small firms out of the market.

For TPI, ARV competition from other Tanzanian manufacturers may also emerge. A project is underway in the School of Pharmacy at Muhimbili University College of Health Sciences to assess the viability of a pharmaceutical plant located at the University to both train pharmacists and produce essential medicines, including ARVs. More imminent, Tanzania’s largest drug manufacturer, Shelys Pharmaceuticals, was recently acquired by Sub-Saharan Africa’s largest generic ARV manufacturer, Aspen Pharmacare of South Africa. As of late 2008, it is uncertain whether Aspen intends to expand ARV production into Tanzania. If either of the two ARV initiatives develops, domestic competition increases for TPI. This would effectively remove TPIs competitive advantage as other domestic manufacturers would also receive preference in the tender system. Aspen, in particular, would have the greatest access to tenders as its products are FDA approved and WHO prequalified. Aspen will likely seek these accreditations for its Tanzanian plant as well.
Without prequalification standards met, TPI is able to compete only in tenders supported by Ministry financing, where bids only require local DRA approval. This occurs, for example, within the ministries of health in countries such as Brazil and Thailand, which use government funds to procure ARVs from their 100% state-owned enterprises. Donor assistance, then, is used for other portions of HIV/AIDS programs in these countries. Although there are a few tenders with government financing in Tanzania, it has proven difficult to convince the Tanzanian government, with a much larger population on ARVs and heavy reliance on donor aid, to finance its ARV programs entirely. In 2007, TPI bid on an ARV tender that was financed by MoHSW. Although the tender not been awarded fully at the time of data collection, quality, in addition to price, was noted at MSD as a major concern.

A 2006 procurement of ARVs manufactured by the Indian generic firm Emcure sparked complaints over drug quality as well as corruption in the tender process after the public was informed that the ARVs were not WHO prequalified. This example was used by informants at the NACP and MSD, to express that their interest in ARV production and self-sufficiency lagged behind their attention to ARV quality and price. They also noted concerns over transparency as the Ministerial Tender Board, which contains little pharmaceutical expertise, procured ARVs under the Public Procurement Act of 2001 and not MSD, the common drug procurer and distributor. Ironically, this Act placed all government procurement under the Ministerial Tender Board in an effort to reduce corruption. Informants at MSD speculated on both the origin of the tender financing and the relationship between the Ministerial Tender Board and the supplier.
Regional ARV Competition

With neighbouring countries facing high HIV prevalence and large treatment plans, TPI aims to expand its export business and enter EAC markets as well as those in the South African Development Community (SADC). In terms of exports, Tanzanian manufacturers are small players in the regional pharmaceutical market, and TPI’s ability to compete with ARVs is limited. In 2007, the Sub-Saharan African region produced US$1 billion of generic pharmaceuticals, of which than 70% was manufactured in South Africa alone (IFC, 2008). The next largest exporting countries included Kenya, Nigeria, and Ghana, which together produced 20% by value. Of these three countries, Kenya, is the only one that produced notable export volume with 35% to 45% of revenue derived from EAC and Common Market for Eastern and Southern Africa (COMESA) countries (IFC, 2008).

In addition, most of Tanzania’s preferred export countries are similarly dominated by the donor-financed tenders seen in Tanzania, which require WHO prequalification. Furthermore, TPI’s products must be registered with each importing country’s DRA. These qualifications add both time and financial cost to enter an export market—where preference is given to its own manufacturers if prices are comparable. Therefore, competition for TPI is even more difficult in the export market as TPI must achieve both WHO prequalification and DRA approval, while simultaneously offering a lower price than all competitors (as there is no price equalization factor). Currently, this seems quite difficult.

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22 Due to the 30 August Decision, countries manufacturing ARVs in a region where at least 50% of the countries are of LDC status, generic drugs may be exported to any country in the region.
23 The countries within the Common Market for Eastern and Southern Africa are Burundi, Comoros, Djibouti, Egypt, Eritrea, Ethiopia, Kenya, Libya, Madagascar, Malawi, Mauritius, Rwanda, Seychelles, Sudan, Uganda, Zambia, and Zimbabwe.
Second-Line ARVs

The manufacture of second-line ARVs changes many of the above market characteristics because, even though there is less competition, there are higher development costs and an even smaller market than first-line ARVs. With IP protection in developed countries and developing countries newly compliant to the TRIPS Agreement (such as India), and with the small number of patients on second-line drugs, these ARVs are produced mainly by patent holders at much higher profit margins than first-line ARVs. In 2006, Roche’s saquinavir and nelfinavir and Abbott’s lopinavir/r (all three of which are second-line protease inhibitors) were procured by JSI under PEPFAR from the two patent holders for US$932, US$920, and US$500 pppy, respectively (GPRM, 2008). While efforts are underway in countries such as India, Thailand, Brazil and South Africa to produce generic versions of many crucial second-line drugs, their market entry has been delayed. This is because of pending patents in their home countries, time to achieve WHO prequalification and DRA approval, the greater technological complexity and higher development costs, and the small production volumes that make cost reduction difficult. Waning’s (2007) research on second-line ARV treatments found that median transaction prices for generic ARVs in 2006, ranging from US$948 pppy to US$4,245 pppy, were often higher than those procured from patent holders, ranging from US$865 pppy to US$2,577 pppy.

Currently in Tanzania, less than 1% of patients are on second-line ARV treatment. With new WHO guidelines on improved first-line treatment and therapy switch rates estimated by the WHO (2006c) at 3% per year, alternative first- and second-line regimes will become a larger part of the ARV market and incentive will increase for LDC firms to produce these drugs. In 2007, two small tenders for the alternative first-line ARV tenofovir (funded by UNITAID and
Missionpharma) were filled by generic manufacturer Aspen Pharmacare and patent holder Gilead Sciences for the same unit price of US$0.56 (GPRM, 2008a). Despite the small tenders, they show difficulty of achieving significant price reductions with only one generic competitor on the market. While a number of Indian generic firms manufacture tenofovir, only Aspen’s generic product is FDA approved, making the drug eligible for PEPFAR financing. It also questions whether this unit price is a collusive result of the distribution agreement between the two manufacturers or simply the inability of Aspen to reduce its costs without the large-scale production volume seen with first-line drugs.

Most second-line drugs in Tanzania are not tendered by MSD, but financed and procured by PEPFAR (often through SCMS or JSI). As mentioned, this is done both as a result of lack of confidence in the domestic tender process as well as the ability of PEPFAR to pool procurement across its focus countries. Market penetration is impossible without FDA approval and tenders are unlikely to give local manufacturers preference. The ability of TPI to enter this higher value chain is constrained both because of Tanzania’s limited demand for second-line ARVs and TPI’s limited manufacturing capacity.

**Discussion of Case Study Findings**

The “make-or-buy” debate, in the context of ARVs in Tanzania, exemplifies the challenges of local manufacturers. The strength to attract investment in the transfer of technology for domestic ARV production is weak. In addition, TPI’s ability to manufacture ARVs more affordably than international generic firms is also low. Figure 7 shows the interaction of conditions that affect the case study results as well as TPI’s relationships with donors and NGOs. In this model,
government policy, particularly TRIPS-compliance, and firm financing affect the type of technology transfer arrangement that is developed, while TPI’s ability to capture the ARV market and its manufacturing capacity affect the affordability of TPI’s ARVs.

**What Influences the Transfer of Technology?**

TPI, as a partially state-owned enterprise under a system of undefined IP, presents little to attract patent holders and generic drug multinationals, but attracts development aid organizations seeking to fill public health objectives and build capacity in Tanzania. By not incorporating the TRIPS Agreement’s minimum standards of patent protection into domestic legislation, there is little incentive for patent holders to transfer technology to Tanzania. This would reward a country for not protecting IP, on which the success of the research-based pharmaceutical industry relies. Similarly, research-based pharmaceutical firms are built on the principle of free markets. Licensing technology to state-owned facilities promotes undesirable government intervention in a country where bureaucracy and corruption are noted barriers to investment.

By comparison, attracting technology transfer is a challenge even for developing countries that do protect IP in domestic legislation. Only after struggles in both Kenya and South Africa, where pharmaceutical firms are financed privately, were voluntary ARV licenses issued on reasonable terms (with pressure from the Ministry of Health and the Competition Commission, respectively). Thailand and Brazil, both TRIPS-compliant and with state-owned enterprises also faced constant battles over the development of first- and second-line ARVs. Their state-owned institutions did not receive voluntary licenses from patent holders, but issued compulsory licenses for the alternative first-line ARV efavirenz (and the second-line protease inhibitor
lopinavir/ritonavir in Thailand). Both Thailand and Brazil not only have the necessary legislative provisions for compulsory licenses, but the manufacturing capacity and market size to leverage steep price discounts from patent holders with threats of compulsory licenses. This leverage was used effectively by the Brazilian government against Roche to reduce the price of the ARV nelfinavir by over 65% (Cohen and Lybecker, 2005).

The examples of Brazil and Thailand reflect the complex relationship between state-owned firms and the research-based pharmaceutical industry. Important considerations arise over the motives of each party to enter or forego negotiated agreements, such as voluntary licenses. Even though patent holders may be deterred from licensing their technology to state-owned enterprises, countries with manufacturing capacity and a substantial market, such as Brazil and Thailand, may feel that they do not benefit from the entanglements and restrictions of licensing arrangements, which may include geographical market boundaries and purchasing requirements for APIs. In addition, government’s close relationship with, and control over, state-owned manufacturers could mean greater coordination between a country’s ministry of health and ministry of trade and industry to support local manufacturing initiatives. As such, there would be greater willingness and incentive to invoke compulsory licenses and use state-owned facilities to promote both public health and technological development. Unfortunately, in Tanzania the necessary manufacturing capacity and market value do not exist, leaving domestic firms no leverage with patent holders.

Without TRIPS-compliant protection of pharmaceutical patents, more likely Tanzania could have attracted firms from developing countries experienced with generic ARV manufacturing,
such as India or Thailand. These firms have greater experience in the small margin ARV industry, using limited resources and economies of scale to generate profit, particularly in a country with poor infrastructure and weak manufacturing capacity. Here, investment in technology transfer might specifically attract generic industries unable to manufacture second-line ARVs in their own countries due to patent restrictions and who are, thereby, willing to develop a manufacturing subsidiary in an LDC. For example, generic pharmaceutical firms in India (which developed through loose patent laws and reverse engineering capabilities) might view an LDC’s 2016 transition period under the TRIPS Agreement as an opportunity to manufacture ARVs that are under patent review in India. Yet, with neither the appropriate financing in Tanzania for infrastructure and drug development, nor TRIPS flexibilities incorporated into legislation, nor commitment from government to develop pharmaceutical industry incentives, it would have been difficult to attract investment from generic firms.

Additionally, with India’s compliance to the TRIPS Agreement, the strategies of Indian generic firms will be dictated by “survival needs” and not by issues related to ARV access (Shadlen, 2007, p. 575). Though they are the largest provider of ARVs to developing countries, the shift in IP protection will change many Indian firms’ market strategy from generic production towards innovation. As such, investments by large generic firms might be more prominent in developed country markets. This is unless the appropriate incentive and financing are drawn by developing countries to attract technology transfer. The recent joint venture between Cipla in India and Quality Chemical in Uganda is evidence of this. Financing likely plays a prominent role, with multinational generic firms requiring upfront investment by domestic manufacturers or their government in order to attract technology transfer.
Unable to secure substantial loans or investment by private or public investors, TPI cannot attract joint ventures with large generic firms, while poor government commitment to the industry has reduced the possibility of state-state collaborations. Within the India-Uganda joint venture, however, culture might also play a role. The cultural ties that exist between the Indian-owned firm and Uganda’s large Indian population may have favoured collaboration. By comparison, state-state collaboration was sought between the governments of Tanzania and Thailand for the manufacture of a number of pharmaceutical products. Yet, cultural barriers and the poor standard of living in Tanzania were cited by informants as factors that led to the project’s demise.

As a result, TPI appealed to other sources for technology transfer and financing from the non-commercial sector. Action Medeor, on behalf of TPI, applied for and received approximately US$6 million from the European Commission to build an ARV plant. This financing was part of a budget-line allocated specifically for the transfer of technology to manufacture ARVs or other essential medicines in developing countries. The strategic reasons for this funding are varied. An arrangement financed by a development agency and NGO does not rely on profit, strong markets, or existing capacity. Here, investment is more attractive when supplying ARV technology can be viewed as serving a public health and development need, not a market. This fills a mandate to assist not only HIV-infected individuals, but to build the capacity and self-sufficiency of the country.

European Commission grants do not require immediate return on investment, can make use of Tanzania’s TRIPS flexibilities, and build human resource and pharmaceutical technology capabilities. This fulfils European countries’ obligations under Article 66.2 of the TRIPS
Agreement and the 30 August Decision, which prompts developed countries to incentivize the transfer of technology in pharmaceutical manufacturing, specifically to LDCs. Given the relatively small contribution of development aid funded by the European Commission to Action Medeor and TPI, this investment is low risk for the Commission, but gives it a certain amount of positive press from media, developing countries, and certain drug access advocates.

Finally, the European Commission grant was only available to a European NGO operating in a developing country in conjunction with a local partner. Funds were transferred to Action Medeor specifically to be allocated and distributed at TPI. European Commission informants contended that channelling funds through registered NGOs ensures appropriate management and accountability of resources. However, developing country informants were more sceptical. They noted that, often, project consultants, personnel, materials, and machinery are not recruited or procured in-country, but outsourced. Intentionally or unintentionally, significant portions of these grants do not remain within LDCs, but returns to donor countries. Although this may be an indication of the low skill level in LDCs, local informants suggested that greater effort to train and strengthen domestic capability is needed.

Does Domestic Production Produce Affordable ARVs?

Questions arise over the short-term nature of the technology transfer project (48 months) and whether US$6 million can successfully fund construction of a WHO GMP-compliant facility that will produce affordable ARVs. This objective is difficult to meet. As of late 2008, TPI had yet to match its US$600,000 portion of the grant and plant construction was not complete. If construction and WHO GMP certification are achieved, the necessary investment for WHO
prequalification of its ARV products will be the responsibility of TPI (and not covered under the European Commission grant). In addition, under the terms of the grant, TPI agreed not to profit on its ARV pricing in the public sector during the project period and, once the project is complete, to make a limited profit for 5 years. Considering the highly competitive ARV market and the limited manufacturing capacity at TPI, its ability to match the price of international firms, even on a non-profit basis, is extremely difficult. As such, the arrangement aiming for high-quality, low-cost ARVs has questionable affordability and, therefore, questionable long-term viability. This is important in a larger context where Khoubessarian (2009) warns that global health initiatives, such as the European Commission grant, often put a number of important initiatives in competition with each other for funding. Vertical programs fixate on short-term crisis management as opposed to fostering long-term public health strategies. If the current initiative in Tanzania is not viable, the opportunity costs are high.

The sustainability of TPI’s technology transfer arrangement is also affected by the commitment of the Tanzanian government to incentivize pharmaceutical manufacturing. Poor infrastructure remains in Tanzania, and few resources have been devoted to higher education for pharmacists and to other fields of science and technology. The limited manufacturing capacity of TPI, combined with the country’s lack of skilled labourers, has placed TPI in a position that requires investment in building infrastructure and human resource capacity.

Despite MoHSW’s attempt to bolster the industry (through preferential registration, GMP-compliance assistance, and MSD’s 15% price equalization during tenders), TPI’s prices are not competitive. Further, its production costs are high as a result of its poor development and
production capacity and lack of vertical integration. Unable to finance the costs of development and quality accreditation, TPI’s eligibility for large donor-financed tenders is barred. As a result, TPI cannot compete on price and increase affordability within Tanzania.

**Policy Implications**

By assessing the domestic conditions affecting the development and affordability of locally manufactured ARVs in Tanzania, the case study results are useful to developing country governments faced with securing low-cost essential medicines for their populations as well as building their countries’ technological capacity. Within the “make-or-buy” context, this research highlights the difficulty of domestic manufacturers to supply affordable medicines when a large number of high volume international competitors exist. This case study suggests that LDCs, with little financing, have limited opportunities to attract the transfer of technology, regardless of their IP status. LDC governments must carefully consider their options when reforming patent legislation to comply with standards of the TRIPS Agreement. An increase in patent protection may have little bearing on the incentives for patent holders to transfer technology as they are compelled to do under Articles 7 and 66.2 of the TRIPS Agreement and the 30 August Decision of the General Council.

The transfer of technology particularly may be a concern for firms with some state-ownership. Patent holders stress caution about corruption, transparency, and bureaucracy in the management of state-owned firms. LDCs should ensure that the appropriate safeguards within domestic legislation are in place to keep drug access and public health at the forefront of public policy.
These include provisions for domestic compulsory licenses, third party compulsory licenses, and parallel importation, as well as for narrowing the scope of ARV patentability.

Articles under the TRIPS Agreement promoting the transfer of technology and public health flexibilities are often criticized for not being operational. There are no measures to determine their success (Correa, 1999; UNCTAD, 2000). For example, given the vague technology transfer definition under Article 7, what constitutes the transfer of technology is often left to the discretion of WTO Member countries. This disadvantages developing countries and LDCs in ensuring that the provision is put into practice at the advantage of more dominant developed countries. The result has researchers calling the TRIPS Agreement a “bad faith” bargain for countries like Tanzania that, with little negotiating power, hoped to exchange technology transfer for patent protection (Correa, 1993; Finger, 2007).

The TRIPS 2016 transition period in LDCs has even greater bearing on second-line and future ARV regimens. As many international generic firms are unable to produce second-line ARVs due to patent restrictions, competition and price are less of a barrier for market entry by LDC firms. Yet, the markets for these drugs are currently very small in developing countries and LDCs, and these drugs tend to be more complex technologically, requiring greater technical capability and more skilled human resources. Given the difficulty of TPI to produce affordable first-line ARVs, LDC firms must be cautious when entering ARV manufacturing arrangements for both first- and second-line products. Government and industry must assess the capability to formulate and produce ARVs at an internationally competitive price while achieving stringent quality accreditation from FDA or WHO.
The research findings of this case reinforce Cohen-Kohler’s (2009) suggestion that even though TRIPS provisions offer governments the ability to put health before trade objectives, many developing countries and LDCs simply cannot utilize these provisions. In these situations, barriers in administration, politics, policy, and capacity debilitate their use of TRIPS flexibilities. In addition, when developing countries search for a technology transfer partner, other factors such as cultural relationships can help or hinder a project’s feasibility. These factors should be addressed upfront by developing country governments and firms, along with other noted barriers, to evaluate whether or not the initiative is viable.

Finally, due to the limited resources of LDCs, successful technology transfer arrangements and manufacturing initiatives require long-term coordination and planning across health, industrial, and science and technology sectors. This planning also includes industrial policies that are tied to education reform. The limited skilled labour force in Tanzania is a challenge common to most Sub-Saharan African countries. The appropriate focus on secondary and tertiary education, as well as human resource training, is essential, not just to increase the capacity of industry but to increase the availability of health care professionals to provide ARV treatment and meet public health objectives. Most important, however, if a technology transfer initiative cannot produce competitively priced ARVs, resources should be allocated to another area of drug access that would allow greater marginal benefit overall. This includes the appropriate training of health professionals and improvements to basic health care and health infrastructure.
Conclusion

This chapter used the case of ARV production by Tanzania Pharmaceutical Industries (TPI) to identify the conditions that influence the development of technology transfer initiatives and the production of low-cost ARVs. This case study identified four important conditions within the domestic arena: the policy environment, ARV market conditions, as well as the manufacturing capacity, and financial structure TPI. In Tanzania, lack of patent protection along with TPI’s poor financing and state-ownership gave it few options when seeking a technology transfer partner. Not-for-profit donors entered the arrangement with a development and public health agenda. When considering the disputed “make-or-buy” framework, entry into domestic tenders is limited without ARV WHO prequalification. Also, TPI does not produce the volume necessary to make use of economies of scale to manufacture ARVs at an internationally competitive price. As a result, TPI has no impact on increasing the affordability of ARVs in Tanzania.

While this case is limited in terms of generalizability, it provides a framework for LDC governments to understand the important considerations of ARV production. LDCs preparing to revise their patent legislation for the 2016 TRIPS deadline should recognize the possible implications on the transfer of technology. Attracting technology transfer relies not only on the IP system in place, but on domestic firm ownership and financing. The degree of donor assistance in ARV procurement and manufacturing capacity must be assessed as they highly influence firms’ ability to compete on the market.

This research engages both policy makers and researchers to consider (both theoretically and practically) how technology transfer arrangements can be addressed in LDCs. In particular, an
LDC needs to assess the ability of local manufacturers to meet both the country’s development and public health objectives in an affordable manner prior to developing technology transfer arrangements. If deemed viable, appropriate resources and policy strategies should be dedicated to their development. However, if an initiative cannot produce competitively priced ARVs, resources should be allocated to another area of drug access, such as human resources training and improvements in basic health care and health infrastructure.

**Summary and Introduction to Chapter 3**

This chapter assessed a case of one type of technology transfer arrangement: an imitation arrangement at Tanzania Pharmaceutical Industries (TPI) in Tanzania. In Chapter 3, this research analyses a case study of the second type of technology transfer arrangement: a voluntary licensing arrangement. This arrangement is found in South Africa between its domestic ARV manufacturers, Aspen Pharmacare (Aspen), and patent holders GlaxoSmithKline (GSK) and Boehringer Ingelheim (BI). Using the same methods as the case study in Chapter 2 and outlined in Chapter 1, Chapter 3 analyzes the domestic conditions affecting the development of the voluntary licensing arrangements at Aspen as well as the factors influencing the firm’s ability to manufacture ARVs and compete in the public sector with affordable prices.
Chapter 3: A Public Affair? Voluntary licenses for the Local Production of Affordable ARVs in South Africa

Introduction

South Africa’s experience with HIV/AIDS and antiretroviral (ARV) drug treatment has been followed internationally by media, activists, researchers, donors, the pharmaceutical industry as well as international organizations. As a compliant member of the World Trade Organization’s (WTO) Agreement on the Trade Related Aspects of Intellectual Property (TRIPS), South Africa protects pharmaceutical patents for 20 years from their filing date. As stated in Article 7 of the TRIPS Agreement, the protection and enforcement of intellectual property (IP) “should contribute to the promotion of technological innovation and the transfer and dissemination of technology” (WTO, 1994, p. 323). Patent holders most commonly transfer technology in the form of voluntary licenses to outside firms. This can lead to the manufacture of generic ARVs prior to patent expiry, to increase competition in the market and reduce prices. Having the largest HIV-infected population in world (approximated at 5.7 million) and a high prevalence rate, at 18.1% (UNAIDS, 2008), the South African government also could opt to use provisions within the TRIPS Agreement and the subsequent Doha Declaration on TRIPS and Public Health to call a national emergency and allow the manufacture of generic ARVs, without patent holders’ consent.

This chapter is a case study examining the South African conditions that affected the transfer of technology to local manufacturer Aspen Pharmacare (hereafter called Aspen) for first-line ARVs lamivudine, zidovudine, and nevirapine. In addition, this case study also analyzes Aspen’s ability to produce ARVs affordably for the public sector. Domestic conditions pertinent to this case
include South Africa’s policy environment and ARV market characteristics (such as size, competition, and tender requirements) as well as Aspen’s manufacturing capacity and financial structure (including its ownership and access to financial capital). The framework in Figure 7 (seen in Chapter 3) demonstrates how these conditions interact within the political and social context of the country as well as with civil society\textsuperscript{24}, international organizations, and multinational patent holders. These relationships influence both the type of technology transfer arrangement that Aspen secured as well as the affordability of its generic ARVs.

This chapter argues that the strong IP system in South Africa, combined with the poor commitment of the Mbeki Administration to ensure ARV treatment rollout and access to affordable ARVs, left the government unwilling to utilize its flexibilities within domestic legislation and under the TRIPS Agreement to issue a compulsory license. Within an internationally scrutinized policy environment, Aspen leveraged its well-financed publicly-traded firm and growing relationships within the research-based pharmaceutical industry to seize its market opportunity and negotiate the world’s first voluntary ARV licenses. Throughout this process, civil society (through the Treatment Action Campaign [TAC]), mobilized public pressure and utilized the judicial system to shift government policy and influence ARV licensing negotiations between Aspen and the patent holders. Actions by civil society ensured both a national ARV rollout program and a number of reasonably termed ARV licenses to increase competition in the domestic market.

\textsuperscript{24} Civil Society is defined as both informal and formal groups and/or organizations that act independent of the government and the market. These groups are outside of public and private sectors and can include voluntary organizations, community groups, charities, and non-government organizations.
Next, this chapter argues that the affordability of Aspen’s domestically manufactured ARVs was influenced by its ability to capture a large and consistent market share, its capacity for raw material production to maximize economies of scale, and its competition to reduce price. Capturing market share not only depends on competition, but on Aspen’s ability to achieve the international quality requirements of lucrative donor-financed tenders: meeting standards of the World Health Organization’s (WHO) Prequalification Programme or the United States’ Food and Drug Administration (FDA) under the Bush Administration’s President’s Emergency Plan for HIV/AIDS Relief (PEPFAR). Volume and the capacity to bring all the stages of production (from raw materials to packaging) under the firm, affects manufacturing costs. Most notably, this includes extraction or synthesis of active pharmaceutical ingredients (APIs) used to formulate the ARVs to reduce the component costs of production. Currently, Aspen does not have API production capacity for ARVs in South Africa. Finally, competition within South Africa’s domestic market is restricted due to patent protection and slow drug regulatory authority (DRA) approvals. These factors keep Aspen’s prices above what could be achieved on the international open market.

Using the strategy to become the first generic market entrant through the acquisition of new ARV licenses, this chapter argues that Aspen increased first-line ARV affordability from patent holders to meet comparable international generic prices. However, without government tendering of triple fixed-dose combinations (FDCs) and without sufficient competition in the market for alternative first-line products, Aspen’s treatment costs remain higher than those in neighboring Sub-Saharan African countries.
This chapter is an analysis of the development of Aspen’s voluntary licenses and the factors influencing ARV affordability. It has six sections. First, a brief background is provided of South Africa’s health and pharmaceutical sectors. Second, each of the four conditions affecting the development of technology transfer arrangements and affordability is discussed in turn: South Africa’s policy environment, Aspen’s financial structure, its manufacturing capacity, and the ARV market characteristics. Third, policy implications of the case study will conclude the chapter.

**Background**

South Africa is one of the richest countries in the Sub-Saharan Africa region, with a per capita Gross National Income (GNI) of US$5,760 in 2007 compared with the 2007 regional average of US$952 (World Bank, 2008b). Despite this wealth, apartheid left South Africa with one of the highest disparities in income equality in the developing world: in 2000, the richest 20% of the population accounted for 62.2% of income in the country (UNDP, 2008). Table 6 lists economic, health and pharmaceutical industry indicators in South Africa. As a result of this income disparity, the health care system has been highly segregated along socioeconomic lines. In 2006, 20% of South Africans were covered by a private health system consuming US$300 (R2 000) per capita per year, while or 80% of the population, nearly 40 million South Africans, depended on the public system at a support level of less than US$15 (R100) per capita per year (Maloney & Segal, 2007).
Table 6: Socio-Demographic and Pharmaceutical Industry Indicators in South Africa

<table>
<thead>
<tr>
<th>I. Socio-demographic Indicators</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gini Coefficient (2006)</td>
<td>57.8</td>
</tr>
<tr>
<td>Human Development Index</td>
<td>0.674</td>
</tr>
<tr>
<td>HIV Prevalence (aged 15-49)</td>
<td>18.1%</td>
</tr>
<tr>
<td>Adults (aged 15 and up) living with HIV</td>
<td>5.4 million</td>
</tr>
<tr>
<td>Population on ARV Treatment (2008)</td>
<td>487,000</td>
</tr>
<tr>
<td>2008 ARV Treatment Target</td>
<td>500,000</td>
</tr>
<tr>
<td>Expenditure on health as percentage of GDP (2005)</td>
<td>8.7%</td>
</tr>
<tr>
<td>Private Expenditure on Health (as percentage of total health expenditure, 2005)</td>
<td>58.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Pharmaceutical Industry Indicators</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Registered Pharmaceutical Firms</td>
<td>98</td>
</tr>
<tr>
<td>Pharmaceutical Industry Sales</td>
<td>US$2.6 billion</td>
</tr>
<tr>
<td>Patent System</td>
<td>Yes</td>
</tr>
<tr>
<td>TRIPS Compliance</td>
<td>1996</td>
</tr>
<tr>
<td>Domestic Firm in Case Study</td>
<td>Aspen Pharmacare</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Technology Transfer Arrangement</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Arrangement</td>
<td>Voluntary License</td>
</tr>
<tr>
<td>Patent Holders</td>
<td>GSK and BI</td>
</tr>
<tr>
<td>Year Production Announced</td>
<td>2001 and 2002</td>
</tr>
<tr>
<td>ARVs Produced (under GSK and BI license)</td>
<td>Lamivudine (3TC), zidovudine (AZT), Nevirapine (NVP)</td>
</tr>
</tbody>
</table>

Note. GDP= Gross Domestic Product, TRIPS = Agreement on the Trade-Related Aspects of Intellectual Property, GSK= GlaxoSmithKline, BI=Boehringer Ingelheim

Furthermore, initiation of a national ARV rollout program in South Africa was slow. A major driving force behind the commencement of South Africa’s ARV program was TAC. Founded in 1998, TAC is an activist organization that campaigns for “equitable access to affordable treatment for all people with HIV/AIDS… [and challenges, through] litigation, lobbying, advocacy and all forms of legitimate social mobilisation, any barrier or obstacle, including unfair
discrimination, that limits access to treatment for HIV/AIDS in the private and public sector” (TAC, 2006, TAC’s Strategic Objectives). In addition to organizing treatment-literacy campaigns, mass protests, local demonstrations and disseminating educational informational, TAC brought legal action against both the South African government and the research-based pharmaceutical industry on behalf of people living with HIV/AIDS, to fight for greater access to affordable ARVs.

South Africa constitutes 0.3% of the world market for pharmaceuticals, the largest in the African continent, which totals only 2% of the world market (Combe, Pfister, & Zuniga, 2003). In 2006, the South African market was valued over US$2.6 billion. Only 25% percent of this value (US$662 million) was spent on local South African drugs and the remainder on those imported (IFC, 2008). However, within Sub-Saharan African, South African manufacturers are the dominant generic manufacturers. In 2007, they accounted for more than 70% of the US$1 billion in pharmaceuticals produced regionally (IFC, 2008). Currently, Aspen is the leading manufacturer of affordable generic medicines in South Africa. The firm is involved in the manufacturing, sourcing, sale and distribution of over 1200 products that fall into 7 categories: ethical drugs, generic products, over-the-counter pharmaceuticals, personal care products, nutraceutical25 products, consumer goods, and infant nutrition formulations.

As a regional leader, Aspen was the first pharmaceutical company to receive voluntary licenses for the production of ARVs. The licenses were issued in 2001 from patent holder GlaxoSmithKline (GSK) for the combination zidovudine+lamivudine (AZT+3TC) and its individual components. This was followed by a license from Boehringer Ingelheim (BI) for

25 Food or supplement that claims to have medicinal effect.
nevirapine (NVP) in 2002. Restricting Aspen’s generic ARVs to the private and not-for-profit market in South Africa, the terms of these licenses expanded in 2003 to include the public sector as well as the Sub-Saharan market. This was after an excessive pricing complaint was brought by TAC and others before South Africa’s Competition Commission against GSK and BI. In January 2005, Aspen received FDA approval for a number of its ARVs, including a co-packaged generic combination of these products (AZT+3TC co-packaged with NVP). Since that time, Aspen has become involved in additional strategic licensing agreements with patent holders Bristol-Myers Squibb (BMS), Gilead Sciences (Gilead), Merck & Co. (Merck), and Hoffmann-La Roche (Roche) for the manufacture and distribution of a number of ARV products.

Policy Environment of ARV Treatment, Cost, and Manufacturing

Under the Administration of former President Thabo Mbeki, the policy environment in South Africa surrounding ARV treatment was both complex and controversial. Poor governance, exhibited by denialist behaviour and faltered political leadership on HIV/AIDS policies, produced no coordination for an ARV treatment program in the public sector. Inaction on treatment allowed South Africa’s strong patent system to dominate the use legislative provisions, such as compulsory licensing, to bring affordably priced generic ARVs to the market. As a result, few incentives were put in place by government to foster growth of a generic ARV industry in South Africa. However, with an advanced legislative framework in place, the civil society organization TAC consistently drove policy change, lobbying the state and using the judicial system.
Engagement of civil society shifted government policy leading to a public ARV treatment program and several voluntary licensing arrangements between generic manufacturers and patent holders (including Aspen’s licenses with BI and GSK). Together, these licenses led to a growth in the generic ARV industry and subsequent recognition by the South African government of the need to review industrial, and science and technology policies to further develop the pharmaceutical industry.

**The Right to Treatment**

The factors driving the rollout of ARV treatment in South Africa are important to understand in the context of this case. They underline the unwillingness of the Mbeki Government to provide treatment to its citizens, which set the terms of the country’s ARV market. With the transition from apartheid to democracy in 1994, formal structures and a progressive HIV/AIDS framework were already in place—with the creation of the National AIDS Convention of South Africa and the National AIDS Plan in 1992 and 1993, respectively (Nattrass, 2007). When Nelson Mandela assumed the presidency in 1994, a number of health policies issues needed to be addressed in addition to HIV/AIDS. The enactment of Constitution of the Republic of South Africa in 1996 entrenched the duty of government to create a legal framework that provides access to health care services for all citizens. Although the Constitution legally put an end to the inequality experienced during apartheid, the resulting redistributive health policies faced daunting obstacles when the number of patients increased by 6.5 million between 1996 and 2005 (Forman, 2005). The focus and financial resources of the Department of Health (DoH) were then allocated to increase the availability of basic care and services during the mid-1990s when the HIV/AIDS epidemic grew exponentially.
HIV/AIDS did not appear to be a priority during the first years of the Mandela presidency; with former President Mandela himself later admitting that he refrained from addressing HIV/AIDS publicly out of fear of losing the next presidential election (Nattrass, 2007). By 1999, the prevalence of HIV/AIDS had risen to 22.4% among pregnant women attending antenatal clinics, and 4.2 million South Africans were HIV-infected (approximately 7% of the general population) (DoH, 2000). Question remains whether this rise in prevalence resulted from a public policy failure of the Mandela Administration or an unavoidable effect of the number of HIV strains in the region and South Africa’s geographical and economic position, which attracted a high number of migrants (Iliffe, 2006).

**AIDS Denialism under the Mbeki Administration**

With the transition of the African National Congress (ANC) leadership from former President Nelson Mandela to former President Thabo Mbeki on June 14, 1999, activity on HIV/AIDS faltered into denialist behaviour. Under his Mbeki’s Presidency, government policies and actions surrounding ARVs, patents, and treatment programs remained under intense public scrutiny, not just domestically, but internationally as well. With a larger population requiring more services from the public sector, the Mbeki Government was slow to develop an HIV/AIDS strategy. Government rationalized the absence of public programming for ARV treatment as a result of scare financing; however, scholars cite the AIDS denialism\(^{26}\) of Mbeki’s Administration for the failing political leadership to rollout a comprehensive ARV program (Barnett & Whiteside, 2006; Crewe, 2000; Forman, 2003; Forman, 2005; Friedman, 2006; Mbali, 2003; Nattrass, 2007;  

\(^{26}\) AIDS denialism is attributed to a group of dissidents who did not believe in a causal link between HIV and AIDS. Instead, they often attributed immune failure to the toxicity of ARVs, and in Africa, from poverty-related malnutrition and illness treatment. While this theory was quickly disproved scientifically, it remains popular among a small number of researchers (Forman, 2003; Nattrass, 2007).
Simkins, 2001; Sitze, 2004; Sprague & Woolman, 2006; van der Vliet, 2001; Wang, 2008). Questioning a causal link between HIV and AIDS, former President Mbeki, through his “involvement with denialists undermined AIDS prevention and treatment with ARVs and haunted the policy environment through his silence” (Nattrass, 2007, p. 35). Often, Mbeki displayed denialist behaviour not by direct actions, but by inaction—in developing the appropriate HIV/AIDS policies. Forman (2005) notes that Mbeki’s leadership was “weak, confusing, counter-productive and even obstructive. Rather than guiding government's response to HIV/AIDS, he has constrained it” (p. 717).

An example of the Mbeki Administration’s AIDS denialism was the removal of state funding by former Health Minister Dr. Tshabalala-Msimang’s for a program to distribute zidovudine (AZT) to pregnant HIV-infected women for the prevention of mother-to-child transmission (PMTCT) in 1999. Butler (2005) suggests that the government withheld resources because an ARV rollout would require approximately 12% of the health budget at a time when other development issues were priority. In doing so, Dr. Tshabalala-Msimang stated that the resources were better allocated to prevention programs (Baleta, 1999). This budgeting logic, however, was disputed on a number of occasions; it is seen as a cover for the Mbeki Government’s AIDS denialist mentality.

First, Nattrass (2008a) questions the validity of the budgeting argument, given the fact that a rollout program would actually reduce the number new HIV cases and hospitalizations for opportunistic infections, and create overall cost savings for the public health care system. Omission of the appropriate cost analysis for ARV rollout underscored the Mbeki
Administration’s poor effort to address the HIV/AIDS epidemic and reinforced theories of AIDS denialism within the highest levels of government (Nattrass, 2007).

Second, in response to the government’s AZT treatment retraction, BI offered a 5-year donation of nevirapine (NVP), another effective single dose therapy for PMTCT. Again, citing concerns about the drug’s toxicity and efficacy in addition to resource constraints, its implementation was denied by government (Forman, 2005).

Third, instead of the appropriate monitoring and evaluation of a pilot ARV project in the Western Cape township of Khayelitsha, the Mbeki Administration instilled fear of treatment among its citizens. An ANC statement in 2000 shunned the project as a “total disregard for the well being and safety of our people who are being used as guinea pigs and conned into using dangerous and toxic drugs that are detrimental to their own health” (Nattrass, 2007, p. 36). The poignant language in official statements by the leading party and the Health Minister frightened patients by suggesting ARVs were “poison” (Nattrass, 2007, p. 99), leading some to refuse treatment. Only after public outrage incited civil society lobbying did a 2 year pilot program begin at 18 sites. Yet, a year later in 2001, few sites were operational, and any other access to ARV treatment through the public health system was blocked until the government could be adequately assured of its safety and efficacy. These actions clearly pointed to the Mbeki Administration’s denialist behaviour given the fact that, by this time, NVP had been approved by stringent DRAs in most of the developed world, including in the United States and the European Union (in 1996 and 1997, respectively) and was in use by HIV-infected patients globally.
At this point in 2001, pressure from civil society and the international media grew against the Mbeki Government’s inaction on ARV treatment rollout. TAC mobilized civil society to demand ARV treatment as a right to health care services as provided under section 27 the Constitution, and TAC brought a suit against the DoH for its policy on NVP for PMTCT (Hassim, Heywood, & Berger, 2007). The Constitutional Court’s decision *Minister of Health v Treatment Action Campaign (No 2) 2002 (5) SA 721 (CC)*, agreed with the rights of the patient. In July 2002, the Court ruled that the “government had acted unreasonably in (a) refusing to make an antiretroviral drug called nevirapine available in the public health sector …[and] (b) not setting out a timeframe for a national programme to prevent mother-to-child transmission of HIV [PMTCT].” In doing so, it ordered the government to “permit and facilitate the use of nevirapine [NVP]” (Constitutional Court, 2002, p. 3). The decision of the Constitutional Court reflected the capacity of the judicial branch of government to enforce greater accountability on the state with regards to its national HIV/AIDS policies. It also illustrated the ability of civil society to successfully challenge government policy and deliver a judgement in keeping with the human rights obligations of South African Constitution (Forman, 2003).

Yet, even with the Constitution Court ruling, the DoH resisted introducing ARVs until a Cabinet revolt assumed control of HIV/AIDS policies. In November 2003, Cabinet adopted the Operational Plan on Comprehensive HIV and AIDS Care, Management and Treatment for South Africa (Operational Plan). Emphasizing the unwillingness of top DoH officials to support HIV/AIDS programming, and to improve relations with civil society, the Deputy President, Phumzile Mlambo-Ngcuka, was placed as the coordinator of the government’s response instead of Health Minister Dr. Tshabalala-Msimang (Nattrass, 2007).
**The Right to Affordable Treatment**

In Paragraph 90.5 of the Executive Summary, the Operational Plan emphasizes that negotiations with patent holders should seek to make drugs affordable and accessible. It also promotes the transfer of technology for the local production of ARVs and APIs. This echoes South Africa’s National Drug Policy of 1996, which encourages the local manufacture of essential medicines and the procurement of a sustainable supply of low-cost medicines to achieve a successful medicines rollout strategy. With little government support for ARVs, it did not address the high, unregulated prices of patented ARVs available only in the private market. The government took no measures, either through price negotiation with patent holders, the use of parallel importation, or compulsory licensing, to increase ARV affordability.

**IP Constraints and ARV Price**

Calling for a sustainable supply of low-cost ARVs, the Operational Plan’s goal was restricted by South Africa’s patent legislation. South Africa’s patent system is guided by the Patents Act of 1978.\(^\text{27}\) The 20-year patent term for pharmaceutical products and processes under Article 33 of the TRIPS Agreement already existed in South Africa prior to the Agreement’s ratification, seen in the 1983 amendment to the Patent Act s.5 no.67. This early patent system stemmed from the former nationalistic apartheid regime as well as political pressure from developed countries, such as the United States (Kapczynski, 2002). Barred from the global trade community during apartheid, the country developed a strong scientific base to maintain self-sufficiency (Motari, et al., 2004). This included a strong IP system. Although concern has been raised over the effectiveness of the country’s IP enforcement (Teljeur, 2000), the strength of South Africa’s IP

system ranks ahead of all middle-income countries and in the top 20% of 115 countries surveyed in the 2008 International Property Rights Index. This index is a measure of the legal and political environment, physical property rights enforcement, and protection of IP globally (IPRI, 2008).

As a result of this early, and arguably strong, patent protection for a developing country, generic drug access has been far more constrained in South Africa than in other comparable developing countries, such as Brazil and India. This is because, under the TRIPS Agreement, there are a number of implementation periods available to developing countries that could not be utilized in South Africa. These transition periods were included to allow developing countries time to reform their patent legislation and build the appropriate capacity to review and evaluate patent applications.

First, the TRIPS Agreement only requires protection on pharmaceutical patents filed after the date of implementation (January 1, 1995). Importantly, many first and some second-line ARVs were patented in the 1980s and early 1990s and have not been subject to patents in transition countries. Under the TRIPS Agreement, developing countries such as Brazil, which only created its patent law in 1996, were able to import or manufacture without repercussion ARVs that were patented in many other countries. In contrast, South Africa, like most developed countries, had already patented these ARVs prior to the TRIPS Agreement. This made the country ineligible for the transition period, and so the patent terms had to be respected until their expiry (Attaran, 2004).

However, some pipeline patents were awarded in Brazil. This included drugs patented prior to TRIPS implementation in 1995, but that had not entered the market as they were still undergoing clinical trials and market authorization.
Second, a transition period until 2005 for pharmaceutical product patent enforcement was granted to developing countries. Those countries that had either no patent system at all or only process patents in place at the time of ratification of the TRIPS Agreement were granted the transition period to adapt the requirements into legislation. India, which only protected process patents at the signing of the TRIPS Agreement, used this time to manufacture generic ARVs for both domestic use and export.\(^{29}\) The transition period led to an exponential growth in India’s pharmaceutical industry, and the country is currently the largest supplier of low-cost generic ARVs to developing countries (Shadlen, 2007). Again, in South Africa, this transition period did not exist because the country’s pre-existing patent system granted both product and process patents even before the TRIPS Agreement came into effect.

Unlike Brazil and India, domestic ARV manufacturing in South Africa was restricted to patent holders or generic firms to which the product was licensed. It was not until October 2001 that the first licenses were issued by GSK to Aspen, and the AZT was approved by the South African Medicines Control Council (MCC) in 2004. During this time, in 2002, MSF gained notoriety when it contravened the Patents Act and imported unregistered generic ARVs manufactured in Brazil to treat HIV patients in the township of Khayelitsha (even though it was authorized to do so by MCC). The generic first-line regimen, AZT+3TC+NVP, was purchased for US$1.55 per person per day (pppy) instead of US$5.50 offered in the private sector and US$3 offered by patent holders to government. This vast price difference highlighted the constraint that IP protection placed on treatment price in South Africa, compared with other developing countries such as Brazil (MSF, et al., 2003).

\(^{29}\) This transition period was under the condition that, at the end of the transition period in 2005, the Indian Patent Office would review patent applications that had accumulated since 1995.
Government Willingness to Use TRIPS Flexibilities

Balancing the country’s strong IP system, South Africa also has the most advanced regulatory framework in the region (Avafia, Berger, & Hartzenberg, 2006), which includes a number of TRIPS flexibilities. These flexibilities are provisions within the TRIPS Agreement and domestic legislation that allow government, under certain conditions, to abrogate patents in favour of increasing drug access through the Patents Act (1978), the Medicines and Related Substances Control Act (1965 and 1997), or the Competition Act (1988). Failure of the Mbeki Administration to rollout comprehensive ARV treatment undermined the government’s capability to use any of the TRIPS flexibilities that could substantially lower the price of ARVs. This failure was attributed to the AIDS denialism of the government, led by former President Mbeki and former Health Minister Tshabalala-Msimang, and to mounting international pressure by the research-based pharmaceutical industry and the United States on the South African government to remain TRIPS-compliant.

International pressure on the South African government was highlighted during a debate over Section 15c of the Medicines and Related Substances Control Act. This Act outlines mechanisms for the MCC to ensure the quality, safety, and efficacy of medicines. Under former President Mandela’s Administration, and shortly after the TRIPS Agreement was ratified, amendments within Act 90 of 1997 introduced the Essential Drug List, and Section 15c enabled the Health Minister to “prescribe conditions for the supply of more affordable medicines in certain circumstances” (DoH, 1997, p. 10). It was assumed that these provisions could be used introduce price competition through parallel importation, promotion of generic substitution, or compulsory licensing. Even though the Act stipulated these provisions could not contravene the Patents Act,
the Pharmaceutical Manufacturers’ Association of South Africa (PMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) viewed Section 15c as an infringement of property rights and a violation of the TRIPS Agreement. In response, 39 research-based pharmaceutical firms represented by PMA brought the South African government to the Pretoria High Court in February 1998.

Described as pitting the multinational research-based pharmaceutical industry against the developing world (CABSA, 2002), the trial depicted “power politics at its most raw and rarefied” (Sprague & Woolman, 2006, p. 362). PMA and PhRMA, initially backed by the United States government30 as well as the European Commission, contended that the amendment of Section 15c violated both the South African Patents Act and the TRIPS Agreement, and discriminated unfairly against the pharmaceutical industry. They added that this infringement negatively affected South Africa’s ability to maintain and attract foreign investment (CABSA, 2002). Government faced threats of unilateral sanctions by the United States Trade Representative (USTR). The South African government, however, attested that it was implementing the principle of international exhaustion31 of patent rights for parallel importation, while AIDS and human rights activists supported the government’s use of Section 15c for compulsory licensing, in order to protect the right to affordable treatment.

The international media followed the trial and, in 1999, with a United States presidential election underway, activists began to protest at American campaign rallies and the court case turned into a “public relations disaster” for both the pharmaceutical industry and the United States

30 In 1997, six of world’s major pharmaceutical companies had headquarters in the United States.
31 Once a product has been placed on the market by the patent holder, the exclusive rights to the product expire and cross-boarder resale of the product cannot be opposed.
government. Activists argued that industry was placing “profit above lives” (CABSA, 2002, p. 1) and, by the time the case was presented in court in 2000, the United States government had officially changed its policy and withdrew its support of the pharmaceutical industry (‘t Hoen, 2003).

During the court hearing, the South African government was supported by a large number of AIDS and human rights activist groups and organizations (such as TAC, ACT UP, Health Gap Coalition, MSF, Oxfam) and well respected political leaders (‘t Hoen, 2003). Forman (2009) points that former President Mandela publicly criticized the pharmaceutical industry for charging excessively high ARV prices, and that WHO, in addition to supporting the government’s defence, went so far as to facilitate legal assistance. MSF launched a global petition “Drop the Case”, which was signed by nearly 300,000 individuals in over 130 countries (MSF, 2001). In March 2001, the court accepted TAC as amicus curiae32 in the case to testify and present evidence. TAC strategically focused its testimony on the cost of patented ARVs within South Africa (Nattrass, 2007).

The case was withdrawn in April 2001, and the South African government claimed victory. The validity of this victory, however, is questionable. Even though the amendments to the Medicines and Related Substances Control Act were put into force in May 2003, Section 15c remains ambiguous and unused. During litigation from 1998 to 2001, government maintained that Section 15c would only be used for parallel importation. In doing so, it effectively abandoned the opportunity to utilize the clause for compulsory licensing unless willing to face further litigation.

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32 A Latin term meaning *friend of the court*. It is used in law to refer to an individual or organization that is not party to a particular litigation, but has strong interest in the matter and petitions the court to submit information, such as a brief or legal testimony not solicited by either party, which directly affects the case.
(Hassim, Heywood, & Berger, 2007; Sacco, 2004). Using game theory, Cleary and Ross (2002) argue that, as a result of mass demonstrations by AIDS activists, the trial’s public relations cost diminished the value infringement suit to the PMA. Similarly, the value of securing the right to issue compulsory licenses faded under Mbeki’s Administration because it did not want to be accountable to rollout ARV treatment. McIntyre, Thomas and Cleary (2004) also suggest that the government not wanting to jeopardize its status as a “model WTO citizen” (p. 147) claimed victory when the case was withdrawn, even though it conceded defeat on the issue that prompted the case in the first place—compulsory licensing.

Despite rendering the amendment to the Medicines and Related Substances Act unworkable and souring relations between South Africa and the research-based pharmaceutical industry, the court case over Section 15c had massive implications for drug access in the international arena. Forman (2009) suggests that the first implication, within a number of United Nations and international statements, was the articulation of treatment as a human right and the obligation of governments to provide ARVs to their citizens. Second, with negative press emerging from the South African court case, including media coverage of ARV access issues, and support from similar access movements in Brazil, momentum grew among developing countries to push for the acknowledgment of public health priorities in the context of international trade. Concern over health security in United States also increased after the terrorist attacks of September 11, 2001 and the dispersion of the bacterium anthrax in the country. To avoid jeopardizing trade talks during the Doha Round of WTO negotiations with drug access issues, the Doha Declaration on TRIPS and Public Health was adopted in November 2001. The Doha Declaration empowers developing country governments to issue compulsory licences in cases of national emergency or
public health crises. In doing so, they can manufacture generic drugs locally without repercussion from developed countries or the pharmaceutical industry. This can be done provided that the necessary provisions are made in domestic legislation.

Although the South African government has yet to use any flexibility within its domestic legislation, specific provisions for compulsory licensing are outlined in the Patents Act. Section 4 of the Patents Act permits state use of patented products for public purposes “on such conditions as may be agreed upon with the patentee” (Republic of South Africa, 2002). If no agreement is made, the case can be brought to a hearing before the Commissioner of Patents at the Pretoria High Court, where a compulsory license can be issued. Section 56 enables compulsory licensing to cease abuse of the rights of a patent, and Section 78 allows acquisition of patents by the Minister of Trade and Industry on behalf of the state. Requests have been made to government by a number of organizations and firms, such as the AIDS Law Project (ALP), TAC, MSF, Congress of South African Trade Unions, Oxfam, and generic manufacturer CiplaMedpro to issue a compulsory license under Section 4 #33 (Kaiser Network, 2002a; TAC, 2005). All of these requests were ignored. In 2001, then Health Minister Tshabalala-Msimang reinforced the government’s disinterest to use compulsory licensing to bring down the cost of ARVs, stating:

…compulsory licensing is only one way of addressing the issue of affordable medicines and it is useful only in specific circumstances. If we want to make a meaningful impact

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#33 While Section 56 allows for any interested party to apply for a compulsory license, this is only if the rights of the patent are being abused. This is seen as a provision providing a more narrow scope than what is required under the TRIPS Agreement (a so-called TRIPS-plus provision). It is within this provision that two barriers exist: 1. the interested party must be within the business of drug manufacturing or importing. So, civil society does not qualify. 2. a number of examples where rights are considered abusive must be provided, such as not satisfying demands on reasonable terms from excessive pricing. This is extremely difficult to prove (Hassim, Heywood, & Berger, 2007).
on the overall cost of medicines in this country, in the public and private sectors, for AIDS drugs and many other essential medicines, we need a comprehensive approach. (Sacco, 2004, p. 44).

This statement solidified the unwillingness of the Mbeki Administration to use its TRIPS flexibilities while faced with the country’s HIV/AIDS epidemic. This statement could have been a result of the mounting pressure on the government from PhRMA and the United States during the court case as well as the government’s fear of damaging relationships with important trade and donor partners. However, if these concerns were the primary cause for Health Minister Tshabalala-Msimang’s statement, the government would have sought other means to achieve its “comprehensive approach” to ARV access, aside from compulsory licensing. Yet, that same year DoH brushed off ARV price reductions offered by GSK. Its combination drug, 3TC+AZT, was offered at US$2 pppy. Apathetic about negotiation, Minister Tshabalala-Msimang reportedly responded that the purchase of ARVs would simply “bankrupt the health department” (Kaiser Network, 2001a). Despite price reductions offered by a number of pharmaceutical firms, the government chose not to engage in negotiation.

It was during this time that Aspen took the initiative to negotiate with GSK the world’s first ARV voluntary license for AZT, 3TC, and the combination, AZT+3TC. This license was limited to supply the public and not-for-profit sectors and required a 30% net of sales royalty paid to GSK. Even with Aspen’s license, however, the government did not address the possibility of providing low-cost generic treatment in South Africa. Besada (2009) reinforces this notion of inconsistent political leadership, suggesting that the greatest indicator of South Africa’s
inadequate health governance was low ARV coverage in the face of numerous concessions by pharmaceutical companies, both in terms of price and voluntary licenses for domestic production.

To test the Mbeki Government’s leadership on ARV treatment, Nattrass (2006; 2008b) developed a model to assess developing countries’ responses to HIV/AIDS. She measured the effect of political will on ARV coverage rates in developing countries given what would be predicted based on international indicators, such as the respective countries’ health and demographic challenges as well as their economic and institutional constraints. Despite the obvious difficulty of this study to measure political will quantitatively, her work nevertheless provides a useful insight to understand how countries like South Africa fell short on ARV treatment rollout given their economic and health environments. Nattrass concluded that, given its resources and capacity (such as per capita income), the South African government both could and should have achieved higher ARV coverage than what it experienced. She found that the overall public sector rollout was much less than what would be expected in South Africa, a result of ineffective leadership under the Mbeki Administration. This was evident in the slow initiation of the ARV treatment plan, where less than 30% of the treatment target was reached in 2005 (Nattrass, 2006).

The results of Nattrass (2006; 2008b) were consistent with the theory that ideological reasons, not resources, constrained ARV treatment rollout and reinforced the South African government’s international reputation as a poor leader on HIV/AIDS policy. Despite numerous attempts during the course of this research to interview members of the DoH, to address these and other issues,
no appointment was ever made available. Although this was a notable limitation to the case study, key-informants pointed out that the DoH’s reluctance to engage in discussion or present information on South Africa’s HIV/AIDS policies further revealed poor government leadership on these issues.

*Complaint on Excessive ARV Pricing*

Government inaction to increase ARV affordability in South Africa led civil society to turn to the judiciary again in 2002. This time, TAC focused on the pharmaceutical industry and charged GSK and BI with excessive pricing of their ARVs, prohibited under Section 8 of the Competition Act. The aim of the Competition Act (1998) is to promote economic growth through the regulation and protection of competition among firms, by prohibiting the abuse of dominance and restrictive practices and by regulating merger control. Applicable to ARV access, Sections 8 and 9 prohibit excessive pricing and price discrimination, respectively.34 In 2002, TAC and 12 other complainants brought the complaint *Hazel Tau and Others v GlaxoSmithKline and Boehringer Ingelheim* before the Competition Commission to challenge the high private sector prices of ARV medicines in South Africa (at that time there were few available in the public sector). They alleged that GSK and BI were abusing their market dominance by charging excessive prices for 3TC+AZT and NVP, respectively (Hassim, Heywood, & Berger, 2007). It was during this compliant, and likely under pressure, that Aspen secured a license for NVP from patent holder BI to supply the public and not-for-profit sectors, paying BI a 20% royalty.

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34 The Competition Act and its relationship with patent law is complex as the aim of patents is to limit competition during the patent duration. Therefore, the ALP (2007b) noted that this was a particularly difficult case to present before the Commission.
Even with GSK’s and BI’s licenses issued to Aspen, in October 2003, the Competition Commission found that GSK and BI used their exclusive rights to deny appropriate licences to other domestic manufacturers while also engaging in excessive pricing. The Commission referred the case to the Competition Tribunal, the legal body able to enforce a ruling in South Africa. If brought before the Tribunal, both GSK and BI would have been required to disclose information on ARV pricing and profit margins. As this type of information is closely guarded by industry, GSK and BI agreed to issue voluntary licenses with a number of local manufacturers, with negotiations brokered by TAC. In December 2003, GSK and BI entered separate settlement agreements with four and two local generic manufacturers, respectively, which included Aspen. These voluntary licensing agreements removed many of the restrictions of Aspen’s previously licenses with GSK and BI. Under new licensing terms, Aspen was able to cover the public, not-for-profit and private market in both South Africa and Sub-Saharan Africa, and the royalty rates were reduced significantly, to no greater than 5%.

The excessive-pricing complaint by TAC and others is essential to understanding the context of voluntary licensing arrangements in South Africa, for a number of reasons. First, South Africa has an advanced regulatory framework that includes provisions in the Medicines and Related Substances Control Act and the Patents Act to ensure a supply of affordable medicines. However, the government proved unwilling to use any of these measures, including parallel importation and compulsory licensing. Second, while inaction on these provisions may have been an overt display of South Africa’s staunch IP compliance to the TRIPS Agreement, the DoH simultaneously refused to enter any price negotiations, even at the suggestion of patent

35 The local manufacturers that received licenses from GSK were Aspen, Thembalami, CiplaMedpro, and Sonke Pharmaceuticals for AZT, 3TC, and their combination, AZT+3TC. From BI, only CiplaMedpro and Aspen were licensed NVP.
holders. This inaction revealed more than fiscal conservatism and pointed to the AIDS denialist behaviour of the Mbeki Administration.

Third, even though Aspen and GSK had already entered into a voluntary license arrangement for domestic generic production prior to the complaint, prices were still prohibitive. Aspen’s products had not come to market and, with the required royalty of 30% net of sales (as well as market restriction that excluded the private sector) and no generic competition, its prices would not likely reduce substantially from those of GSK. Fourth, as a result of government and industry ineffectiveness in reducing prices, civil society utilized provisions in the Competition Act to enact change in the ARV market. TAC’s complaint reinforced that, even though South Africa had the necessary regulatory framework and active industry for generic production (both often not found in Sub-Saharan African countries), it was neither government nor industry, but civil society that pressured multiple reasonably termed voluntary licenses for generic ARV manufacturing in the country.

The ruling of the Competition Commission, together with mass social and political pressure as well as large investments by the local generic ARV industry, finally persuaded the South African government in August 2003 to rollout ARVs nationally in its public health care system (Avafia, Berger, & Hartzenberg, 2006). With the Operation Plan in place, the ARV tender process only began six months later in February 2004 calling for Expressions of Interest from manufacturers. Noticed by media and civil society, the Mbeki Government used the tender as a political tool to gain public approval, announcing it shortly before the 2004 presidential election (Forman, 2005; Sacco, 2004). With President Mbeki’s re-election, the tender awards were further delayed until
March 2005; emergency provisions had to be instituted for provincial governments to procure ARVs in the interim.

Nattrass (2007) points to the active role Health Minister Tshabalala-Msimang played to undermine the ARV rollout. She delayed the ARV tender, questioned the safety of ARVs, and interfered in provincial governments’ efforts to gain access to Global Fund grants for ARV procurement, including $US72 million awarded to the provincial government of KwaZulu-Natal. Chigwedere and colleagues (2008) estimate that the government’s avoidance of a “feasible and timely” (p. 410) rollout between 2000 and 2005 cost South Africa 330,000 lives. The constant struggle that civil society endured to instate a public ARV treatment rollout highlights not only the importance of effective policies and regulations, but institutions that are willing and able to implement applicable policies and legislation (Avafia, Berger, & Hartzenberg, 2006). The strong IP system in South Africa, supported by the denialist mentality of the Mbeki Administration, required civil society to take measures to ensure that these policies were implemented in the face of wavering government commitment.

**The Need for Industry Incentives**

The investment climate in South Africa is positive for a developing country; it ranks 45th of 134 countries in terms of global competitiveness, behind India and China, but ahead of Brazil and all African countries (Porter & Schwab, 2008). South Africa also ranks among the top three Sub-Saharan African countries for its sustainable economic opportunities (including macroeconomic stability, financial integrity, and wealth creation) on the 2008 Ibrahim Index of African Governance (Mo Ibrahim Foundation, 2008). Despite this positive investment climate,
comprehensive policies to foster the growth of the generic pharmaceutical industry have yet to be
instated. Previous research suggests that one of the key issues facing South Africa is the
country’s inability to identify the value of its generic drug industry (Kaplan & Laing, 2005).
Recent policy shifts toward a comprehensive framework might be in response to the growing
success of the generic drug industry.

Generally, financial and tax incentives are used to spur investment in the South African
pharmaceutical manufacturing sector. The Department of Trade and Industry (DTI) provided
fiscal incentives to encourage private sector participation in research and development (R&D)
through its Strategic Industrial Projects 2002-2004. The aim of this program was to “significantly
contribute to growth, development and competitiveness of specific industry sectors by providing
industrial investment allowances” (DTI, 2005, p. 4). This program provided tax relief to Aspen
when it invested US$28 million (R180 million) in a new oral solid dose (OSD) manufacturing
plant for ARVs in 2002 (Sprague & Woolman, 2006).

Through DTI, industrial policy in South Africa’s science and technology sector is based
primarily on the National System of Innovation (NSI). The NSI is a set of institutions and
policies that uses economic incentives to advance both economic and social objectives. Among
these, South Africa’s National Research and Development Strategy recognizes the critical role
that government plays in enabling innovation and research as well as building human capital to
meet socioeconomic development challenges (DTI, 2002; Sprague & Woolman, 2006). Recently,
the Department of Science and Technology (DST) announced its 10 year plan (2008-2018),
which provides impetus for biotechnology and pharmaceutical solutions to relieve the burden of
illness on South Africa. It envisions South Africa to become “one of the top three emerging economies in the global pharmaceutical industry, based on an expansive innovation system using the nation’s indigenous knowledge and rich biodiversity” (DST, 2007, p. 4). The government has invested more than US$63 million (R450 million) in biotechnology since 2004, and a number of innovation centres and other facilities have strengthened the country’s R&D base.

Unfortunately, however, the South African government’s efforts and expenditure have been thinly spread. DST acknowledged that greater support for start-up firms is needed, in addition to second- and third-round funding to support the innovation process (DST, 2007). Currently, only 1.3% of the total manufacturing labour force in South Africa is employed in pharmaceuticals, or approximately 16,000 individuals (Maloney & Segal, 2007). The sector is small, and government focuses primarily on developing a high-technology manufacturing industry with innovative capabilities, as opposed to job creation. According to the Global Competitiveness Report 2008-2009, South Africa’s capacity to innovate is ahead of any African country, ranking 36 of 134 countries, but behind the prominent generic manufacturing countries China and Brazil (Porter & Schwab, 2008). Whereas the average middle-income country spends 0.85% of GDP on R&D, South Africa spends 0.76%. This is well below Brazil (0.98%), Russia (1.17%), India (0.84%), and China (1.44%), and even fellow Sub-Saharan African country Uganda (0.82%) (UNDP, 2008). Opportunity remains for greater public sector investment to facilitate both innovation and private sector investment.

In 2006, movements were made by government toward a comprehensive program geared to the pharmaceutical industry. The South African Presidency launched the Accelerated and Shared
Growth Initiative for South Africa (AsgiSA). This initiative strives to halve poverty and unemployment rates in the country by stimulating economic growth. To reduce unemployment below 15% and poverty to fewer than one in six households, the government aims to achieve an average 4.5% GDP growth rate between 2004 and 2009 and 6% between 2010 and 2016 (Presidency Republic of South Africa, 2004). By September 2007, AsgiSA surpassed its 2004-2009 targets achieving 4.9% growth and reducing unemployment to 23% from 31.2% in March 2003 (Presidency, Republic of South Africa, 2007).

Under AsgiSA, the pharmaceutical industry was identified as a potential candidate for priority status and strategic promotion. Both representatives from the National Economic Development and Labour Council (Nedlac)\textsuperscript{36} and the pharmaceutical industry agreed that a strategy is needed to foster the expansion of domestic drug production and ensure affordable medicines in the public sector. As a result, the President nominated a commission to assess the industry’s relevance to AsgiSA and recommend a multi-sector strategy to support the development of the pharmaceutical industry. In late 2008, however, no progress on the commission had been made.

Targeted policies and investment incentives by government in the domestic pharmaceutical industry were limited until the above mentioned developments in 2006. In addition, the South African government has begun to consider comprehensive incentives to foster the local industry, including API development capacity, in order to increase technological and innovation capacity as well as provide low-cost generics to its population. This shift toward a targeted policy approach for the pharmaceutical industry may be a result of the success Aspen and other local

\textsuperscript{36} A government agency funded by the Department of Labour. The Department of Trade and Industry, Public Works and Finance are also centrally involved in Nedlac. The goal of Nedlac is to make economic decision making more inclusive and promote economic growth and social equity.
generic manufacturers achieved expanding the country’s generic drug industry, particularly through multiple ARV voluntary licenses. It is this growth of the pharmaceutical industry that has affected policy change within government.

**Shifts in Stakeholder Influence and Support for Domestic ARV Manufacturing**

Numerous events transpired in the South African policy environment that preceded the development of the voluntary licensing arrangements entered by Aspen, GSK and BI. These included the fight for South African’s right to treatment (in the Constitution Court) and access to affordable treatment (during the patent infringement case in the Pretoria High Court and the excessive pricing complaint in Competition Commission). From these events, a shift in stakeholders’ support of, and influence on, domestic ARV manufacturing policies occurred before and after the issuance of GSK’s and BI’s renegotiated licenses. Figure 8 shows the movement of stakeholder positions on domestic production policies in South Africa by their level of policy support, on the x-axis (opposed or supportive), and their level of policy influence, on the y-axis (high influence or low influence). Generally, it demonstrates that, over time, stakeholders began to converge, increasing their support for ARV manufacturing in South Africa.

Figure 8 prominently highlights the level of influence that both civil society and domestic manufacturers gained within the policy arena. Highly supportive of local ARV production, civil society (for reasons of ARV treatment and price) and domestic manufacturers (for reasons of market access and profitability) increased their presence and position in the policy arena. Civil society mobilized to use the judicial system to push for treatment rights and negotiate licensing
terms with GSK and BI after charging them with excessive pricing in the Competition
Commission. Similarly, Aspen’s growing relationships with patent holders and increasing
numbers of voluntary licenses (discussed in the section *Aspen’s Financial Structure*), increased
local manufacturers’ lobbying power within government. While the position of DoH under the
Mbeki Administration remained unchanged (highly influential, but neither supportive nor
opposed), there was movement by DTI and DST. DTI and DST, which have high influence to
affect change in industrial policies, shifted toward an increasingly supportive role in domestic
ARV manufacturing policies identifying areas for growth and industry incentives in the period

Finally, the position of patents holders as highly influential on South Africa’s domestic
production policies noticeably decreased after the South African government claimed victory on
the IP infringement case (in the Pretoria High Court) and after the implementation of the Doha
Declaration internationally. Also, their level of support for domestic production noticeably
increased as it became clear that voluntary licensing strategies were being perused by domestic
firms, avoiding compulsory licenses and negative media attention. Patent holders, however, split
their level of policy support. Patent holders, such as Abbott Laboratories, have remained opposed
to voluntary licensing arrangements. Other patent holders, such as BMS, Roche, and Gilead,
have shifted their strategy in developing country markets to licensing technology to domestic
manufacturers, such as Aspen (discussed in the section *Aspen’s Financial Structure*).
**Figure 8: Stakeholder Positions on South Africa’s ARV Manufacturing Policies, by Level of Influence and Support, before and after Initial ARV Licenses**

Legend
Stakeholder positions before ARV licenses are circled. Stakeholder positions after the ARV licenses are in **bold**. Rx&D = Patent holding pharmaceutical firms, DoH = Department of Health, DTI = Department of Trade and Industry, DST = Department of Science and Technology

**Note.** Figure 8 demonstrates the general shift in key-stakeholders positions by their level of policy support, on the x-axis (opposed or supportive), and their level of policy influence, on the y-axis (high influence or low influence). Generally, this figure demonstrates that, after the ARV voluntary licenses were first issued, stakeholders began to increase their support for ARV manufacturing in South Africa.
**Aspen’s Financial Structure**

The financial structure of Aspen, as a publicly-traded pharmaceutical firm, has provided the firm with access to the necessary capital to purchase IP, expand its operations internationally, and integrate vertically. With the assistance of civil society complaints against patent holders, these financial attributes have increased Aspen’s negotiating power with patent holders to acquire voluntary licenses. In line with many generic firms, Aspen’s mission is to supply affordable medicines to South Africa and the international market; yet, like most publicly-traded pharmaceutical firms, this goal, must also ensure a substantial return on investment for its shareholders. With ARVs, Aspen’s prevailing strategy has been to align itself with the research-based industry to acquire voluntary licenses and distribution agreements. This strategy enables generic ARV market entrance ahead of other manufacturers, allowing both increased affordability from the patented ARV price and significant profits.

**Ownership and Access to Financing**

Aspen was founded in South Africa in 1997. Beginning as a private pharmaceutical firm with a R118 million (approximately US$25.6 million) turnover, Aspen acquired the publicly-traded firm Medhold in July 1998 to allow rapid listing on the Johannesburg Securities Exchange (JSE). At the time, Aspen’s share price was listed at just 53¢ and had a market capitalization\(^{37}\) of R130 million (US$23.4 million). With its R1.92 billion (US$314 million) reverse takeover of South Africa’s oldest pharmaceutical firm South African Druggist in 1999, Aspen became the second largest pharmaceutical firm in terms of size in South Africa and the largest pharmaceutical company listed on the JSE, with a market capitalisation of over R2.4 billion (almost US$280

\(^{37}\) Market capitalization is the value of a firm. It equals the value of the shares multiplied by the number of shares outstanding.

South Africa ranks high internationally in terms of its market sophistication. To foster a competitive industry, the financial sector must allocate resources efficiently and have capital available for private sector investment through transparent banking institutions, securities exchanges that are regulated appropriately, and access to venture capital (Porter & Schwab, 2008). There are 19 stock exchanges across Sub-Saharan Africa, with a market capitalization of US$1 trillion, of which the JSE accounts for US$800 billion (IFC, 2008). In the Global Competitiveness Report 2008/2009, South Africa ranks 29th of 134 countries for its availability of venture capital and among the top 10 countries for its local equity market financing, regulation of securities exchanges, and investor protection (Porter & Schwab, 2008). After 5 years of operation in 2002, 51.6% of Aspen’s shareholders included major banks and unions, such as Standard Bank, Nedbank, and CEPPWAWU Investments (the investment arm of the Chemical, Energy, Paper, Printing, Wood and Allied Workers' Union), reflecting the ease of access to financial capital the firm experienced (Aspen, 2002a). It is with this competitive advantage that Aspen was able to raise the necessary capital, often not found in Sub-Saharan African countries, to expand into the ARV market.

Since 2002, major investors have shifted to 13% of shareholdings (48 million shares)\(^{38}\) under the direct ownership of Black Economic Empowerment (BEE) funds (Aspen, 2007a). BEE is an

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\(^{38}\) These shareholders include Imithi Investments (Pty) Ltd (3.8%), which is a broad-based BEE consortium, subsidiaries of the CEPPWAWU Development Trust (7.6%), the COSATU (Congress of South African Trade
initiative of the South African government to promote participation in the economy by groups
disadvantaged during apartheid. BEE has important implications in the tender system as
preference-points are given to those local firms with BEE ownership. Additionally, in 2006/2007
the Public Investment Corporation (PIC), an investment manager with public sector clients, such
as pension and social security funds, became a major shareholder of Aspen, acquiring 6.8% of its
shares (Aspen, 2007a). PIC placed the Minister of Finance as its shareholder representative. It is
uncertain whether PIC’s investment in Aspen has, or will have, implications for the
government’s engagement in comprehensive policies and incentives to expand the domestic
pharmaceutical industry.

With financing available from its inception, Aspen emphasized global expansion and vertical
integration early. In the 1990s, the flurry of multinational mergers in the global pharmaceutical
arena\textsuperscript{39} left opportunities for companies such as Aspen to purchase both IP and operating
divisions that had been abandoned a result of the mergers (Jones, 2000). In response, Aspen
bought the United Kingdom based Co-pharma Ltd. and also formed Aspen Australia Pty Ltd., in
2001. That year, Aspen recorded revenue of R1.1 billion.

Aspen’s main distribution and revenue derive from the domestic market, both public and private.
In addition to its two manufacturing facilities in South Africa, in March 2004 Aspen purchased
Fine Chemicals Corporation, a specialist manufacturer and supplier of off-patent APIs,
predominantly for analgesic medicines. More recently, effective March 2008, Aspen entered a

\textsuperscript{39} Examples include the merger of Zeneca and Astra in 1998 (AstraZeneca) and of Monsanto and Pharmacia &
Upjohn in 1999.
50/50 joint venture with India’s Strides Arcolab to expand into Latin America, acquiring Cellofarm in Brazil, Solara in Mexico, and Sumifarma in Venezuela, for US$152.5 million (Aspen, 2007b). Aspen used its assets in September 2008 to acquire an additional 1% interest from Strides, for US$ 2.8 million. This agreement gave Aspen management control and the right to 100% of the profits and dividends⁴⁰ (Aspen, 2008a). Finally, in May 2008 Aspen acquired a 60% stake in Shelys Africa Ltd., a holding group of pharmaceutical companies in East Africa with principal operations in Kenya and Tanzania.

In terms of performance, the Aspen Group (the umbrella organization of these firms), has had mixed performance across its different operations; however, the South African business’ performed “exceeding well” with revenue growth of 14%, to R1.18 billion (US$167 million) in 2007 (Aspen, 2007c; Summit TV, 2007). In 2007, the total revenue of Aspen’s pharmaceutical division grew 17%, with revenue for ARVs alone increasing 79%, or US$52.9 million (Aspen, 2007b). ARVs have had a year-on-year growth of 65% (Aspen, 2007a). This was achieved through new product launches and significant growth in ARV production volumes in the South African private and public sectors as well as in the African export market (Aspen, 2007a).

**IP Strategy**

Although in the business of manufacturing off-patent products, much of Aspen’s strategy since its inception has focused on purchasing IP for various markets and building strategic partnerships with multinational patent holders. This is seen through Aspen’s eagerness to conclude both pre- and post-patent agreements with right holders (Jones, 2000). In 2000, Aspen concluded a 10-year agreement with GlaxoSmithKline for the right to produce and market their products in South Africa. This agreement was highly beneficial for Aspen, as it allowed them to access the patented technology of GlaxoSmithKline, which helped them to enter the South African market and expand their operations. Aspen has since continued to develop and expand its IP strategy, acquiring rights to various patented products, including those for HIV/AIDS, cancer, and other diseases.

⁴⁰ Portion of profit paid to shareholders.
co-marketing agreement with AstraZeneca for a number of products in order to increase Aspen’s quality recognition internationally. These arrangements have given Aspen leverage over other generic companies when negotiating voluntary licenses with patent holders. It was with this base that Aspen entered the ARV market in 2001.

Aspen’s strategy also avoids any “legal minefield” or disruption of supply due to IP infringement (Dionisio, et al., 2008, p. 31). Informants at Aspen argued that compulsory licensing is neither practical nor appropriate for expediting drug access to developing countries and only increases tension with the research-based pharmaceutical industry. Aspen also identified three strategic imperatives: to build sufficient capacity for finished dose formulations, maintain a consistent supply of APIs, and develop a continuous pipeline of ARV products (Dionisio, et al., 2008)—the latter two of which compulsory licenses may jeopardize.

Side-stepping compulsory licensing, the Pretoria High Court case of PhRMA against the South African government and Section 15c of the Medical and Related Substances Control Act put Aspen in a strong position to negotiate with patent holders. The case damaged the reputation of the research-based pharmaceutical industry, both domestically and abroad, as its high patented prices denied ARV access to individuals in a country with one of the largest HIV/AIDS prevalence rates in the world. Once the case was withdrawn in April 2001, Aspen strategically approached GSK and negotiated a voluntary license for AZT, 3TC, and their combination 3TC+AZT. An Aspen informant highlighted that the firm used South Africa’s HIV/AIDS plight as one of its strongest bargaining tools. Table 7 lists some of the characteristics of this license, as well as the other licenses that followed.
As the first generic manufacturer in the world to receive a voluntary license for an ARV, Aspen made a number of concessions in the agreement that were deemed unreasonable by TAC. The agreement with GSK included a 30% of net sales fee and confined distribution to public and not-for-profit sectors only. From GSK’s perspective, a license with these restrictions had little effect on its profitability since, in 2001, the ARV market was concentrated in the private sector, and, if a public market did develop, GSK would still receive 30% royalty. From Aspen’s perspective, in addition to early generic entry, Aspen established its reputation as a generic firm that enforced IP and was able to collaborate with patent holders. This agreement with GSK was eventually renegotiated in 2002, when TAC’s excessive-pricing complaint came before the Competition Commission, and TAC brokered more flexible licensing terms with a number of generic manufacturers in South Africa. These terms expanded Aspen’s geographical market to both the private and public sectors throughout Africa, for a royalty fee of no more than 5%.
<table>
<thead>
<tr>
<th>Patent Holder</th>
<th>ARV</th>
<th>Date</th>
<th>Terms</th>
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| GlaxoSmith-Kline (GSK) | Lamivudine, zidovudine, lamivudine+ zidovudine (3TC+AZT) | • October 2001  
• December 2003 | • 30% fee on net sales  
• Royalty of no more than 5% | • Public sector and not-for-profit organizations and charities in South Africa  
• Public and private sector South Africa and Sub-Saharan Africa |
| Boehringer Ingelheim (BI) | Nevirapine (NVP) | • October 2002  
• December 2003 | • 15% royalty  
• Royalty no more than 5% | • Public and not-for-profit sector of South African Development Community Region (Angola, Botswana, the Democratic Republic of Congo, Lesotho, Malawi, Mauritius, Mozambique, Namibia, Seychelles, Swaziland, Tanzania, Zambia and Zimbabwe)  
• Public and private sector South Africa and Sub-Saharan Africa |
| Bristol Myers Squibb (BMS) | Stavudine (d4T), Didanosine (ddI)  
Atazanavir (ATV) | • July 2001  
• August 2003  
• February 2006 | • Immunity from suit  
• Licensing terms unknown  
• Non-exclusive, royalty-free distribution and manufacture with technology transfer provision | • Public and private system throughout Africa  
• World Bank Tier 1 designated countries (approximately 70 countries) |
| Gilead Sciences | Tenofovir, tenofovir+ emtricitabine (TDF+FTC) | • April 2005 | • Non-exclusive, 5% royalty, licensing and distribution agreement | • Public and private system throughout Africa |
| Merck & Co. | Efavirenz (EFV) | • July 2005 | • Non-exclusive, royalty-free | • Public and private system throughout Sub-Saharan Africa |
| Hoffmann-La Roche | Saquinavir (SQV) | • September 2006 | • Non-exclusive, royalty-free with technology transfer provision | • All Sub-Saharan Africa and other least-developed countries |
| Tibotec | Darunavir | • April 2007 | • Distribution until demand warrants manufacture | • 20 Countries in Sub-Saharan Africa |

This strategy by Aspen to increase partnerships with patent holders was supported by its subsequent agreements with BMS. Around the same time of Aspen’s licences with GSK, BMS publicly granted immunity from suit any generic firms in Africa wishing to manufacture its ARVs didanosine (ddI) and stavudine (d4T). Even though Aspen was free to produce these drugs without any IP infringement dispute by BMS, it awaited a formal agreement with BMS before beginning production. These events set in motion Aspen’s growing relationship with ARV patent holders.

Able to leverage multinational relationships to expand its product base, and with continued pressure from civil society on the pharmaceutical industry, Aspen maintained a positive and growing relationship with patent holders. As seen in Table 7, a number of ARV licensing arrangements were reached across multiple patent holders. Aspen now produces more licensed ARV products than any other generic drug firm. This includes the alternative first-line ARV tenofovir (TDF) as well as the combination tenofovir+emtricitabine (TDF+FTC) from patent holder Gilead, under the non-exclusive distribution and licensing agreement signed in 2005. The most recent WHO (2006a) treatment guidelines recommend tenofovir as a preferred ARV in alternative first-line treatment regimes; it will likely become an increasingly important drug in the South African market.

Voluntary licenses are particularly important for some second-line protease inhibitors (PIs) where patent barriers exist in developing countries with ARV manufacturing capabilities, such as Brazil, Thailand, and possibly India. Building on its relationship with BMS, in February 2006 Aspen signed a non-exclusive license and technology transfer collaboration agreement for the
manufacture and distribution of the PI atazanavir (ATV). It was one of only two licenses granted, with the other to Indian manufacturer, Emcure. In its annual report, Aspen suggests that the firm’s position, presence, and market coverage have placed pressure on multinational drug firms, resulting in their greater cooperation in licensing negotiations (Aspen, 2007b).

From 2001 to 2006, Aspen invested US$60 million in pharmaceuticals (Aspen, 2007a), of which a large portion was directed to ARV development and registration. From 2002 to 2004, in order to ensure a sustainable ARV supply, Aspen invested approximately US$28 million (R180 million) in a new OSD facility to increase its production capacity and assure quality. Under DTI’s Strategic Industrial Projects, Aspen claimed the Strategic Investment Project tax allowance (under section 12G of the Income Tax Act) to reduce the tax on the investment by R31.9 million (US$4.7 million) (Aspen, 2006a). This plant opened in 2004 and is accredited by MCC, FDA, and WHO, among others. Aspen’s investment in a quality approved facility enabled ARV registration at both WHO and the FDA. This accreditation effectively increased Aspen’s reputation with patent holders and increased its export capabilities.

In keeping with its imperative to provide a continuous supply of APIs, in September 2005 Aspen entered in a joint venture with Indian-based Matrix Laboratories to vertically integrate and manufacture APIs. Integrating all stages of production within the firm, from raw material production to the final finished dosage form, can not only assure Aspen a continuous supply, but reduced final product costs. Using its assets, Aspen acquired 50% of an API manufacturing facility in Hyderabad, India, for US$36.5 million (which included IP and technology transfer from Matrix to Aspen for the manufacture of certain APIs) while Matrix received 50% of
Aspen’s own API facility, FCC for US$20 million. The facility was renamed Astrix and became Aspen’s main supplier of APIs for generic ARVs (Aspen, 2005; Cullinan, 2005).

Although Astrix’s profit margin fell in 2007, its contribution to Aspen’s revenue increased by 82% to R82 million (approximately US$11.6 million) (Aspen, 2007a; Aspen, 2007c). This venture divested, however, in October 2008. Aspen disposed 50% of its share to Matrix and regained its 50% share of FCC. In doing so, Aspen acquired the rights, to distribute domestically, a number of new generation ARV combination products and secured a long-term supply of APIs from Matrix. The details of the agreement remain uncertain. However, with outright ownership of FCC, Aspen may plan to develop API capabilities to produce ARVs in South Africa. As mentioned, integrating API production for ARVs has large implications for ARV affordability and will be explored in section, Aspen’s Manufacturing Capacity.

With Aspen’s purchase of IP across the pharmaceutical spectrum and its recent expansions, the firm was carrying a R5 billion debt accumulated in the first months of 2008 (Khanyile, 2008). Currently, Aspen’s challenges include the difficulty to access financial capital internationally, paybacks (i.e., recovering the cost of its investments) given costs of capital and the overpayment of its acquired enterprises (Aspen, 2007b). To date, this has not deterred Aspen from expanding its manufacturing base globally. Since listing on the JSE, Aspen has maintained access to financial capital facilitating IP purchases, development of a strong production base, and expansion of its global operations. It is this access to financial capital that increased the firm’s leverage with patent holders to negotiate voluntary licenses and to enter strategic partnerships with both generic and research-based drug firms to build its manufacturing capacity.
Aspen’s Manufacturing Capacity

Development Capability

South Africa is the only country in Sub-Saharan Africa with a long established generic drug industry that has both manufacturing capacity and expertise (Avafia, Berger, & Hartzenberg, 2006). In the late 1990s, there was a large presence of research-based pharmaceutical subsidiaries in South Africa until mergers and acquisitions saw eight facilities close, belonging primarily to multinationals. Now, a majority of the 94 registered pharmaceutical operations in South Africa are sales and marketing offices with R&D and production overseas. The Pharmaceutical Manufacturers’ Association of South Africa estimates that 10 firms have manufacturing facilities in South Africa and an additional 6 firms use local companies for contract manufacturing and packaging (Maloney & Segal, 2007).

The Aspen Group has grown exponentially in recent years and currently employs more than 3,100 individuals in its generic, over-the-counter, and health care products businesses as well as its sales offices, regulatory affairs and human resources departments. Aspen has over 1200 products, supplying branded pharmaceuticals and generic medicines as well as healthcare products. Aspen’s ARV products include zidovudine, lamivudine, nevirapine (and their combination), didanosine, stavudine, efavirenz, tenofovir, tenofovir+emtricitabine, atazanavir, and darunavir. The latter two products had not come to market by December 2008.

Generally, ARV and pharmaceutical manufacturing require few, but highly skilled, employees to develop product lines. Kaplan and Laing (2005) argue that the development skill of a domestic pharmaceutical industry is linked to the country’s education system. Secondary education
supplies the basis for technical and maintenance expertise, and tertiary education develops talent for scientific innovation (Kaplan & Laing, 2005). According to the *Global Competitiveness Report 2008-2009* South Africa’s inadequately educated workforce is the most problematic factor for doing business in the country. In particular, the quality of math and science education in South Africa ranks 132nd of the total 134 countries surveyed (Porter & Schwab, 2008). Only 5.1% of the total unemployed population has a tertiary degree in South Africa whereas the corresponding figure in India is nearly 32% (Maloney and Myburgh, 2007). South Africa has 307 researchers per million people, compared with 708 in China, 344 in Brazil, and 118 in India (UNDP, 2008). While these figures may suggest that South Africa exceeds India in research capability, India’s large population produced 11,076 scientific and technical journal articles in 2001, compared with 2,372 in South Africa (World Bank, 2006). The sheer size of India’s skilled population magnifies the industry’s development potential and reduces labour costs, compared with Sub-Saharan Africa.

Limited skilled labour in South Africa may inhibit operating in higher-value parts of drug development and production without the country’s increased investment in its innovative capacity and education (Maloney & Segal, 2007). For example, Aspen was slow to develop and bring its ARVs to market. Licensed in 2001, Aspen’s generic versions of lamivudine and zidovudine took 3 years to come to market. This may be part by the lack of development capacity at Aspen as well as the lack of resources at the MCC to evaluate the ARVs, causing significant registration delays. Additionally, unlike many Indian manufacturers, Aspen has yet to register a triple fixed-dose combination (FDC) ARV. FDCs are highly coveted due to their ease of use, reduced pill burden, and low prices. Currently, Aspen manufactures single-source ARVs
and two FDCs, lamivudine+zidovudine co-packaged with nevirapine (AZT+3TC and NVP) and tenofovir+emtricitabine (TDF+FTC).

Admittedly, Aspen has experienced problems with capacity and capability, spending R1 billion (approximately US$146 million) since 2003 to build an appropriate base (Summit TV, 2007). Aspen also entered cooperation agreements with multinationals to increase its capabilities, including a leading Indian generic ARV manufacturer, Strides Arcolab. Aspen’s need for development assistance is also evident as South African firms have neither the skill nor the capacity necessary to manufacture APIs to formulate ARVs. In order to produce an ARV a number of different APIs are required, often from a number of different production facilities each requiring a high degree of technological capacity to synthesize (Maloney & Segal, 2007; Sprague & Woolman, 2006).

In response to the country’s low skill level, Aspen entered a joint venture with Matrix in 2004 to for the WHO, MCC and FDA accredited API manufacturing facility in India, Astrix, where technological capacity for ARV manufacturing is high. Even though this venture divested in October 2008, this facility still supplies many APIs to Aspen. The divestment also indicates that Aspen is looking to vertically integrate API manufacturing domestically. Informants noted that government is considering providing incentives to assist Aspen to develop the country’s API manufacturing base.

To formulate its ARVs from imported APIs, Aspen completed construction of a nearly US$30 million OSD facility in 2004. This facility supplied 70% of the ARVs for the first 3 years of the
public ARV rollout (Sprague & Woolman, 2006) and has enough operational capacity to facilitate the production volume required of an international business (Aspen, 2007a). Needed to capture the domestic and international market, the OSD Facility is accredited by the FDA, MCC, United Kingdom’s Medicines and Healthcare Products Regulatory Agency, Australian Therapeutic Goods Association, and WHO.

With APIs from Astrix and formulation and production at Aspen’s OSD facility, Aspen’s co-blister pack, AZT+3TC and NVP, and its individual components were approved by the FDA under PEPFAR in January 2005, followed by the approval of tenofovir and the combination TDF+FTC in 2006. IFC (2008) notes that the comparative advantage of large-scale manufacturers to achieve WHO prequalification over small manufacturers, results from a greater knowledge-based, and the technical and financial resources required to submit product dossiers.

Meeting international quality standard makes Aspen’s products eligible for donor financed tenders in Sub-Saharan African countries. In addition, the William J. Clinton Foundation selected Aspen to produce certain generic ARVs for its program. Aspen’s quality accreditations, investments in capacity building, along with its initial voluntary licensing arrangements further leveraged Aspen’s negotiations with patent holders to incorporate terms that included technology assistance for product development. Agreements with BMS and Roche for the second-line PIs, atazanavir and saquinavir, respectively, contain specific technology transfer provisions, such as human resource training, not found in licensing agreements with GSK and BI (which only authorized the exploitation of the patents). Atazanavir and saquinavir are substantially more
complex to formulate and manufacture and cooperation from these technology transfer provisions may allow a more timely market entry.

Another key component of Aspen’s capacity is its regulatory affairs department. With its increased product base and international market, in 2007 Aspen’s regulatory affairs department doubled the number of submissions to the MCC and other DRAs, for registration throughout Africa. The regulatory affairs department maintains more than 1000 dossiers on Aspen’s generic and branded products (Aspen, 2007a). Aspen has 337 dossiers registered abroad, for export to over 30 countries. As mentioned, international certification expands Aspen’s potential market considerably, as long as it is able to compete on price.

**Maintaining Production**

Aspen managed to keep pace with increasing ARV demand in the South Africa government’s first ARV tender, beginning with ARV treatment for 18,000 patients in 2005 and increasing to over 350,000 in 2007 (Summit TV, 2007). Having built an appropriate base, Aspen aims to consolidate and utilize its facilities and operations to double its turnover and increase its international business (Summit TV, 2007). In 2008, Aspen’s ARVs were treating approximately 600,000 patients in the African region. Aspen’s production capacity is estimated to be similar to that of large Indian firms (1.2 billion tablets per year), falling within the IFC’s (2008) estimated conversion-cost scale efficiencies of 1.0 to 1.5 billion tablets per year. This gives Aspen a substantial cost advantage over other Sub-Saharan manufacturers; yet, Aspen remains at a 10% cost disadvantage to Indian firms. This cost disadvantage is a result of South Africa’s higher
wages, lower labour productivity levels, lower contracted ARV volumes, and higher import costs (IFC, 2008). As a result, Aspen has reduced profit margins to keep prices competitive.

The most important component of ARV price is the cost of APIs, which drive 70 to 80% (Orsi, et al., 2003) or even up to 90% (Pinheiro, Autunes & Fortunak, 2008) of the cost of ARVs. Vertical integration of Aspen, to include all manufacturing processes from API production to packaging, is highly advantageous in the ARV market to reduce component costs. As mentioned, API manufacture for ARVs is not yet underway in South Africa due to limited technological capacity; however, Aspen may develop this industry in upcoming years. Each API facility, in addition to requiring the appropriate skills, necessitates its own high-volume demand to create the economies of scale to warrant investment (Maloney & Segal, 2007; Sprague & Woolman, 2006).

In addition to increasing Aspen’s technological capability and reducing API costs, Aspen’s vertical integration would ensure a sustainable supply of APIs in South Africa. A constant supply is important to the health security of the country and sustainability of the ARV rollout. As ARV treatment demand in India and China increases, concern increases that these countries will not have the production capacity to serve other countries sufficiently. This is an even greater concern as demand also continues to rise in Sub-Saharan Africa (Maloney & Segal, 2007). Even though Aspen secured a long-term agreement with Matrix for API procurement, the development of a domestic API industry for ARVs would provide greater security of supply for South Africa.

Currently, APIs for ARVs are still imported and they, along with other imports, affect final product costs and profit margins. In South Africa, there are no tariffs on finished drug products,
but tariffs do exist on other drug inputs, such as APIs. As APIs are not a specific trade category, it is unclear which APIs are subject to tariffs; duty is left to the discretion of industry. There are approximately 140 pharmaceutical inputs not produced in South Africa that are also subject to tariffs. With no duty on imported finished drugs, tariffs on materials to formulate ARVs in South Africa can actually put domestic products at a price disadvantage to imported ones (Maloney & Segal, 2007). Furthermore, Aspen’s imports have been affected by the depreciating rand. South Africa’s fluctuating exchange rate affects the import of APIs and other input costs, which constitute a large portion of final drug costs (Aspen, 2007b). The constraints imposed by tariffs as well as continued volatility and depreciation of currency requires Aspen to either decrease profit margins or increase the end price of the ARVs, which has obvious negative implications for affordability.

The South African ARV Market

The public sector rollout of ARVs by South Africa’s government has been fraught with numerous delays causing a highly politicized backlash by civil society. The ARV market is large, providing incentive for local manufacturers, such as Aspen, to enter the industry; however, margins are small and treatment uptake has been unpredictable within the South Africa’s complex tender system. Competition is affected by the slow drug registration process and restricted by the strong patent system, which requires voluntary licenses from the patent holder to manufacture most first-line ARVs. These factors negatively impact the affordability of medicines in the public sector market.
**Generic Market Access and Size**

With the exponential increase of HIV/AIDS in South Africa during the 1990s, the country’s TRIPS-compliant IP system gave patent holders the exclusive right to supply ARVs. No generic manufacturer was permitted to enter the South African market unless it was licensed to do so by the patent holder. A generic ARV market did not exist until 2001 when GSK granted Aspen its first license and BMS announced immunity from suit for the manufacture of its ARVs, stavudine and didanosine. BI followed with its license for NVP in 2002. At this point, the market theoretically opened to generic competition.

Though ARV licenses were granted as early as 2001, the generic market for ARVs was restricted until 2005 for four reasons. First, under the terms of Aspen’s licenses with GSK and BI, the private sector was off limits and the licensed ARVs were only eligible for tender in the public and not-for-profit sectors. Without government rollout of ARVs, the voluntary licenses accrued by Aspen did little to make ARVs available to the general population.

Second, the market began to change in December 2003 after the Competition Commission referred TAC’s complaint of excessive ARV pricing by GSK and BI to the Competition Tribunal. This recommendation sparked negotiations between patent holders and local generic firms that eventually reduced Aspen’s royalty rate and opened the license to the private sector, making ARVs available to all individuals able to pay the high private sector prices. Although the private sector only accounts for only one-third of pharmaceutical supply and demand, it is where a firm accumulates much of its profit that subsequently enable costs reductions in the public sector. In South Africa, the private sector accounts for 75% of the total market value with drugs.
typically priced 30% higher than those in the public sector (CABSA, 2002). Therefore, even with Aspen’s renegotiated licenses, without a public sector rollout, ARVs would remain relatively inaccessible to the general public because private sector prices were still too high.

Third, Aspen’s generic ARVs key to the triple therapy regimen, 3TC+d4T+NVP, were not available to either the public or private sector until MCC registration in 2004. This left only expensive patented ARVs for procurement until that time. Fourth, national ARV procurement did not occur until March 2005. The public market for ARVs largely began to open in 2003 (when the Operation Plan announced its goal to treat 500,000 individuals by 2008); however, it was not until February 2004 that the request for bids on the government tender was made, and it was not until March 2005 that the tender contract was awarded.

There are a number of reasons why the public ARV rollout was so slow. The movement from apartheid to a democratic state focussed on increasing infrastructure and basic care and theories of lack of fiscal capacity for ARV rollout prevailed. Most important, however, the then President Mbeki and Health Minister Tshabalala-Msimang questioned a link between HIV and AIDS as well as the safety and efficacy of ARVs. The DoH and other members of the Mbeki Administration avoided price negotiations with manufacturers and stalled ARV rollout nationally. Emphasizing the negative side effects of ARVs, Health Minister Tshabalala-Msimang supported unproven claims of nutritional interventions as therapeutic alternatives to ARVs, including a diet of beetroot, lemon, garlic, and African potato. To many in South Africa, Minister Tshabalala-Msimang placed much greater importance on diet than ARVs for the treatment of HIV/AIDS, stating “ARVs do not cure and they have side effects. I don’t know of any side effects of eating proper food” (Nattrass, 2007, p. 143).
With ARV rollout finally announced in 2004, two tenders were awarded, one for the period 2005-2008 and the one for 2008-2010. The total value of the first tender was R3.4 billion (or US$572 million) over 3 years. With the number of patients receiving treatment increasing dramatically, so did market size. A supply gap emerged for South African generic drug companies, such as Aspen, to fill. Table 8 lists the awardees for the 2004 tender and their percentage of the contract. Although Aspen was allotted over 50% of the tender volume, it only secured 16.9% of its value. By contrast, research-based firms Abbott and Merck together accounted for nearly 70% of the tender value for its patented ARVs, but less than 33% of the volume (Hassan & Berger, 2008).

Table 8: South African Government 2004 ARV Tender

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Origin</th>
<th>Tender Volume</th>
<th>Tender Value</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspen Pharmacare</td>
<td>South African generic manufacturer</td>
<td>50.8%</td>
<td>16.9%</td>
<td>Stavudine Lamivudine nevirapine</td>
</tr>
<tr>
<td>Abbott Laboratories</td>
<td>Multinational patent holder</td>
<td>18.3%</td>
<td>69.8%</td>
<td>Lopinavir/ ritonavir</td>
</tr>
<tr>
<td>Merck &amp; Co.</td>
<td>Multinational patent holder</td>
<td>14.4%</td>
<td></td>
<td>Efavirenz</td>
</tr>
<tr>
<td>Cipla-Medpro</td>
<td>South African – Indian generic importer</td>
<td>6.5%</td>
<td>1.6%</td>
<td>Stavudine</td>
</tr>
<tr>
<td>GlaxoSmithKline (GSK)</td>
<td>Multinational patent holder</td>
<td>4.35%</td>
<td>2.4%</td>
<td>Lamivudine Zidovudine Abacavir</td>
</tr>
<tr>
<td>Boehringer Ingelheim (BI)</td>
<td>Multinational patent holder</td>
<td>3.4%</td>
<td>7.3%</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>Bristol-Myers Squibb (BMS)</td>
<td>Multinational patent holder</td>
<td>2.15%</td>
<td>2%</td>
<td>Stavudine Didanosine</td>
</tr>
</tbody>
</table>

By December 2005, however, only 111,786 of the year’s targeted 389,644 patients (or 30%) were receiving treatment (Nattrass, 2006). Then, by April 2008, DoH announced that 487,000 patients were receiving ARVs from the public sector, approaching its target of 500,000 (IRIN, 2008a). As a result of the mass scale-up, ARV quantification was a challenge. Sporadic treatment uptake had various implications for Aspen. The quantities reflected in the tender contracts were estimates and no guarantee was given as to the actual amount that would be ordered. Monthly production was highly variable and this, along with dosage changes, made production scheduling for manufacturers a challenge (Gray, 2008). The general principle in tenders is that no less than 80% or more than 120% of the quantity specified in the tender will be procured; however, the 36 month total of stavudine tendered was 346% of the predicted amount (Gray, 2008). Over-ordering exposes the supplier to risk because additional APIs and inputs must be procured on short notice (Gray, 2008) and can drive up costs both for the manufacturer and the government.

The first installment of the 2008 government ARV tender, outlined in Table 9, was valued at R3.615 billion (US$455.8 million) for 10 commonly used ARVs and their combinations over a 2 year period. By 2011, South Africa’s National Strategic Plan for HIV and AIDS targets to provide ARV treatment for 80% of those in need, or 1.3 million individuals. While volume increases contribute to Aspen’s growth, an unstable uptake will have implications for affordability and sustainability.
Table 9: First Round of South African Government 2008 ARV Tender

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Origin</th>
<th>Tender Value</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspen Pharmacare</td>
<td>South African generic manufacturer</td>
<td>56.8%</td>
<td>Lamivudine (100mg/ml, 80% of 150mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stavudine (15mg, 20mg, 80% of 30mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Efavirenz (30% of 200mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nevirapine (200mg, 240ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Zidovudine (100mg, 300mg, 20ml, 200ml)</td>
</tr>
<tr>
<td>Adcock Ingram</td>
<td>South African generic manufacturer</td>
<td>20.9%</td>
<td>Efavirenz (70% of 200mg)</td>
</tr>
<tr>
<td>Sonke Pharmaceuticals</td>
<td>Indian (Ranbaxy) – South African (Community Investment Holdings) generic manufacturer</td>
<td>4.5%</td>
<td>Didanosine (25mg, 50mg, 100mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stavudine (20% of 30mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lamivudine (20% 150mg)</td>
</tr>
<tr>
<td>Merck &amp; Co.</td>
<td>Multinational patent holder</td>
<td>9.1%</td>
<td>Efavirenz (200mg)</td>
</tr>
<tr>
<td>Cipla-Medpro</td>
<td>South African – Indian generic importer</td>
<td>1.9%</td>
<td>Lamivudine (300mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nevirapine (20ml)</td>
</tr>
<tr>
<td>GlaxoSmithKline (GSK)</td>
<td>Multinational patent holder</td>
<td>6.9%</td>
<td>Lamivudine+zidovudine (150mg+100mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abacavir (200mg, 20mg/ml)</td>
</tr>
</tbody>
</table>


When the terms of GSK and BI licenses opened to include the private sector as well as countries in Sub-Saharan Africa and other LDCs, as seen in Table 7, the regional market for Aspen’s ARVs in countries that also have large HIV-infected populations grew exponentially. Currently, Aspen provides ARVs to 600,000 patients in South Africa and the African region across both the public and private sector. As of 2007, 74% of Aspen’s revenue was from the South African market and only 5% from the rest of Africa (Aspen, 2007c).
South Africa is a member of Southern African Customs Union (SACU) and the Southern African Development Community (SADC), and Aspen’s opportunities to reach further into African markets are being pursued. For example, the 51% acquisition of Shelys Pharmaceuticals with operations in Tanzania and Kenya may prove important to ARV contracts in the EAC. Further, Aspen hopes to supply ARVs to a more lucrative American market once patent terms expire (Aspen’s Upward Slope, 2005). Competition in export markets, however, is fiercer than in South Africa. Tender requirements vary across countries, particularly when IP standards vary. Aspen’s market access is favored South African tenders that contain local preference provisions and where competition is restricted to a small number of manufacturers.

**Tender System Requirements**

The conditions under which South Africa’s national ARV tenders must abide are described in the Public Finance Management Act of 1999. The Act outlines aspects of state expenditure, policies on financial management for the procurement of goods and services, and the efficient use of limited resources to maximize government service delivery. Under the Operation Plan, the South African government is obliged to ensure that drugs are tendered at the lowest possible price (Sprague & Woolman, 2006).

Much scrutiny exists of South Africa’s ARV tender system and process. For example, after the ARV bid announcement in 2004, it took more than a year for tenders to be awarded, and emergency provincial government procurement had to be used in the interim. The tender lasted 3 years and included a predetermined price escalation at a time when prices were rapidly declining. In addition, a senior researcher at ALP noted a “severe lack of transparency or participation”
(IRIN, 2008b) in the 2008 tender specifications by government with civil society. In particular, ALP and the Joint Civil Society Monitoring Forum (JCSMF) submitted concerns to the South African National AIDS Council (SANAC), which included lack of openness and accountability in tendering procedures, but these were never addressed by the Council. The 2008 contract duration, though shortened from 36 to 24 months, did not heed ALP’s suggested 18 month duration. An 18 month contract would allow new products already awaiting MCC approval to enter the market during the tender period. Additional concerns were raised by ALP: the local manufacturing preference system as well as ARV registration requirements (Berger, 2008).

Tender bids are adjudicated on a 90/10 preference-point system under the Preferential Procurement Policy Framework Act (2000). This system awards points based on the bid price (maximum 90 points) and the achievement of specified goals (maximum 10 points). In the 2004 tender, the latter goals included four preference-points for equity ownership by a BEE group,\(^4\) two points for the promotion of small businesses, and four points for the promotion of local manufacturers. Although the 2004 tender supported local manufacturers, it was open to manipulation and could inadvertently favour importers over domestic producers because it was not based on the local-value contribution of the firm within South Africa (Maloney & Segal, 2007). This meant that an importer, such as the South African-Indian joint venture, CiplaMedpro, could open a small office staffed to meet BEE requirements, but inject little into the national economy in terms of value-added and employment generation (IFC, 2008).

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The 2008-2010 tender modified these and other conditions, but retained the 90/10 preference-point system. This most recent tender awarded only one point for equity ownership by a BEE group and nine points for local production. In contrast to the 2004 tender, local production was assessed based on value of local contribution; with nine points awarded to a manufacturer if its local component accounted for 50% of the bid price. This value requirement removed the above issues of importer manipulation to obtain preference-points. It also kept competition between local producers and foreign firm closer seeing as no domestic manufacturer meets the full local components (no manufacturer produces APIs domestically). With the importation of APIs, it is suggested that Aspen, at best, adds 20% to 30% local value, making it eligible for a maximum two preference-points as well as one point (or part of one point) for BEE equity ownership (Berger, 2008). This places Aspen at a price advantage of less than 5% over foreign firms in national tenders, keeping the premium paid by DoH to support local industry low.

Registration of ARVs, both in South Africa and in other countries, poses a number of obstacles for South African manufacturers, such as Aspen. In Sub-Saharan Africa, donors finance US$750 million to US$1 billion for the procurement of drugs related to HIV/AIDS, tuberculosis, and malaria. Unlike in many other Sub-Saharan African countries, in South Africa a large portion of the national ARV tenders are financed by government, and not donor agencies. The South African government finances approximately 88% of HIV/AIDS programs from domestic resources. Although South Africa is one of PEPFAR’s 15 priority countries, it is unclear what proportion of PEFPAR funding is directed to the procurement of ARVs. This means that the government is able to set the terms of the tender without having to abide by a standard donor requirement: that manufacturers and their products be prequalified by WHO, or FDA in the case
of PEPFAR. This is as a major constraint for many manufacturers in developing countries, such as Tanzania Pharmaceutical Industries in Tanzania, where the majority of ARV tenders are financed by donors. Even though these firms’ ARVs are registered by their country’s local DRA, market access is barred due to a lack of international accreditation. FDA approval and WHO prequalification processes are often lengthy, costly, and they delay market entry. Technically, in South African government financed tenders ARVs need only be registered by the MCC.

Necessitating MCC registration in government tenders, however, also poses barriers to market entry for two reasons. First, some multinational firms have become notorious for failing to register their products in developing countries where these firms see little market potential. For example, the alternative first-line ARV tenofovir was registered by Gilead in both the United States and Europe in 2001 and 2002, respectively, but was never registered with the MCC in South Africa. Only with MCC registration can a product be added to the national treatment guidelines and, subsequently, be made available on the market and eligible for tender. Finally, in 2006, Aspen’s tenofovir license from Gilead handed Aspen the responsibility of product registration in a list of countries throughout Sub-Saharan Africa. These registration challenges were heightened in the 2008 tender, as the request for bids excluded manufacturers that had yet to receive MCC approval, even if the drugs were accredited internationally by the WHO or FDA. This has price and affordability implications given that many Indian generic firms with WHO prequalified and FDA approved ARVs, but pending MCC registration, were ineligible to bid on tenders.
Second, under the General Regulations (2 May 2003) of the Medicines and Related Substances Act, MCC must fast track applications (in a maximum of 9 months) for the registration of medicines essential for national health – if the firm pays double the R12,500 fee (Hassim, Heywood, & Berger, 2007). Yet, local manufacturers have faced delays from 2 to 3 years for registration of priority products. As mentioned above, in early 2006 Aspen submitted a dossier to MCC for priority review of tenofovir. The review lasted nearly 18 months (Ford, Gray, & Venter, 2008). Increasing numbers of applications and the lack of capacity within the MCC to meet time restrictions have caused outraged among civil society, because during these delay the products remain unavailable and its manufacturers are unable to bid on tenders. Even if these ARVs are approved and enter the domestic market at a lower price than the contracted ARVs, they are not eligible for procurement under the tender. This restricts competition and potentially keeps prices unnecessarily high.

Even though Aspen’s licenses span most of Sub-Saharan Africa, making its potential ARV market vast, Aspen also depends on each country’s tender system requirements to gain market access. Similar to the procedure in South Africa, in Sub-Saharan African countries a manufacturer and its products must be registered with the local DRA. These countries, in addition, rely heavily on donor financing for their drug procurement. The two major donors, the Global Fund and PEFPAR require WHO prequalification and FDA approval, respectively (Appendix G details the Global Fund’s quality assurance policy). To achieve WHO prequalification, a rapid review is granted to products already approved by a stringent DRA, such as the FDA, the European Medicines Agency or Health Canada. Thus, if a manufacturer is accredited and its product approved by the FDA, it does not undergo a full review at WHO.
Currently, Aspen has five individual ARVs and two fixed-dose combinations approved by the FDA and subsequently placed on the WHO prequalification list: d4T, 3TC, AZT, NVP, tenofovir, tenofovir+emtricitabine, and the co-blister pack AZT+3TC with NVP. Table 10 lists 15 Sub-Saharan African countries, outside of South Africa, in which Aspen’s ARVs are registered. The majority of these products are also WHO/FDA approved. Eight countries have registered some of Aspen’s ARVs that are approved only by their local DRA and are not WHO/FDA accredited. Whereas WHO prequalified products are eligible for any international competitive tender financed by donors, Aspen’s products that are registered only by the local DRAs (such as didanosine) are eligible for government financed tenders only. Aspen’s efavirenz, which is approved by the MCC alone, is not eligible for tender outside of South Africa.
<table>
<thead>
<tr>
<th>Country of Registration</th>
<th>WHO Prequalified/FDA Approved</th>
<th>Local Drug Authority Approval Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>TDF+FTC, TDF</td>
<td></td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>3TC, d4T, NVP, AZT and [AZT+3TC]+NVP, TDF+FTC</td>
<td>3TC, NVP, AZT (Oral Liquids), d4T (capsules)</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>TDF+FTC, TDF</td>
<td></td>
</tr>
<tr>
<td>Ghana</td>
<td>3TC, d4T, NVP, AZT and 3TC+AZT</td>
<td>ddl</td>
</tr>
<tr>
<td>Guyana</td>
<td>TDF+FTC, TDF</td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>TDF+FTC, TDF</td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td>3TC, d4T, NVP, AZT and [AZT+3TC]+NVP</td>
<td>3TC, AZT (oral liquids) d4T (capsules)</td>
</tr>
<tr>
<td>Mozambique</td>
<td>3TC+AZT and [AZT+3TC]+NVP, TDF+FTC, TDF</td>
<td></td>
</tr>
<tr>
<td>Namibia</td>
<td>d4T, 3TC+AZT, [AZT+3TC]+NVP, TDF+FTC, TDF</td>
<td>ddl, d4T (capsules)</td>
</tr>
<tr>
<td>Nigeria</td>
<td>3TC+AZT, [AZT+3TC]+NVP, TDF+FTC</td>
<td></td>
</tr>
<tr>
<td>Rwanda</td>
<td>3TC+AZT, [AZT+3TC]+NVP, TDF+FTC, TDF</td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>3TC, d4T, NVP, AZT, AZT+3TC, [AZT+3TC]+NVP, TDF+FTC, TDF</td>
<td>ddl, 3TC, NVP, AZT (Oral Liquids), d4T (capsules), EFV</td>
</tr>
<tr>
<td>Uganda</td>
<td>3TC, d4T, NVP, AZT, 3TC+AZT, [AZT+3TC]+NVP</td>
<td>3TC, AZT, d4T</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>3TC, d4T, NVP, AZT,3TC+AZT, [AZT+3TC]+NVP</td>
<td>3TC, AZT, d4T</td>
</tr>
<tr>
<td>Zambia</td>
<td>d4T, 3TC+AZT, [AZT+3TC]+NVP, TDF+FTC, TDF</td>
<td>d4T</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>3TC, d4T, NVP, AZT,3TC+AZT, [AZT+3TC]+NVP</td>
<td>3TC, AZT (oral liquids), d4T</td>
</tr>
</tbody>
</table>

**Note.** All products are tablets unless otherwise specified in parenthesis. Some drug names may appear in both categories. These drugs vary either in dosage or drug form (liquid, capsule or tablet). 3TC = lamivudine, AZT = zidovudine, NVP = nevirapine, d4T = stavudine, ddl = didanosine, TDF = tenofovir, TDF+FTC = fixed-dose combination tenofovir with emtricitabine, EFV = efavirenz, [AZT+3TC]+NVP = fixed-dose combination zidovudine and lamivudine co-packaged with nevirapine.

Source: WHO (2008d)
The Place for Competition

In South Africa, the competitive state of the pharmaceutical sector is weak (Maloney & Segal, 2007). Due to IP enforcement, competition in ARV tenders has been limited predominantly to patent holders and the generic firms they have licensed to enter the market. This requirement eliminates a large number of generic manufacturers from India, a country from which 80% of the ARV market by volume and some of the lowest ARV prices derives. The ALP notes that the mounting complexities in South Africa’s ARV market are due to both the slow pace of registration, as discussed above in Tender System Requirements, and the lack of a sufficient number of locally-based manufacturers granted voluntary licenses on reasonable terms (Berger, 2008), either for import or manufacture.

With South Africa’s patent system intact, Aspen faced limited ARV price competition when it entered the country’s public sector market. The 2004 tender highlighted the effect of restricted competition; only two generic firms competed, Aspen and CiplaMedpro, a South Africa-India joint venture, which imports ARVs. Demonstrated in Table 8, seven manufacturers (five patent holding firms) were awarded the tender. Aspen received 50.8% of the tender by volume, but less than 17% by value.

Competition in South Africa, however, was enough to initiate price reductions greater than those offered by patent holders. Aspen’s initial tendered price for lamivudine was US$60 per person per year (pppy), almost 20% lower than GSK’s tendered price of US$74. As illustrated in Figure 9, Aspen’s price was also lower than the median transaction price for lamivudine, 3TC, in the Sub-Saharan African region (US$70 pppy) and in upper-middle-income countries (US$69 pppy)
Yet, as the tender offered a 3-year fixed term that included price adjustments after 18 months, the price difference between Aspen and GSK bids decreased to 11%, with both firms’ respective prices increasing to US$71 pppy and US$80 as the contracts approached their end. At a time when competition would have intensified to lower prices, a predetermined price escalation occurred (Gray, 2008).

Figure 9: Annual Treatment Cost of Lamivudine in the South African Tender System and Median Transaction Prices in the Sub-Saharan African Region and Upper-middle-income Countries, 2004-2008

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42 The South African tender prices discussed here exclude value added tax (VAT), which the National Treasury stipulates must be included in the tender bid price, in order to generate a closer comparison to median transaction prices used in the Global Price Reporting Mechanism (GRPM).
The 2004 South African ARV tender and its 3-year fixed term sheltered Aspen from competition during its first few years of ARV manufacturing. This enabled the firm to stabilize its production base and accumulate growth, but it did so at the expense of ARV affordability in South Africa. As Figure 9 demonstrates, by the end of 2007 the median transaction price of lamivudine was lower in Sub-Saharan African countries and upper-middle-income countries than in South Africa. In Sub-Saharan African countries, this price was 30% lower (US$49) than the South African government tender. Media also reported that approaching the end of the 2004 tender (at the end of 2007), the South African government was paying twice the price for nevirapine than was available in the private sector (where prices are typically substantially higher) (IRIN, 2008b). While caution should be exercised when comparing prices from different sources, it is important to understand the potential impact that the South African tender system, and its fixed term contracts, can have on price.43

Profitable for Aspen, South Africa’s tender system has negative implications for price and affordability. Many criticized the length of the tender process and contract duration as inappropriate, given the rapidly changing ARV market. Not only did new generic ARV entrants come on the market during the 2004 tender period, but ARV procurement volumes increased and manufacturing processes became more efficient. In 2004, the individual components of the triple therapy regimens lamivudine, stavudine, and nevirapine (3TC+d4T+NVP), together, had a best tender price of approximately US$169 pppy (Gray, 2008). By comparison, that same year, Figure 10 demonstrates that upper-middle-income countries (most of which were compliant to

43 GPRM quoted prices are median international transaction prices. These are not necessarily the prices paid at the country level. The latter prices can be higher as a result of taxes and tariffs, transportation, and mark-ups—or lower due to subsidies. As a result, extreme caution must be taken when comparing GPRM prices with South African tender prices.
the TRIPS Agreement) paid a median international transaction price of US$217 pppy (GPRM, 2008), making Aspen’s price significantly more affordable. However, few upper-middle-income countries face the high prevalence rates and large number of HIV-infected individuals requiring ARVs seen in South Africa (with the exception of Brazil, whose ARV prices were not included in the GPRM database). In India, this same combination of ARVs, 3TC+d4T+NVP, was procured in 2004 from Cipla for US$121 pppy and Ranbaxy for US$96, under WHO Contracting and Procurement Services (GPRM, 2008). India, a country where patent restrictions do not apply for first-line ARVs, was able to procure 3TC+d4T+NVP for a fraction of the cost the South African government paid, in a fixed-dose form that is more desirable for patient adherence. By the end of the South African government’s 3-year contract in 2007, South Africa’s tender price of US$165 pppy remained relatively unchanged while the same upper-middle-income countries were paying a median transaction price of US$101 pppy, nearly 40% less. Figure 9 illustrates that the restricted 2004 tender created higher prices than would have occurred if the tender period was shorter, and open to all generic manufacturers and FDCs.

The 2008 South African ARV tender posed greater risks to Aspen’s profits than the 2004 tender, but created an opportunity to increase ARV affordability. Increased competition from the growing number of domestic ARV producers put pressure on Aspen’s profit margins and price (Summit TV, 2007). Consolidation of local and foreign generic businesses, such as Ranbaxy South Africa and Sonke Pharmaceuticals, led to the emergence of larger and better resourced competitors. Table 9 displays the preliminary results of the 2008 tender; contracts for six drugs had yet to be awarded at the time of announcement. The number of generic firms awarded contracts increased from two firms in the 2004 tender (CiplaMedpro and Aspen) to four local
firms in 2008 (Aspen, CiplaMedpro, Sonke, and Adcock Ingram). Despite this new competition, Aspen’s share of the tender increased from 2004; it was awarded nearly 57% of the first-round procurement volume (up from 50.8% in 2004).

Figure 10: South African Government Tender Price and Median Transaction Price by Country Income Level for Annual Treatment of 3TC+d4T+NVP, 2005-2008

Prior to the announcement of the 2008 tender in June, Aspen was facing increased competition in the regional market for its first-line ARVs (as illustrated in Figures 9 and 10) and in the domestic market. Though Aspen’s fixed tender price for lamivudine at the end of 2007 was US$71, its price for the same drug in donor-financed tenders in South Africa dropped to as low as US$52 pppy, possibly due to the new generic drug firm entrants in South Africa, Sonke Pharmaceuticals.
and Adcock Ingram (GPRM, 2008). With the end the 2004 tender and a new bid announced, competition increased affordability of first-line treatment (seen in Figures 9 and 10). The 2008 tender result for lamivudine, split 70/30 between Aspen and Sonke Pharmaceuticals, lowered the drug prices to US$42.50 and US$42.55, respectively. Increasing the number of suppliers drove the tender to a commodity-based market, with large contracted volumes and tight profit margins. The shortened contract duration (from 3 years in 2004 to 24 months in 2008) will avoid some of the discrepancies seen between tender price and available market price at the end of the 2004 tender. However, sceptics argue that tender periods should be even shorter (no longer than 18 months) to ensure the lowest prices (Berger, 2008).

In the 2008 tender, another limitation affected price: the tender did not specify bids for FDC first-line treatments, such as 3TC+d4T+NVP. Even though individual drug prices, such as lamivudine, were lower than those in upper-middle-income-countries, the total treatment cost of triple therapy was more expensive. The individual products of Aspen’s triple therapy 3TC+d4T+NVP cost US$112 pppy in the 2008 tender. Figure 10 demonstrates that, although this price dropped more than 30% since the end of the 2004 tender, the median transaction price for this FDC in upper-middle-income countries has fallen more than 60%, to US$86 pppy (GPRM, 2008). Aspen’s ARV licenses from GSK and BI do not prohibit Aspen from manufacturing FDC 3TC+d4T+NVP; yet, the tender announcements did not call for them specifically. Even Aspen’s co-blister pack (3TC+AZT packaged with NVP) has yet to be tendered. This has large consequences for price (as the large scale manufacturing processes for triple therapy FDC are often more efficient than those for three individual products) and for drug access (as the combined formulation treatments can raise adherence rates significantly).
Even though Aspen won the bulk of the 2004 and 2008 tender for first-line drugs, Aspen moved quickly to expand its product base to newer ARVs (where competition is lower and profits are higher), such as alternative first-line and second-line ARVs. The South African National Economic Development and Labour Council found that 80% of a manufacturer’s profits on a generic drug will be captured within 18 months of the generic coming to market (Maloney & Myburg, 2007). Currently, Aspen is the exclusive provider of tenofovir in South Africa, granting it an effective monopoly.44 Competition for efavirenz, which has the highest value in the South African tender system (Avafia, Berger, & Hartzenberg, 2006), is restricted to the patent holder (Merck for 200mg and 600mg efavirenz) and the two licensed firms, Aspen and Adcock Ingram (for 600mg efavirenz). The use of tenofovir and efavirenz has been increasing as a result of new WHO (2006a) guidelines on alternative first-line treatment (see Appendix A for a discussion of the treatment regimes). Like the licensed ARVs before them, they face little to no competition in the South African market compared with other developing country markets not constrained by IP protection.

Importantly, Aspen’s tenofovir did not increase in affordability in the 2008 tender. Under its licensing and distribution agreement with Gilead, Aspen faced no competition for tenofovir in South Africa. The government contract was award at US$227 pppy, which is 20% higher than the US$207 pppy offered under Gilead’s Global Access Program to eligible African and low-

44 Aspen’s tenofovir remains the sole competitor on the South African market for two reasons. First, the voluntary license between Gilead and Aspen included distribution rights in South Africa and parts of Sub-Saharan Africa. As a result, Gilead does not intend to market its product in the licensed countries, effectively making Aspen the sole distributor. Second, although tenofovir is not under patent in South Africa, manufacturers that are not bound by licensing terms and also manufacture tenofovir are not currently registered by the MCC, which prevents their products from entering South Africa.
income countries (which includes South Africa). Without competition (even against the patent holder), Aspen can set the price relatively free, as long as it is within its licensing terms.

Figure 11 compares 2008 median transaction price of tenofovir across 10 Sub-Saharan African countries, where competition is less restricted than in South Africa. In the Sub-Saharan African region, compared to the median unit price of $0.79 in South Africa, Aspen offered a much lower unit price (and equal to Gilead’s access price) of US$0.57 to a number of procurement agencies, including MissionPharma, UNITAID, and Supply Chain Management System (SCMS). This unit price was constant in spite of substantial quantity variations (from 1440 units in Nigeria, a lower-middle-income country, to 1,846,890 units in Ethiopia, a designated LDC) (GPRM, 2008). The generic competitor by Matrix Laboratories (FDA approved since December 2007 and WHO prequalified) was procured in 2008 under Global Fund and PEPFAR financing for a median price of US$0.46 (GPRM, 2008). Though competition for tenofovir is still limited in the region, this price difference (up to 26% in Sub-Saharan African countries and 50% from the highest unit price paid in South Africa) highlights the affect that adding one competitor may have on Aspen’s price.

Limited market competition has significant implications for drug affordability. With the largest ARV program in the world and a national tender system in place, the South African government’s monopsony power and purchasing volume should, theoretically, result in some of the lowest ARV prices in the world. Yet, comparing Aspen’s price with those in the Sub-Saharan African region, competition not volume (or even country income status), has influenced price

45 Under the Global Price Reporting Mechanism (GPRM) those Sub-Saharan African countries where Aspen’s ARV tenofovir have been procured include Benin, Botswana, Cote d’Ivoire, Ethiopia, Kenya, Namibia, Nigeria, Rwanda, Tanzania, Uganda.
reduction. TAC argued this logic when it decried Aspen’s ARV licenses from GSK and BI insufficient to reduce price substantially in South Africa. During negotiations with GSK and BI, TAC advocated for a minimum of four licenses per product, to allow competition to reduce price. This logic follows the WHO (1999) “rule-of-five” which assumes that five bids on a tender engender enough competition to ensure the lowest contracted price. As the sole provider of tenofovir, Aspen’s high price in the South African market could cause supply constraints for the government. Given the same resources as other countries in the region, the government can only procure a smaller volume, treating fewer patients than it could if the price was lower.

**Figure 11: Median Transaction Unit Prices in South Africa and Sub-Saharan Africa for 300mg Tenofovir by Manufacturer, 2008**
While Aspen has managed to dominate the local market, replicating its success abroad is likely much more difficult (‘Aspen’s upward slope’, 2005) where competition is greater. Many Sub-Saharan African countries’ tender systems are not yet confined by IP compliance and, as such, any qualified generic manufacturer may bid, regardless of whether they have a license from the patent holder. This opens the competition to the aggressive high volume, low price Indian manufacturers. Though this has positive effects on price and affordability, it has consequences for manufacturers such as Aspen looking to expand its market share. Aspen increased the affordability of first-line ARVs in South Africa in a market previously dominated by patent holders; yet, the limited competition in South Africa has enabled Aspen to keep its margins higher than if it were competing in the open market. To compete internationally, it will have to find a way to cut its prices substantially, otherwise ensure its products are the first generics on market to offer lower prices than patent holders, but achieve greater profits than would be experienced with generic competition.

**Policy Implications**

**What Influences the Transfer of Technology?**

Aspen was able to align itself to the research-based pharmaceutical industry to secure a number of voluntary licenses for two reasons: it is a well-financed publicly-traded company and it supports IP compliance. Discussed here are a number of implications this licensing strategy has in South Africa and in developing countries more broadly, both in terms of technology transfer and ARV affordability.
Importantly, Aspen’s first voluntary licenses (from GSK and BI) were only granted on reasonable terms after extreme pressure from civil society brought GSK and BI before the Competition Commission. Given the strength of IP protection in South Africa and the country’s challenge to access affordable generic medicines, this case raises a number of important issues for developing countries. This case suggests that technology might not readily transfer simply as a result of IP protection, as indicated by the TRIPS Agreement. South Africa, with arguably the strongest IP system among developing countries, acquired reasonably termed voluntary licenses only after court challenges by civil society. The highly publicized licenses between GSK, BI, and Aspen led some to suggest that these voluntary licenses were, in fact, coerced or compulsory voluntary licenses.

The case in South Africa also demonstrates the importance of domestic firms’ investment in capacity and high-quality manufacturing facilities to attract licenses from the research-based pharmaceutical industry, who may provide little by way of technology transfer and capacity building assistance (as in the case with the GSK and BI licenses). These financing requirements raise a concern for developing countries: premature IP strengthening may stifle both access to affordable medicines and prospects of growing a domestic industry in developing countries when drug firms lack access to financial capital and manufacturing capacity is limited.

Additionally, in the face of poor political leadership, the power of civil society to hold the South African government and the pharmaceutical industry accountable for patients’ health and should be noted in developing countries that also struggle to make governments accountable. Public pressure is often needed for governments to enforce citizens’ right to health care services,
including access to ARVs, as well as for the pharmaceutical industry to lower ARV prices. In South Africa these policy changes were achieved primarily through the judicial system (with civil society arguing that Section 27 of the Constitution included ARV provision as a citizen’s right to health, and using Section 9 of the Competition Act, which prohibits excessive pricing of pharmaceutical firms in the market). Forman (2009) reinforces the important role of civil society in government policy. She states that the power of a rights-based approach, along with public coercion, can increase access when powerful actors have long-established interests, both political and economic.

These judicial actions in South Africa underscore the opportunity for civil society to look beyond the Doha Declaration and toward other measures within a country’s legislative framework to affect change if TRIPS flexibilities, such as compulsory licensing, are not available. In developing countries such as Brazil and Thailand, civil society and HIV/AIDS activists have pushed governments to deliver affordable, universal treatment. These upper-middle-income countries, however, generally have better organized and resourced civil society movements than those in LDCs. In addition, LDCs are less likely to have advanced legislative frameworks that contain the types of provision seen in South Africa for civil society to use. In this regard, the South African case may have limited generalizability to other Sub-Saharan African countries.

South Africa’s experience signals developing countries and LDCs to instate appropriate provisions within their legislation to prioritize public health interests over those of trade and industry. This includes placing the right to health within national constitutions, developing sound public procurement legislation that requires international competitive bidding, as well as pricing
and competition policies to ensure that affordable medicines are available. Countries should enact domestically those flexibilities within the TRIPS Agreement, the Doha Declaration and 30 August Decision for parallel importation, use of transition periods, and compulsory licensing—either for domestic production or importation if manufacturing capacity is a challenge.

The case of South Africa also signals a number of opportunities and constraints with voluntary licenses, compared with compulsory licenses. Since Aspen’s voluntary ARV licenses with GSK and BI were issued under tenuous terms, a number of patent holders have moved toward voluntary licensing strategies, evidenced by the variety of agreements Aspen has negotiated with numerous patent holders.

Advantageous to domestic firms, voluntary licenses are less controversial than compulsory licenses and have fewer transaction costs. These costs are attributable to the arduous procedures required for compulsory licensing under WTO. Compulsory licenses are also inadequate long-term solutions to the global ARV access problem; whereas, voluntary licenses from patent holders can be more sustainable in the long-term. Compulsory licenses often impose time restrictions and do not necessarily come with technical assistance to develop and manufacture ARVs. Voluntary licenses, by comparison, have begun to include technology transfer provisions and can last until patent expiry and even beyond. This assures a continuous and sustainable supply of ARVs, which is often a concern in developing countries.

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46 These are costs that are incurred when making an economic exchange, including bargaining, enforcing, and policing the terms of the exchange.
Patent holders can also find voluntary licenses valuable. These agreements avoid threats of compulsory licenses and negative media attention. Also, even though drug royalties are increasingly uncommon due to public pressure, voluntary licenses often come with geographic market restrictions, such as Aspen’s restriction to Sub-Saharan Africa. This assures that licensed firms will not enter the markets most valuable to patent holders. In addition, voluntary licenses, like those issued by Gilead to Aspen and a number of Indian manufacturers, require that the necessary APIs come from the right holder. APIs are the main cost driver of ARV prices, and this stipulation ensures that patent holders maintain some control over the market, even if they do not sell the product in the region. Furthermore, long-term licensing arrangements can ensure that generic firms rely on patent holders even after patents expire. Finally, Friedman, den Besten, and Attaran (2003) suggest that pairing developing country firms’ experimental rights with patent holders’ right of first refusal to share or co-market any new product developments can be beneficial to both parties.

Although voluntary licenses can benefit both patent holders and domestic drug firms, voluntary licenses can come at a disadvantage to drug affordability in developing countries. The example of tenofovir in South Africa shows that a licensed manufacturer does not necessarily reduce its price under a distribution agreement when there is little competition. Price reductions from a sole licensed manufacturer are much smaller than if there numerous competing generic manufacturers. It was for this reason that TAC fought patent holders GSK and BI to license their products to a minimum of four competing generic manufacturers. When South Africa’s ARV market began to engender a larger number of generic manufacturers in 2008, prices declined.
Therefore, licensing arrangements can foster a drug’s profitability over affordability, unless a number of licenses are issued.

Striving to acquire the first license for each new ARV, Aspen aims to produce the first generic alternative first- and second-line ARVs to capture the largest market share and profit. Although this can reduce ARV prices below those of patent holders, these reductions will not be substantial and sustained without sufficient competition. The impact voluntary licensing strategies have on the market prices of a number of products has yet to be measured, but it likely depends on the number of licenses patent holders are willing to issue in order to stimulate competition.

**Does Domestic Production Produce Affordable ARVs?**

Developing country governments must be aware that neither voluntary nor compulsory licenses are a strategy for immediate ARV price reduction. They are medium-term strategies that seek to meet industrial development goals as well as public health objectives. The case of Aspen highlights the large input costs and time needed for product development and DRA approval domestically (as well as regionally and internationally) before a product can enter the market and bring down price. Even then, it is not certain that a locally produced product will be more affordable than those imported. Here, competition is crucial. In the case of Aspen in South Africa, the firm was able to increase first-line ARV affordability from patent holder prices, but Aspen’s prices for many, particularly newer, ARVs did not increase affordability over what could be imported (if patents were not a barrier).
Developing country governments and domestic manufacturers need to assess opportunities and constraints of developing a domestic ARV industry and whether an initiative of this type can produce ARVs cheaply. As the case of South Africa stresses, access to a large market and capacity to manufacture APIs through economies of scale, as well as competition, are essential to reducing ARV costs. Building capacity has proven difficult for Aspen, which is only now considering domestic API production, and it would be even more challenging for developing countries and LDCs. Developing countries and LDCs often have nascent pharmaceutical industries and have tenders funded by donors, which require international competitive bidding and ARV accreditation by WHO or FDA. Meeting these standards often necessitates large upfront investment to build high quality manufacturing facilities as well as appropriate resources to develop ARVs and test quality assurance.

Even with a domestic preference system in place, competition with vertically integrated international manufacturers is strong; their production of APIs and large scale volumes reduce costs substantially. To its favor, patent compliance in South Africa shelters Aspen and the firm’s ARV licenses from the intense competition seen in other Sub-Saharan African countries. Whereas Aspen earns the largest procurement volumes in South African tenders, whether it can compete regionally with the prices of Indian generic firms remains to be seen.

When considering local manufacturing, it is imperative that governments understand which policies (development or health) will be given priority to identify the appropriate measures to achieve sustainable, affordable medicines access. Developing countries and LDCs must weigh the opportunities and constraints of using TRIPS flexibilities for local ARV production. If local
manufacturing is to ensue, the appropriate multi-sector policy framework must be in place to ensure both industry incentives and access to capital are available to attract industry to transfer the required technology and to build a substantial manufacturing base. This should be done only after a thorough assessment of the market to determine the feasibility of local initiatives to lower drug prices. Most important to drug access, during the time it takes to bring a locally manufactured product to market, no change in price will be seen unless the appropriate access strategy is also in place. Immediate cost-reduction strategies, such as price negotiations with patent holders, bulk procurement, parallel importation, and competitive tenders, must be tied to long-term production goals to maximize ARV affordability.

The case of South Africa reinforces the large role that governments play in ensuring the lowest drug prices, particularly within tender system stipulations. Although the most commonly considered constraint is patents, there are a number of limitations that tender specifications impose that negatively impact drug affordability. A tender that fixes price over a lengthy term, when new generic manufacturers are continually entering the market and production is becoming more efficient, keeps prices artificially high. With respect to ARVs, the omission of combination products in favor of their individual components burdens not only affordability, but adherence rates. Finally, requiring DRA approval at the time of bidding (as opposed to at the time of the awarded contract) even when the product is WHO or FDA approved, removes competition by foreign, high-quality generic drug manufacturers that are awaiting slow DRA approval.

Both manufacturers and patients are frustrated with the cumbersome and slow DRA approval processes in a number of Sub-Saharan African countries. The limited capacity of developing
country DRAs to review dossiers in a timely manner makes treatment availability a major obstacle to drug access. Ensuring the quality of products entering the market is, without question, an imperative in every country. However, appropriate steps should be taken to simplify or harmonize registration processes across regions and train human resources on drug dossier evaluations. Taking these steps will make priority drugs available sooner, particularly if international quality accreditation was already awarded.

**Conclusion**

The case study of Aspen Pharmacare in South Africa analyzed the domestic conditions affecting the transfer of ARV technology to Aspen Pharmacare and the ability of the drug manufacturer to produce affordable ARVs. It revealed that the strong patent system in South Africa, combined with government’s poor commitment to rollout ARVs or ensure their affordability, mobilized civil society to force policy shifts and negotiate voluntary licenses. Within this environment, Aspen, a well-financed equity firm, was able to leverage its resources, capacity, and IP compliance to foster relationships with patent holders and negotiate the world’s first voluntary ARV licenses. Aspen’s struggle to acquire these licenses indicates to developing countries that technology, through voluntary licenses, may not readily flow simply as a result of IP protection, as suggested by the TRIPS Agreement. Developing countries need to ensure that TRIPS flexibilities are incorporated into domestic legislation, to enable the domestic production of patented ARVs, along with political commitment to utilize these flexibilities when appropriate.

This case study also revealed that the affordability of South Africa’s domestically manufactured ARVs was influenced by Aspen’s ability to capture a large, consistent market share and its
capacity to integrate vertically and generate economies of scale. The case also strongly reflects the importance of competition in the generic drug market and the procurement of FDCs to reduce treatment cost. Limited competition and lack of combination ARVs in South Africa’s tender system keeps prices above those on the international open market. Though Aspen has been able to fulfill the international quality requirements of lucrative donor-financed tenders and is able to compete regionally, it remains to be seen whether it can meet the prices offered by high volume, low-cost Indian manufacturers which dominate the generic ARV market. As such, developing countries should thoroughly analyze the ability of initiatives to produce competitively priced low-cost ARVs. Otherwise, additional strategies, such as licensing to import ARVs, parallel importation, or price negotiation should be pursued to ensure the most affordable treatment options for their populations.

Summary and Introduction to Chapter 4

The findings from the case studies in Tanzania (Chapter 2) and South Africa (Chapter 3) identified the domestic conditions that influence the type of ARV technology transfer arrangement a local firm enters—whether an imitation arrangement or voluntary licensing arrangement. Notably, these conditions included the country’s policy environment (specifically patent compliance) and domestic firm’s financial structure. Both influenced the ability of the domestic firm to attract the transfer of technology, through voluntary licenses or imitation.

With a small-n comparative case study of Tanzania and South Africa, the results are difficult to generalize across developing countries. To extrapolate the findings to other developing countries, the two prominent variables that emerged from the cases are now tested across a number of
developing country ARV manufacturing initiatives. Chapter 4 quantitatively tests the association
between the transfer of technology (via voluntary licenses) and two independent binomial
variables: TRIPS-patent compliance (yes/no) and domestic firm ownership (private/state). This is
followed by a discussion of the results in the context of the Article 7 of the TRIPS Agreement
and their implications for developing countries.
Chapter 4: Patently Influenced? TRIPS Patent Compliance and the Transfer of Technology to Developing Countries: A Multi-Country Analysis

Introduction

Since 2001, a number of developing countries and LDCs have announced their intent to manufacture antiretroviral (ARV) drugs domestically. Generally, ARV manufacturing aims to improve drug access by lowering price, increasing national health security and sustainability of supply, and fostering technological development. Local ARV production occurs through provisions under the World Trade Organization’s (WTO) Agreement on the Trade-Related Aspects of Intellectual Property (TRIPS).

Pursuant to Article 7 of TRIPS, the protection of intellectual property (IP), such as pharmaceutical patents, should “contribute to the promotion of technological innovation and to the transfer and dissemination of technology” (WTO, 1994, p.323). Case studies of Tanzania (Chapter 2) and South Africa (Chapter 3) revealed that, while patent protection positively influences the transfer of technology through voluntary licenses, the type of domestic firm ownership (state-owned or private) also influences the ability of the country to attract licenses. Currently, there is no multi-country study documenting generic ARV manufacturing initiatives in developing countries and examining the trends in technology transfer. This study fills this gap by analyzing the relationship of two independent variables, TRIPS patent compliance and firm ownership, to the dependent variable, transfer of technology.
Research Questions

With reference to the TRIPS Agreement, this chapter answers the following questions:

1. Does the protection of ARV patents result in an increase of ARV technology transfer to developing countries?
2. Does private ownership of domestic drug firms result in an increase of ARV technology transfer to developing countries?

Background

Marked as the first trade agreement to incorporate patents, the TRIPS Agreement was implemented 1995 and has since been signed into effect by 153 WTO member countries. In exchange for trade liberalization and its promised benefits under various WTO agreements, the TRIPS Agreement is the only treaty that requires member states to protect pharmaceutical patents for 20 years from their filing date. One incentive for developing countries to ratify the TRIPS Agreement was an expected increase in the transfer of technology, as mentioned in Article 7. Given the 20-year patent protection term required by the TRIPS Agreement, three provisions exist to enable local production: using the TRIPS 2005/2016 transition period, compulsory licensing, and voluntary licensing.

Developing countries had until 2005, and least-developed countries (LDCs) have until 2016, to integrate the patent requirements of the TRIPS Agreement into their domestic legislation. Most

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47 Other trade agreements under WTO, including the General Agreement on Trade and Tariffs (GATT) and the General Agreement on Trade and Services (GATS), do not cover intellectual property.
48 Originally TRIPS required least-developed countries to implement appropriate patent legislation by 2006. The Doha Declaration on TRIPS and Public Health extended the deadline until 2016 (WTO, 2001).
developing countries complied prior to the 2005 deadline, with the most notable exception of India. The transition period allows the respective countries to manufacture medicines that are patented in TRIPS-compliant countries without fear of repercussion.

Advocates for drug access state that patent protection results in monopoly pricing that leads to unaffordable ARVs in many developing countries (MSF, 2008). They stress that the patent requirements of the TRIPS Agreement do not encourage technology transfer and only increase the patent holders’ market monopoly, overly protecting their rights in a manner insensitive to developing countries (Barton, 1999; CIPR, 2002; Correa, 1999; UNDP, 1999; World Bank, 2001). The Doha Declaration on TRIPS and Public Health stresses the importance of interpreting the TRIPS Agreement in the context of public health. In doing so, it grants developing countries the freedom to declare national emergencies or public health crises and invoke compulsory licenses under Article 31 to forego pharmaceutical patents and manufacture drugs domestically without their patent holders’ consent (WTO, 2001). Yet, poor manufacturing capacity in LDCs left many countries unable to use this provision. The transfer of technology and development of technological capabilities in these countries was addressed in the 30 August Decision of the General Council of 2003. The Decision enabled countries that do have drug manufacturing capacity to export the necessary pharmaceuticals to countries that do not under a third-party compulsory license. Also, pursuant to Article 66.2 of the TRIPS Agreement, developed countries were encouraged to provide industry incentives to transfer pharmaceutical technology and build capacity in LDCs, to create a sound and viable technological base (WTO, 2003a).
Finally, although often referenced in the TRIPS Agreement, *technology transfer* is not explicitly defined. In keeping with the TRIPS Agreement, and for the purpose of this quantitative analysis, *technology transfer* is a formal exchange of rights in the private market to exploit a patent and underlies the movement of technology between a patent holder and an unrelated recipient. With respect to pharmaceuticals, this is achieved through voluntary licensing of technologies by patent-holding firms (such as GlaxoSmithKline [GSK], Boehringer Ingelheim [BI], Hoffmann-La Roche [Roche], Bristol Myers Squibb [BMS], Gilead Sciences [Gilead]) to generic drug manufacturers in other countries.

**Methods**

A study was performed of generic ARV manufacturing initiatives in WTO member developing countries. For this study, a *manufacturing initiative* was defined as the publicly announced production of a generic, adult formulated ARV by a developing country firm. All manufacturing initiatives were considered regardless of their development stage (from the initial announcement to ARV registration and distribution). Therefore, some of the initiatives examined may have stalled or ceased without any ARV being produced. To identify the manufacturing initiatives, a search was conducted of the WHO Regulatory Status Database, newswires, press releases, pharmaceutical firm websites, submissions to governments, as well as key-informant interviews conducted in the case studies found in Chapter 2 (in Tanzania) and Chapter 3 (in South Africa). These data were collected for ARV manufacturing initiatives that occurred between the implementation of the TRIPS Agreement in 1995 and July 2008.
Inclusion/exclusion criteria, displayed in Table 11, were developed to identify manufacturing initiatives and to categorize them among the following dichotomous variables: technology transfer (license/no license), TRIPS-compliant patent (yes/no), and domestic ownership firm (state/private). Congruent with the TRIPS Agreement, this study technology transfer defined as the licensing of a patented product from its patent holder to a generic drug manufacturer. Under this definition, technology can only be supplied by the patent holder and must be received by an unaffiliated firm. TRIPS-compliance means that a country holds a patent on the respective ARV product that complies with the TRIPS Agreement’s minimum 20-year term. Additionally, domestic firms were considered to be those holding a minimum 30% of its ownership within the country. A firm was considered state-owned if at least 30% of its shares were held by its county’s government. This percentage was used as many partially state-owned firms in Sub-Saharan African have at least 30% government ownership. This percentage was also used to distinguish state-owned firms from equity-traded firms that may have government funds as shareholders.

An ARV product was identified by the generic name referring to its chemical identity. Therefore, an ARV product was in a finished dosage form (e.g., tablet, capsule) not an intermediate or active pharmaceutical ingredient (API) state. There were 17 ARV products selected for analysis: abacavir, amprenavir, atazanavir, darunavir, didanosine, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine, saquinavir, tenofovir, and zidovudine.
Table 11: Inclusion/Exclusion Criteria of Data Collection for Multi-Country Analysis

<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
</table>
| Country           | Developing and least-developed member countries of the World Trade Organization (WTO):  
  - WTO recognizes least-developed countries as those countries which have been designated by the United Nations (WTO, 2007).  
  - There are 32 least-developed country members of the WTO.  
  - There are no WTO definitions of developing country. The member countries must announce themselves as such (WTO, 2008).  
  - Developing countries are defined by the World Bank classification as countries with a low- or middle-level Gross National Income per capita of US$11,455 or less (World Bank, 2008).  
  - There are 107 member developing countries.                                                                                                                                                                                                                                                                                                                                                                                | • Non-WTO member countries.  
  • High income countries as defined by World Bank with a Gross National Income per capita greater than US$11,455 (World Bank, 2008).                                                                                                                                                                                                                                                                                          |
| Firms             | • Any state or privately owned generic manufacturer where there is a minimum 30% domestic ownership.  
  • The firm is considered state-owned if the government holds a minimum of 30% of the company. Otherwise, the firm is considered to be held privately.                                                                                                                                                                                                                                                                                                                                 | • Generic subsidiaries without at least 30% domestic ownership.  
  • Research-based pharmaceutical manufacturers and subsidiaries in developing countries.                                                                                                                                                                                                                                                                                                                                                   |
| Technology Transfer | • Voluntary licenses and strategic agreements between patent holders and developing country manufacturers.                                                                                                                                                                                                                                                                                                                                                                                   | • Any arrangement where the technology supplier is not the patent holder.                                                                                                                                                                                                                                                                                      |
| TRIPS-Compliant Patent | • An ARV patent with a minimum 20-year protection period.                                                                                                                                                                                                                                                                                                                                                                                                                               | • Patents not compliant with the minimum 20-year period.                                                                                                                                                                                                                                                                                                       |
Varying dosage forms of the same chemical identity were counted as one product. Though a firm may, for example, manufacture and market two dosage forms of stavudine (30mg and 40mg) the interest of this study was in the chemical entity manufactured, stavudine. In the same regard, a fixed-dose combination (FDC) of two or more ARVs was not considered a distinct product. For example, the combination of lamivudine+zidovudine (AZT+3TC) was not listed as a product, but its single components (lamivudine and zidovudine) were counted as two products in the analysis.

The data were utilized for descriptive statistics. Trends in the transfer of technology were examined at both the country and firm levels using data on TRIPS-compliance and firm ownership. Data were stratified to examine the trends in technology transfer for second-line protease inhibitors (PIs). PIs were classified according to the WHO Treatment Guidelines (2007a). These guidelines recommend strategic approaches for first- and second-line therapies to inform national treatment guidelines, drug regulatory authorities (DRAs) and donor partners about the selection of ARVs, their prioritization, and treatment planning. Products were ranked by WHO (2007a) priority: urgent, high, or important. These products were also categorized by whether or not they had achieved the safety and efficacy standards of WHO prequalification. The WHO Prequalification Programme publishes a list of certified products and manufacturers that meet quality and safety standards, to facilitate public procurement of drugs in developing countries that do not have stringent DRAs to assess the quality of ARVs on the market (WHO, 2004c).
Initially, the intent of this study was to perform a logistic regression analysis to measure the effect of TRIPS-compliance and firm ownership on the outcome variable, technology transfer. However, data characteristics rendered this test impractical. Separation occurred in the analysis of the two-by-two contingency table, where one cell count was zero. Separation primarily occurs in small or sparse samples with highly predictive covariates (Heinze & Schemper, 2002). Logistic regression using the maximum-likelihood method could not adequately deal with this problem.

As a result, association between the independent variables and the dependent variable, technology transfer, was determined by a two-tailed Chi Square test at the 95% confidence level. Additionally, a phi correlation was calculated to measure the degree of association between the variables. Phi correlation is used in the social sciences to measure agreement between dichotomous items (Fleiss, 1981) which also indicates the strength of the relationship (Glenberg, 1996). Phi is calculated using the equation:

\[ \phi = \left(\frac{x^2}{N}\right)^{1/2} \]

where \( x^2 \) is uncorrected Pearson Chi Square statistic, and \( N \) is the total number of observations.

In the social sciences, a phi coefficient less than .2 indicates a weak correlation, between .2 and .4 a modest or moderate correlation, and greater than .4 a strong correlation. Generally, a phi coefficient greater than .3 indicates a meaningful relationship among variables (Kroll and Bachrach, 2005).
Results

Table 12 displays the characteristics of the domestic ARV manufacturing initiatives examined in this study. Collected were 321 manufacturing initiatives in 86 firms across 25 developing countries. Of the initiatives, 294 were within 18 developing countries: Argentina, Brazil, China, Colombia, Cuba, Egypt, Ghana, India, Indonesia, Kenya, Malaysia, Mexico, Nigeria, South Africa, Thailand, Uganda, Vietnam, and Zimbabwe. The remaining 27 initiatives were within 7 LDCs: Bangladesh, Cambodia, Democratic Republic of the Congo, Ethiopia, Mozambique, Tanzania, and Zambia. The contingency tables in tables 13 through 15 summarize the manufacturing initiatives, categorized by the independent variables, domestic firm ownership and TRIPS-compliance.

Table 12: Characteristics of Manufacturing Initiatives in Multi-Country Analysis

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ARV Products</td>
<td>11</td>
</tr>
<tr>
<td>Countries</td>
<td>25</td>
</tr>
<tr>
<td>Developing countries</td>
<td>18</td>
</tr>
<tr>
<td>Least-developed countries</td>
<td>7</td>
</tr>
<tr>
<td>Manufacturing Initiatives</td>
<td>321</td>
</tr>
<tr>
<td>Least-developed countries</td>
<td>27</td>
</tr>
<tr>
<td>Second-line protease inhibitors</td>
<td>81</td>
</tr>
<tr>
<td>Domestic Manufacturers</td>
<td>86</td>
</tr>
<tr>
<td>State-owned</td>
<td>10</td>
</tr>
<tr>
<td>Private</td>
<td>76</td>
</tr>
<tr>
<td>Number of licenses</td>
<td>46</td>
</tr>
<tr>
<td>Developing countries</td>
<td>43</td>
</tr>
<tr>
<td>Least-developed countries</td>
<td>3</td>
</tr>
<tr>
<td>Number of protease inhibitor licenses</td>
<td>12</td>
</tr>
<tr>
<td>Number of protease inhibitors</td>
<td>2</td>
</tr>
<tr>
<td>Number WHO prequalified products</td>
<td>45</td>
</tr>
<tr>
<td>India</td>
<td>28</td>
</tr>
<tr>
<td>South Africa</td>
<td>6</td>
</tr>
<tr>
<td>China</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 13: ARV Manufacturing Initiatives by TRIPS Patent Compliance and Issuance of Voluntary Licenses

<table>
<thead>
<tr>
<th>TRIPS-Compliance</th>
<th>License</th>
<th>No License</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>27</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>No</td>
<td>20</td>
<td>261</td>
<td>281</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>274</td>
<td>321</td>
</tr>
</tbody>
</table>

Chi-Square (Yates) 97.38  p<.0001  
Chi-Square (Pearson) 102.15  p<.0001  
Phi Correlation (ф) .56

Table 14: ARV Manufacturing Initiatives by Domestic Firm Ownership and Issuance of Voluntary Licenses

<table>
<thead>
<tr>
<th>Firm Ownership</th>
<th>License</th>
<th>No License</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private</td>
<td>47</td>
<td>218</td>
<td>265</td>
</tr>
<tr>
<td>State</td>
<td>0</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>274</td>
<td>321</td>
</tr>
</tbody>
</table>

Chi-Square (Yates) 10.26   p=.001359  
Chi-Square (Pearson) 11.64   p=.000645  
Phi Correlation (ф) .19

Table 15: Number of ARV Manufacturing Initiatives by TRIPS Patent Compliance, Domestic Firm Ownership and Issuance of Voluntary Licenses

<table>
<thead>
<tr>
<th>Indicator</th>
<th>License</th>
<th>No License</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent+ Private</td>
<td>27</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Patent + State-Owned</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>No Patent+ Private</td>
<td>20</td>
<td>215</td>
<td>235</td>
</tr>
<tr>
<td>No Patent+ State-Owned</td>
<td>0</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>274</td>
<td>321</td>
</tr>
</tbody>
</table>
Of the 321 manufacturing initiatives, 281 (or 88%) occurred in countries that do not enforce the respective patents for the ARVs being produced. A total of 47 voluntary licenses were issued by research-based pharmaceutical firms. A larger number of licenses were granted in TRIPS-compliant countries (i.e., countries with patents on the respective ARV products), such as South Africa, than in those that were non-compliant (i.e., countries that utilized their TRIPS transition period), such as India. Study results in Table 13 illustrate that patent compliance had a strong significant correlation with ARV technology transfer ($\phi = .55$, $p < .0001$). Of the licenses granted, 57% were to firms in countries upholding ARV patents. Notably, of all 47 licenses issued, no state-owned, or partially state-owned, pharmaceutical firm was granted a license. Every license was issued to a private firm. This resulted in a weak, but significant, negative correlation between state-ownership and technology transfer ($\phi = .12$, $p < .001$). There was no meaningful correlation between the two independent variables, firm ownership and TRIPS-compliance ($\phi = .08$, $p = .19$).

Of all licenses, 77% were granted to pharmaceutical firms in South Africa and India. South Africa also held the greatest variety of ARV licenses. Of the 11 different ARVs licensed (zidovudine, lamivudine, nevirapine, efavirenz, tenofovir, atazanavir, darunavir, saquinavir, emtricitabine, didanosine, and stavudine), South Africa’s Aspen Pharmacare (Aspen) was granted a license for each product. By comparison, Indian and Kenyan firms had 4 ARV product licenses (efavirenz, tenofovir, atazanavir, and emtricitabine in India; zidovudine, lamivudine, nevirapine, and saquinavir in Kenya).
Table 16 lists the generic manufacture of second-line protease inhibitors (PIs), ranked by the WHO Treatment Guidelines and categorized by firm ownership and licensure. This table shows that 9 of the 12 PI licenses were granted by Roche for its drug saquinavir. Abbott’s WHO urgently prioritized treatment, lopinavir/ritonavir, was not licensed. The remaining two licenses were granted by Bristol Myers Squibb (BMS) for the priority PI atazanavir. All of these licenses were issued under the patent holder’s corporate social responsibility (CSR) initiatives. CSR initiatives are those “actions that appear to further some social good, beyond the interests of the firm and that which is required by law” (McWilliams & Siegel, 2001, p. 1) and are not considered commercial ventures by the patent holder.

As of September 2008, only 45 products, out of the 321 product initiatives, were prequalified by WHO. Only three countries have firms that have achieved WHO prequalification: South Africa, India, and China, which respectively acquired 38, 6, and 1 product approvals. Additionally, there are only two PIs on the WHO prequalification list, both manufactured by Indian generic firms: atazanavir manufactured by Emcure (under a license from BMS), and indinavir manufactured by Hetero (without a license and manufactured under India’s 2005 transition period).
Table 16: Second-Line Protease Inhibitors Manufactured in Developing Countries

<table>
<thead>
<tr>
<th>WHO Priority Ranking</th>
<th>Protease Inhibitor (Patent Holder)</th>
<th>Country</th>
<th>Firm</th>
<th>TT</th>
<th>Private owned Firm</th>
<th>Pre-Qual *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lopinavir (Abbott)</td>
<td>China</td>
<td>Anhui Biochem</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Northeast General Pharmaceutical Factory (NEGPF)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>India</td>
<td>Cipla</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Eastern Surgical Company</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Emcure</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hetero</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Matrix</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Strides</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thailand</td>
<td>Government Pharmaceutical Organization (GPO)</td>
<td>No (CL)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Urgent</td>
<td>Atazanavir (BMS)</td>
<td>China</td>
<td>Shanghai Desano Biopharmaceutical Co.</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>India</td>
<td>Emcure</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>South Africa</td>
<td>Aspen Pharmacare</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td>Argentina</td>
<td>Laboratorios Richmond S.A.C.I.F</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td>Brazil</td>
<td>Cristalia, productos quimicos farmaceuticos Ltda.</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colombia</td>
<td>Laboratorios Biogen</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<td></td>
<td></td>
<td>China</td>
<td>Anhui Biochem</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Shanghai Desano Biopharmaceutical Co.</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Xiamen Mchem Pharma Group</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>India</td>
<td>Aurobindo</td>
<td>No</td>
<td>Yes</td>
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<td>Cipla</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Eastern Surgical Company</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Emcure</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Strides</td>
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<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thailand</td>
<td>Government Pharmaceutical Organization (GPO)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>High</td>
<td>Saquinavir (Roche)</td>
<td>Bangladesh</td>
<td>Beximco</td>
<td>Yes</td>
<td>Yes</td>
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TT= Technology transfer, Pre-Qual= WHO prequalification CL= compulsory license
*ARV and manufacturer is prequalified by the WHO Prequalification Programme
† NFV is considered less potent than boosted protease inhibitors and it is suggested by the WHO (2007a) as an option only if higher priority protease inhibitors are not available
‡ Second generation protease inhibitors are a new class of inhibitors that have yet to be reviewed by WHO for priority ranking.

**Discussion**

*Patent Compliance*

Results of the study found a significant and positive correlation between TRIPS-compliance and technology transfer via voluntary licenses. Obtaining 57% of licenses issued, firms in TRIPS-compliant countries did attract voluntary licenses from patent holding firms. On first glance, voluntary licensing arrangements in South Africa and Kenya support this correlation. Neither of these countries utilized their full 2005 transition period, and this arguably early compliance was rewarded with technology transfer through voluntary licenses, as suggested by the TRIPS Agreement.
Yet, voluntary licenses in South Africa and Kenya also have been described as involuntary or coerced (Musungu & Oh, 2006). These licenses came by way of civil society lawsuits in South Africa and government threats of compulsory licenses in Kenya. Although Aspen in South Africa was initially able to secure a voluntary license from GSK for lamivudine and zidovudine in 2001 and from BI for nevirapine in 2002, the royalty rates (30% and 20%, respectively) were high, and the market was limited to the South African public and not-for-profit sectors. In late 2001, an excessive pricing complaint was launched against GSK and BI and presented before the South African Competition Commission by the civil society organization Treatment Action Campaign (TAC). When the Commission referred the case to the Competition Tribunal for a legally binding ruling, voluntary licensing agreements were reached between the two patent holders and a number of local firms, including Aspen. In Kenya, manufacturer Cosmos Ltd. filed an application for government use of the same first-line drugs patented by GSK and BI, under the Industrial Property Act, 2001. Under public pressure and Ministry of Health threats of compulsory licensing, GSK and BI entered voluntary licensing arrangements in 2004 with Cosmos Ltd. These events in South Africa and Kenya resulted in 12 product licenses issued by GSK (for zidovudine and lamivudine) and 3 by BI (for nevirapine) to local firms in order to supply the markets in Sub-Saharan Africa.

Given these heavily pressured voluntary licenses, the relationship between patent compliance and technology transfer is not as clear as the data suggest. The complexity of these events was not captured in the data, as these licenses were influenced by the political environment and the willingness of the Ministry of Health in Kenya and civil society groups in South Africa to use legislated provisions to increase drug access. Removing these coerced voluntary initiatives from
the analysis, however, had no impact on the statistical significance of their relationship. It is important to note, however, that many of the voluntary licenses were issued after pressure was exuded by civil society or government, making it difficult to delineate between those that were coerced and those that were completely voluntary. In South Africa, after the first voluntary licenses were issued, Aspen strategically leveraged these coerced licenses to negotiate additional ARV licenses and strengthened its relationship with the research-based pharmaceutical industry.

Comparable with TRIPS-compliant countries, non-compliant countries also had a large number of licenses, totalling 20 of the 47 licenses, illustrated in Table 13. Non-compliant countries also accounted for the majority (281 of 321) of total manufacturing initiatives (most of which occurred without a license). This is a result of the staged implementation of pharmaceutical patent compliance under the TRIPS Agreement. In many developing countries, ARVs that were patented in developed countries prior to the implementation of the TRIPS Agreement in 1995 remained without patents in developing countries.\textsuperscript{49} Also, some developing countries (such as India) and LDCs (such as Tanzania) made use of their respective TRIPS 2005 and 2016 transition periods to implement pharmaceutical patents. The transition periods allowed countries to manufacture generic ARVs without repercussion from patent holders until the transition period ended or the product patent expired.\textsuperscript{50} India made use of this transition and, without product patents until implementation of the TRIPS Agreement at the end of 2005, an expansive generic ARV industry developed. Indian firms currently supplies 80\% of the ARV market by volume (Cohen-Kohler, Forman, \& Lipkus, 2008).

\textsuperscript{49} Except for countries that were TRIPS-compliant prior to this period, such as South Africa, Kenya and Thailand.
\textsuperscript{50} This transition period is conditional on the implementation of a mailbox system for retroactive recognition of products. The mailbox stores patent applications filed between 1995 and 2005/2016. Upon TRIPS implementation, the patent application will be reviewed and, if approved, the patent term will be awarded for the remainder of the 20-year term (Engdahl, 2005).
**Firm Ownership**

The study results indicate a positive association between patent compliance and voluntary licenses. However, if TRIPS-compliance was the only variable influencing the flow of technology, then compliant countries with large state-owned pharmaceutical firms, such as Brazil and Thailand, should also experience a number of voluntary licenses. Analysis found that local state-owned enterprises did not attract licenses having a weak negative association to technology transfer ($\phi = .12, p<.001$). Furthermore, this result does not appropriately highlight the fact that no patent holder has ever issued one voluntary license to a firm that is partially or entirely state-owned. The weak correlation of the analysis may be a result of the small number of state-owned firms present in the sample, which limited the power of the analysis to identify the strength of the correlation. Its statistical significance, however, does indicate that patent compliance is not the only variable associated with the flow of technology and that government involvement in the pharmaceutical manufacturing industry could be considered a barrier to the flow of voluntary licenses.

Figure 12 conceptualizes the study results at the country-level, categorizing countries by the independent variables: TRIPS-compliance and the type of firm ownership (state or private). Private firms in countries that have TRIPS-compliant pharmaceutical patents received technology transfer through voluntary licensing, as suggested by the TRIPS Agreement and seen in South Africa. This is evidenced by patent holders’ claim that they are extremely reliant on patent protection for their industry’s success (Henry & Lexchin, 2002). State-owned firms in countries where pharmaceutical patents are similarly protected, however, did not see technology
transfer to their domestic firms. Instead, compulsory licenses were the primary means to achieve domestic production of patented ARVs.

Recently, the Brazilian state-owned firm Far Manguinhos was issued a compulsory license for the production of Merck’s efavirenz, and the Thai owned Government Pharmaceutical Organization (GPO) was granted a compulsory license for efavirenz as well as Abbott’s lopinavir/ritonavir (Kaiser Network, 2007; Steinbrook, 2007; TWN, 2007). These countries’ governments have also threatened to use compulsory licenses on the grounds of excessive pricing to reduce patent holders’ prices. With efavirenz, price reductions offered by Merck were deemed inadequate by the Brazilian and Thai governments and each state acted on its threat and issued compulsory licenses. By comparison, threats in TRIPS-compliant countries, Kenya and South Africa, resulted in voluntary licenses.

Licenses, whether voluntary or compulsory, point to the varying strategies firms used to negotiate. The research-based pharmaceutical industry claims to operate on free-market principles with limited government intervention. Scepticism about state-owned firms, bureaucratic inefficiencies, and government corruption remains (Wilson, et al., 2008a). This creates unwillingness by patent holders to collaborate with state-owned enterprises, which supports the finding that firm ownership correlates with the transfer of technology. Yet, notably, no private manufacturer in Brazil was licensed ARV patents. Whether this reflects the political ideologies in Brazil, not just firm ownership, is an important consideration that may influence domestic firm and government strategies when negotiating with patent holders.
Figure 12: Country-Level TRIPS Patent Compliance and Firm Ownership Influence on Manufacturing Initiatives
In addition, state-owned firms may not be keen to enter licensing arrangements with patent holders. Importantly, this research does not indicate whether state-owned firms were interested, or asked, to enter voluntary licensing agreements. It also does not indicate whether licenses were offered by patent holders and then declined by domestic firms. This provides an important implication to consider: some upper-middle-income countries, such as Brazil, have government laboratories with the skilled human resources to develop ARV technology unaided (Fortunak & Antunes, 2007). Currently, the Brazilian state-owned firm Far Manguinhos manufactures a number of first- and second-line ARVs without voluntary licenses and the William J. Clinton Foundation has endorsed Far Manguinhos’ technical capability. This manufacturing capacity along with the necessary legislation for compulsory licenses has leveraged Brazil’s negotiations with patent holders. For example, negotiations with Roche for its PI nelfinavir led the patent holder to offer the Brazilian government a 65% price discount (Cohen & Lybecker, 2005).

It is with this leverage that countries like Brazil and Thailand may feel that they do not benefit from the restrictions of voluntary licensing arrangements. These can include geographic market boundaries, royalties, and requirements to purchase active pharmaceutical ingredients (APIs) from the patent holder. Also, the close relationship of developing country governments with, and control over, state-owned manufacturers may result in greater public policy coordination between a country’s ministry of health and ministry of trade and industry to support local manufacturing initiatives. As such, there may be a strong willingness and incentive by government to invoke compulsory licenses and use state-owned facilities for both public health and technological development purposes. This again confirms the negative association between
firm ownership and technology transfer found in this analysis; yet, it begets the question, on which side does the aversion to licenses reside, the state or the patent holder?

The results of this analysis have a number of implications for state-owned firms. State collaboration with patent holders may not occur, because a country is able to fill its own demand for ARV treatment using TRIPS transition periods or compulsory licenses. Both Thailand and Brazil have been praised by HIV/AIDS and drug access advocates for their commitment and leadership in ensuring affordable ARV access for their citizens. Yet, like any threat, a compulsory license threat is only credible if the country is able to make use of the license (Cohen & Lybecker, 2005; Sprague & Woolman, 2006). The viability of a state-owned firm using a system of compulsory licenses requires not only manufacturing capacity, but the ability to withstand trade sanctions and political pressure from developed countries, such as the United States. Here, Brazil and Thailand are not the norm; this limits their applicability to other developing countries and LDCs.

Although Brazil and Thailand were within their rights under Article 31 of the TRIPS Agreement and the Doha Declaration to issue compulsory licenses in cases of public health interest, they faced threats of unilateral trade sanctions by the United States government. Both countries were placed on the United States Trade Representative’s (USTR) “priority watch list” in its Special Section 301 Report for patent infringement (PIJIP, 2008). This mechanism, along with bilateral and multilateral trade agreements, has been used to not only ensure implementation of the TRIPS Agreement, but also to go beyond the Agreement’s requirement into so-called TRIPS-plus

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51 United States trade law that authorizes the United States Trade Representative (USTR) to undertake an annual review of intellectual property law and practices in foreign countries, and impose sanctions on countries that have failed to revise their patent laws (Cohen-Kohler, Forman, & Lipkus 2008).
provisions. TRIPS-plus provisions press the revocation of safeguards such as compulsory licenses (Correa, 2002a,b), because patent holders and their governments maintain compulsory licenses are infringements that fail to appropriately reward innovation (Henry & Lexchin, 2002).

Many developing countries depend on the United States for trade and financial aid; therefore, the relative power of the USTR to potentially restrict market access or social assistance is feared. An extreme amount of political pressure results from being placed on the priority watch list (Love, 1999). Countries such as Brazil and Thailand are better able to withstand the pressure of these trade disputes with the United States, whereas lower-middle-income countries and LDCs are more likely to avoid these conflicts and forego drug access provisions in their domestic legislation to avoid being viewed as a trade or investment risk by developed countries.

In reality, LDCs are not likely to face similar trade sanctions due to the small value of their pharmaceutical market, the high HIV prevalence among Sub-Saharan African countries, and the fact that the USTR generally does not include LDCs in its annual reporting. Yet, given this leeway, only 27 of the total 321 manufacturing initiatives occurred in LDCs. This small proportion of manufacturing initiatives in LDCs points to the absence of sufficient manufacturing capacity as a greater barrier to local manufacturing initiatives than patent restrictions, given that none of these countries are TRIPS-compliant. LDCs rely largely on donor financing for ARV procurement and may experience pressure from donors in different, or indirect, means that limit the presence of local manufacturing initiatives. Whether intentional or not, the majority of donor financing for ARV procurement requires international accreditation. This includes WHO prequalification or approval by the United States Food and Drug
Administration (FDA). Undoubtedly, quality assurance is essential to ARV provision and access, but it can limit competition and market entrance by domestically manufactured ARVs, because no LDC manufacturers (and only three developing country manufacturers) have international quality accreditations.

**Characteristics of the Voluntary Licenses**

As illustrated in Table 13, voluntary licenses were granted by patent holders to private firms in both TRIPS-compliant and non-compliant countries. Of these licenses, 77% were granted to private firms in India and South Africa. This gives insight into the strategy of both patent holders and domestic firms, particularly during the TRIPS transition 2005/2016 periods. For example, Gilead issued 11 licenses to 11 Indian firms for the alternative first-line ARV tenofovir. As mentioned, India was able to combine its 2005 TRIPS transition period with its capability to reverse engineer ARVs in order to grow a large generic ARV industry. Since the country incorporated TRIPS-compliant legislation in April 2006, the Indian Patent Office has been slow to review the mailbox patent applications that accumulated during the transition period. While remaining TRIPS-compliant, India’s patent legislation has a more narrow scope of pharmaceutical patentability than many other developing countries. In addition, the Indian Patent Act outlines provisions for pre- and post-grant oppositions by any member of society or interested person (Ram, 2006). As a result, the status of the ARVs lopinavir/ritonavir, atazanavir, and tenofovir is at the centre of patent disputes. The 11 licenses for tenofovir could be perceived as a pre-emptive measure by Gilead to persuade patent approval by the Indian Patent Office, backed by the support of the generic firms to which the drug was licensed. In addition, these

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52 The Indian Patent Act states that patents will not be granted to new forms of known substances unless they have significant differences in efficacy.
licenses allow patent holders to retain some control over the market share. Gilead designated boundaries for export (Sub-Saharan Africa and a list of LDCs) and requires the purchase of active pharmaceutical ingredients (APIs) to formulate the product exclusively from the patent holder (Love, 2007). Recently, patents on tenofovir have been removed in countries such as the United States after patent offices determined that it was not a novel compound. This will have implications for the patent application in India as well as the viability of the voluntary licenses.

Licenses for tenofovir were welcomed by those Indian generic firms in the process of transitioning to research-based firms with the change in Indian patent status (Shadlen, 2007; Mandavilli, 2007). By securing these licenses, there is potential to build collaborative relationships with a network of patent holders to establish a generic firm within the research-based industry. Similarly, the South African manufacturer Aspen has aggressively pursued voluntary licenses and maintained a commitment to enforce IP. For example, when BMS announced immunity from lawsuit to generic manufacturers in Sub-Saharan Africa seeking to manufacture stavudine and didanosine, Aspen refused to produce the ARVs until an agreement between BMS and Aspen was reached. This position on patent compliance, along with Aspen’s well-financed operation and previous collaborations, gave the firm leverage when negotiating additional arrangements reached with Gilead, BMS, Roche, Tibotec, and Merck. Currently, Aspen has the most diverse ARV product list licensed by patent holders.

**Voluntary Licenses for Second-line PIs in LDCs**

Not only are the 47 voluntary licenses concentrated among certain developing countries (India and South Africa), but also among ARV products. The actual variety of 12 licenses for second-
line products is limited. As seen in Table 16, among second-line PIs, Abbott’s lopinavir/ritonavir, desired for its heat-table fixed-dose combination (FDC), has yet to be licensed voluntarily. Licensing arrangements, however, were granted by BMS to Aspen and Emcure for another WHO Urgent classified ARV, atazanavir. The remaining 9 of 12 licenses were for Roche’s lower priority drug, saquinavir.

Saquinavir was the only ARV licensed to firms in LDCs. These LDCs include Tanzania, Ethiopia, and Bangladesh. Since 2006, each saquinavir license has come from Roche’s Technology Transfer Initiative. The initiative is open to firms in Sub-Saharan Africa and LDCs and is designed to increase the capacity of domestic firms to manufacture Roche’s second-line ARV (Roche, 2008). Although it is a promising step for technology development in LDCs, additional ARV licenses in Sub-Saharan Africa seem unlikely. Most licenses to firms in India and South Africa are intended to cover the African market and LDCs. Even though Roche’s selection process is based on a firm’s manufacturing capacity and the country’s need for second-line ARVs, the long-term viability of LDC voluntary licenses remains in doubt, as no products were registered locally or internationally at the time of analysis. Additionally, with saquinavir’s high pill burden and lower efficacy, WHO (2007a) Treatment Guidelines suggest limited use of this drug. These results underscore the minimal ARV technology transferred and disseminated to LDCs, even with incentives provided by developed countries under Article 66.2 of the TRIPS Agreement and 30 August Decision.

Informants were cynical of LDC voluntary licenses and manufacturing initiatives. Industry does not view LDCs are viable markets or profitable places for investment and, therefore, these ARVs
are licensed through the companies’ CSR initiatives. These initiatives were suggested as mere public relations tools to improve Roche’s image and a tactic to increase the use and profile of a drug that is not urgently recommended by WHO guidelines. In these types of arrangements, patent holders may also pressure LDCs to become TRIPS-compliant early or ensure the preferred procurement of the firm’s other patented products in exchange for ARV technology. It is also unknown whether Switzerland, the home country of Roche, provided an incentive to the firm with the intent to report Roche’s technology transfer initiatives to the WTO under Article 66.2 of the TRIPS Agreement.

**International Quality Accreditation**

Finally, out of the 321 initiatives, only 43 products were WHO prequalified. Across all 25 countries analyzed, only 3 had firms that achieved WHO prequalification of their ARVs: India, South Africa, and China. Only one ARV by a Chinese manufacturer was approved.\(^{53}\) The majority of approvals resided with Indian firms (28) followed by South African firms (6). Of the second-line manufacturing initiatives, only two PIs were approval by a stringent DRA. Both of these second-line products were manufactured by Indian firms. Emcure’s ARV atazanavir (FDA approved) and Hetero’s ARV indinavir were both WHO prequalified at the time of analysis. No state-owned firm achieved WHO prequalification at the time of analysis. Although state-owned manufacturers may find WHO or FDA accreditation unnecessary, because they predominantly serve domestic markets (where DRA approval was granted locally), their facilities might not meet stringent international quality standards.

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\(^{53}\) Nevirapine by manufacturer Zhejiang Huahai Pharmaceutical Co. Ltd.
The viability of these developing country and LDC initiatives is compromised if they are unable to produce competitively priced, internationally accredited ARVs. ARV market access in these countries is often determined by donor-financed tenders that require WHO prequalification or FDA approval. Currently, the first-line ARV market is dominated by low-cost quality approved products from India. In a recent study, Nunn and colleagues (2007) highlighted quality and price challenges in Brazil. They noted that, although hailed for its AIDS treatment program and its leadership in manufacturing ARVs locally, Brazilian manufacturers could not meet the international competitive prices and quality of high-volume, low-cost generic drug firms in India. This has a number of implications for the development of ARV initiatives in developing countries, particularly where the primary objective is to increase drug affordability.

**Policy Implications**

Developing countries, especially LDCs, should be cautious in expecting implementation of the TRIPS Agreement to increase the transfer of technology. This is particularly the case for countries with state-owned firms. When conforming patent legislation to the TRIPS Agreement, governments should use their full discretion to interpret the Agreement as they see appropriate and resist pressure to implement TRIPS-plus provisions that further restrict drug access, such as removing compulsory licensing and parallel importation provisions and broadening the scope of patentability. Given the negative correlation between state-ownership and ARV licensing, countries with state-owned firms should assess their capacity to negotiate price reductions from patent holders and manufacture ARVs without a license.
Regardless of TRIPS-compliance or firm ownership, manufacturing capacity leverages governments’ negotiations with patent holders. A country with the appropriate safeguards in domestic legislation and the necessary manufacturing capacity poses a threat to patent holders. In Brazil and Thailand, firms’ manufacturing capacity and government support have reduced patent holders drug prices and, subsequently, allowed increases in treatment numbers. Yet, more often than not, these strategies cannot be emulated by developing countries and LDCs that lack manufacturing capacity and sufficient market size.

When the objective of local manufacturing is to decrease price and increase drug access, developing countries and LDCs should be cautious in pursuing local manufacturing, whether through licenses or not. The challenge with domestic manufacturing continues to be with its viability and sustainability on the international market. Even when locally manufactured ARVs reduce prices below those of patent holders, these domestic firms have difficulty competing on the international market with large-scale, low-cost Indian generic drug manufacturers. Few drugs have received the necessary WHO prequalification required by the donor-financed ARV tenders largely seen in developing countries and LDCs. This has important consequences. Firms without this quality standard cannot compete in tenders and cannot increase drug access in their countries. As such, limited conclusions can be drawn about the impact that local manufacturing has on drug access because few initiatives result in actual production or procurement. These countries should consider other strategies to ensure lower ARV prices, such as price negotiations with patent holders and generic manufacturers, pooled regional procurement for bulk discounts, or the use of the 30 August Decision to import generic drugs from low-cost export firms, such as those in India.
**Limitations**

There are a number of limitations of the study conducted in this chapter. The completeness of data remains in question. This study analyzed data on many small firms involved in the manufacture of ARVs, and it is possible that some initiatives in firms across a number of countries were omitted. Many manufacturing initiatives in developing countries remain low profile, possibly as a result of non-compliance to the TRIPS Agreement. Therefore, this omitted data likely concerns non-compliant countries manufacturing ARVs without voluntary licenses. As such, these omissions would have little impact on association between patent compliance and technology transfer. Still, this study does not claim to be comprehensive and calls for a review to be completed.

Logistic regression would have been the ideal analysis method for this study. A logistic regression model is able to determine causal relationships between variables and predict the likelihood of technology transfer occurring based on the independent variables, TRIPS-compliance and firm ownership. As no state-owned firm was granted a license, a separation problem occurred within the data and prevented the use of regression analysis. Phi correlations were, instead, calculated to measure the strength of associations between variables; however, correlation does not prove causation (Glenberg, 1996). Therefore, it cannot be stated with certainty which variable influences the other or if a third variable causes a change in both together. Also, when using phi correlations, the assumptions of normality and homogeneity can be violated if the categories are extremely uneven, as is the case of proportions close to .90, and .95 or .10, and .05. In these cases, the phi coefficient can be markedly attenuated. This may have
been the case with the variable state-ownership, as it accounted for such a small proportion of the total initiatives.

An additional limitation of this study is the scope within which the variables were defined. Under the TRIPS Agreement, technology transfer is difficult to measure, making it a challenge for WTO member countries to ensure that technology is disseminated to developing countries and LDCs (UN, 2001). This also makes it difficult to link association between the variables, particularly when they have diffuse meanings. Therefore, the definition of technology transfer used in this study is a large limitation. Here, the definition limited technology transfer suppliers to patent holders. While this definition fits the construct of the TRIPS Agreement, it does not account for the non-market mediated forms of technology transfer often prevalent in developing countries (Maskus, 2004). These include imitation through reverse engineering for generic drug copying (seen in India and Brazil and in state-state transfer initiatives between Brazil and Mozambique) as well as technology supplied with the assistance of international organizations (such as Action Medeor in Tanzania). For LDCs, technology transfer arrangements with upper-middle-income countries and international organizations are often a substantial, if not the only, means of technology flow.

**Areas for Future Research**

The nature of state-owned firms and the relationship of private firms to their countries’ governments warrant further examination. An in-depth comparison should be made of the dynamics between different ownership structures and government policies toward domestic manufacturing in addition to ownership’s influence on government-issued compulsory licenses.
Many state-owned and private pharmaceutical firms have been capitalized by public funds, in both developed and developing countries. While governments may neither have equity stakes in pharmaceutical firms nor seats on their board of directors, it would be interesting to assess how these relationships affect the strategic decisions of firms regarding generic drug manufacturing and/or licensing ARV technology.

In this study, TRIPS-compliance was defined as the provision of a 20-year patent term in domestic legislation. This study did not intend to measure the degree to which the patent was enforced, as this can vary across countries. However, varying degrees of enforcement has likely implications for the transfer of technology and should be further addressed. Enforcement is often a topic within bilateral or multilateral agreements that include TRIPS-plus provisions and it can vary depending on the measures pursued by domestic firms, patent holders as well as their home countries to ensure the patent term is respected. Thus, an interesting case study would be to compare the different means through which patents are enforced in developing countries and the impact patent enforcement strength has on the transfer of technology. This would indicate whether TRIPS-compliance alone is enough to transfer technology or whether the strength of patent enforcement is also an important determinant.

This study does not consider other important variables that may influence the flow of technology. Mentioned previously, variables such as the developing country’s policy environment and manufacturing capacity were not accounted. It was noted that appropriate legislated provisions to enable compulsory licenses or to hold firms accountable for excessive pricing, combined with government (as seen in Kenya) or civil society (as seen in South Africa)
willingness to use these provisions, undoubtedly influenced the transfer of technology. Additionally, developing countries with manufacturing capacity pose greater threats to patent holders and are in better position to negotiate price discounts or voluntary licensing terms. The relationship of these variables with technology transfer could not be captured by this study, and these elements should be explored further.

Also, the study data included any ARV manufacturing initiatives in developing countries, regardless of their current state (i.e., whether the ARV is in production, registered by the local DRA, or procured and distributed to the domestic population). Some initiatives have stalled; for example, those in Zambia, Mozambique, and Zimbabwe. Comparative research should investigate these initiatives to identify what stalled them and compare them to those initiatives that have reached some measure of success, such as international accreditation or procurement.

**Conclusion**

By analyzing ARV manufacturing initiatives across developing and LDCs, this study found that TRIPS-compliance strongly correlated with the transfer of technology as stated in the TRIPS Agreement. There was also a modest, but, statistically significant negative correlation between state-ownership of domestic drug firms and the transfer of technology. This was observed as no state-owned pharmaceutical firm was licensed an ARV by a patent holder. Additionally, the majority of initiatives were in two countries, South Africa and India, with only 27 of 321 manufacturing initiatives in LDCs. Developing countries, especially LDCs, must be cautious in conforming parent legislation to the TRIPS Agreement, with the expectation of an increased flow of technology transfer. This is particularly the case for those with state-owned firms. These
countries should ensure that they enact appropriate measures to increase drug access, such as parallel importing or compulsory licensing, when faced with public health crises, such as HIV/AIDS and the high price of patented ARVs.

Countries must also be cautious in the using local manufacturing initiatives to secure greater access to low-cost generic ARVs. As shown by the example of Brazil, it is difficult for developing countries to compete on the international market with generics from large-scale manufacturers in India. Similarly, no LDC initiative has achieved international quality accreditation, which limits market access both domestically and internationally. Developing country manufacturers should assess their ability to compete on price with large-scale generic manufacturers prior to undertaking an initiative of this type.

Finally, the varying definitions of technology transfer is important to consider as a variety of transfer modes are not captured by the TRIPS Agreement, but are nonetheless crucial to the technological development and health of developing countries, such as state-state initiatives and assistance from development aid and international organizations. These manufacturing initiatives need to be assessed and compared to understand the most effective means of ensuring a sustainable transfer of technical knowledge for essential medicines to developing countries and LDCs.
Summary and Introduction to Chapter 5

Chapter 4 addressed the key conditions that emerged from case studies in Tanzania (Chapter 2) and South Africa (Chapter 3) that answer the macro-level research question: What domestic conditions influence the transfer of ARV technology to developing countries? Two of these factors were TRIPS-compliance to patent standards and domestic firm ownership type (private or state). To generalize these findings more readily to other developing countries, these binomial variables were tested with data across 25 developing countries and their respective ARV manufacturing initiatives. The results of the multi-country analysis confirmed a statistically significant, positive relationship between patent compliance and the issuance of a voluntary license, as well as a negative association between state-ownership and voluntary licenses.

Chapter 5 integrates the results of the cases studies and the multi-country analysis to discuss their implications for the larger theoretical question highlighted in Article 7 of the TRIPS Agreement: Does the enforcement and protection of intellectual property (IP) lead to an increase in the transfer of technology to developing countries? Then, using the case study results in Tanzania and South Africa, the chapter addresses the second question: Are Sub-Saharan African countries able to increase affordable treatment access through local generic manufacturing initiatives? Finally, implications of the research findings are considered for both research questions, as they pertain to other developing countries facing similar drug access problems.
Chapter 5: Linking the Research Findings

Introduction: Filling the Gap

Filling a noted gap in the literature, this dissertation builds on the dearth of research in the field of technology transfer for essential medicines under the TRIPS Agreement, as well as the local production of ARVs to increase drug access. This research area is often dominated by economic theory and quantitative modeling. Additionally, Sub-Saharan Africa is often overlooked in favour of upper-middle-income countries, such as Brazil, India and China. Interdisciplinary and in-depth case studies on diverging forms of technology transfer arrangements in Tanzania and South Africa provide a unique contribution to understand the relationship between intellectual property (IP) compliance and the transfer of technology.

Interest in drug manufacturing in developing countries, once a focus in the 1970s and 1980s, has returned to the forefront with the rise in HIV prevalence and the implementation of the TRIPS Agreement. Again, with little empirical research to provide thick descriptions of drug manufacturing initiatives, particularly in Sub-Saharan Africa, these case studies re-conceptualized the “make-or-buy” debate. Case studies in Tanzania and South Africa capture the global system of ARV provision dominated by donor financing, WHO prequalification, and the economies of scale of international generic drug firms. They also provide developing countries and least-developed countries (LDCs) a framework (Figure 7) to use when considering the transfer of technology and local production of affordable ARVs.
Finally, the multi-country analysis in Chapter 4 is the first attempt to generate a database of current ARV manufacturing initiatives throughout the developing world. The analysis of this database is the first known quantification of current trends in voluntary licensing of first- and second-line ARVs and its association with TRIPS-compliant patents. Although the general relationship between IP and voluntary licensing has been studied elsewhere, this research identified a new variable that negatively influenced licensing: state-ownership. In doing so, this analysis now provides a broader lens through which to view theoretical issues surrounding IP and the transfer of technology.

This chapter links research findings from the two case studies of technology transfer arrangements and domestic ARV production in Tanzania (Chapter 2) and South Africa (Chapter 3), and the analysis of ARV manufacturing initiatives across 25 developing countries (Chapter 4). These important findings and their implications for developing countries are framed by the two theoretical questions reviewed in the literature. First, does the enforcement and protection of IP lead to an increase in the transfer of technology? Second, does the local manufacture of ARVs increase drug affordability? The chapter concludes with an analysis of the limitations of this study, followed by recommendations for future research.

**TRIPS and the Transfer of Technology**

*Research Contribution: Does IP Increase the Transfer of Technology?*

As highlighted in literature review in Chapter 1, researchers are divided on the protection of IP and its influence on the transfer of technology, where Article 7 of the TRIPS Agreement notes
that IP protection should lead to the transfer and dissemination of technology. The results of the case studies in Tanzania and South Africa as well as the multi-country analysis, found that patent compliance does positively influence the transfer of technology (as defined in this research) to developing countries, as suggested by the TRIPS Agreement and the supporting literature (Maskus, 2000; Rozek, 2000; Yang & Maskus, 2001). However, the results also found that a country’s patent compliance was not the only factor influencing technology flow. In South Africa, some of Aspen’s voluntary licenses were essentially coerced by civil society. In addition, the type of domestic firm ownership, whether state-owned or private, and its financing also affected the development of the technology transfer arrangements: an imitation arrangement in Tanzania and voluntary licenses in South Africa. These two arrangements are assessed comparatively here followed by a discussion of their implications.

Tanzania, an LDC, is exercising its TRIPS transition period until 2016 under the TRIPS Agreement to amend its patent legislation. While the country does have a patent system in place, based on the Patent Act of 1987, the 10-year patent term is half of that required by the TRIPS Agreement. For ARVs that were patented, their terms have already expired. As a result, Tanzania Pharmaceutical Industries (TPI) faces no patent constraints to manufacture ARVs; however, finding a supplier to transfer technology is more complicated. Possibly as a result of its 2016 transition period, the country and its initiatives have slipped under the radar, not only internationally, but nationally as well. Non-compliant to the TRIPS Agreement’s patent protection period, there is little incentive to attract patent holders to transfer technology through voluntary licenses. Tanzania’s IP status, however, does attract a supplier that views non-compliance as a comparative advantage, the non-government organization (NGO) Action
Mederor, who formed an imitation arrangement with TPI with financing from the European Commission.

By comparison, South Africa’s ability to manufacture ARVs locally has come at much greater political and economic costs than in Tanzania. South Africa has faced mounting pressure since the TRIPS Agreement was signed in 1994 to ensure its patent compliance. Even though it was TRIPS-compliant from the Agreement’s inception, tensions grew between the South African government and the research-based industry, which was supported by the United States. A dispute over the scope of South Africa’s TRIPS flexibilities under the Medical and Related Substances Act was brought before the Pretoria High Court in 1998. Section 15c of the Act authorizes the South African government to use parallel importation and override exclusive patent rights in cases where drug access within the country is constrained. Charged with violating the TRIPS Agreement by 39 multinational pharmaceutical patent holders (lead by South Africa’s Pharmaceutical Manufacturers Association [PMA] and the Pharmaceutical Researchers and Manufacturers of America [PhRMA]), this court case was highly politicized both domestically and internationally.

The Pretoria High Court case became the tipping point for many patent holders as they faced sharp criticism from AIDS advocates, civil society, international organizations, and the media. The case also highlighted very publicly the unwillingness of the AIDS denialist Mbeki Administration to use any of the provisions outlined in Section 15c or within the Patents Act to issue compulsory licences for the local production or importation of generic ARVs. It was through this case that domestic manufacturer Aspen Pharmacare (Aspen) approached
GlaxoSmithKline (GSK), and the first voluntary licensing terms were agreed to for GSK’s drugs lamivudine and zidovudine, their combination, lamivudine+zidovudine (AZT+3TC), and subsequently with Boehringer Ingelheim (BI) for nevirapine.

The legal wrangling was not over for South Africa with the issuance of voluntary licenses. With the terms of GSK’s licensing agreement stipulating a 30% net of sales royalty as well as restrictions to the public and not-for-profit markets in South Africa, the court was involved again. This time civil society, led by Treatment Action Campaign (TAC), charged the patent holders, BI and GSK, with excessive pricing of their ARVs, prohibited under the Competition Act of 1988. Afraid of further negative media attention, as well as having to reveal their pricing strategy in court, both GSK and BI issued voluntary licenses to a number of manufacturers, including Aspen, to cover public and private markets across Sub-Saharan Africa.

The domestic drug firms in Tanzania and South Africa that entered the ARV industry were markedly different. Along with their country’s patent compliance to the TRIPS Agreement, firm ownership and financing influenced the type of technology transfer arrangement these firms entered. In South Africa, Aspen is a well-financed company traded on the Johannesburg Securities Exchange (JSE) that, in 2001 (at the time of the initial licenses), was backed by large private banks. With this financing, Aspen accessed the necessary capital to build and expand its manufacturing base. This included an oral solid dosage (OSD) facility dedicated to ARV production that was accredited by a variety of drug regulatory authorities (DRAs), such as the United States Food and Drug Administration (FDA) and WHO. Aspen’s financing also enabled the purchase IP for various drugs, signalling to patent holders its commitment and interest in enforcing IP. As a result of these investments and Aspen’s distant relationship with the South
Africa government (which at the time had a strained relationship with the research-based industry), the firm leveraged its base to acquire voluntary licenses with patent holders and build capacity through ventures with Indian generic drug firms. This ultimately led Aspen to secure the largest number of ARV licenses by any firm globally.

By contrast, Tanzania’s second-largest drug manufacturer, Tanzania Pharmaceutical Industries (TPI), a partially state-owned firm, had limited access to financial capital. This was, in part, a result of a lack of coherent strategy by government, which held 40% shareholdings in the company, to support local manufacturing, as well as the country’s limited access to private investment, either from banks, venture capitalists, or security exchanges. TPI’s poor financial access was compounded by the negative perception state-owned enterprises maintains within many multinational drug firms (whether research-based or generic). Informants noted that state-owned drug firms are often inefficient, bureaucratic, and lack transparency. This partial state ownership, along with poor financing and limited manufacturing capacity, dissuaded private investors. As a result, international NGOs and development agencies were the only institutions that perceived investment in TPI positively. Action Medeor and the European Commission viewed ARV manufacturing at TPI as a capacity building and development opportunity, filling an important need among LDCs. This viewpoint resulted in a US$6 million European Commission grant, sponsored by Action Medeor, to build a WHO prequalified ARV manufacturing facility and develop ARV production capacity.

As a result of the Tanzanian and South African case study findings, a large-\( n \) comparative analysis was performed across 25 developing countries. This analysis tested the correlation
between two independent variables, the countries’ patent compliance to the TRIPS Agreement and their domestic firms’ ownership (state or private), and a dependent variable, technology transfer (defined as voluntary licenses from patent holders). The multi-country analysis supported the results of the case studies and found that patent compliance positively, and state ownership negatively, influenced the technology transfer via voluntary licenses.

Within the disparate cases in South Africa and Tanzania, there was one distinct similarity that impacted the development of their technology transfer arrangements. Important to each was the role of civil society organizations. These organizations, Action Medeor in Tanzania and TAC in South Africa, were crucial to facilitate the use of different provisions within the TRIPS Agreement and domestic legislation. The lack of a coherent strategy by the Tanzanian government or incentives to invest in its own manufacturing facility, and the country’s poor financial climate, led TPI to search for assistance internationally. In place of large government or multinational pharmaceutical industry investment, Action Medeor was the key actor to assist TPI in accessing financial support from the European Commission. Action Medeor simultaneously acted as the technology supplier to build capacity, both physically and technically within the firm. In South Africa, civil society involvement was crucial as strong leadership and policy coherence waned within the Mbeki Administration. Civil society was able to use the judicial branch of government to oppose both government and patent holder policies. This civil society movement, backed by international media attention, played a prominent role in the development of voluntary licensing arrangements in South Africa.
Implications of Research Findings

As mentioned, case studies in Tanzania and South Africa, as well as the multi-country analysis across 25 developing countries, found that patent compliance to the TRIPS Agreement does influence the transfer of technology via voluntary licensing arrangements, as suggested under Article 7 of the Agreement. However, this research also concluded that patent compliance was not the sole condition influencing the flow of technology, and that domestic firm ownership (whether state or private) was also a significant factor influencing the type of technology transfer arrangements entered by firms in Tanzania and South Africa. As a result, these findings uncovered a number of important factors that have notable implications for the transfer of ARV technology to both developing countries and LDCs. A number of implications were previously addressed in each chapter, such as industry perceptions of state-ownership (Chapters 2 and 4), the opportunities and constraints of voluntary licensing strategies (Chapter 3), and the perils of corporate social responsibility initiatives (Chapter 4).

As indicated by the TRIPS Agreement and a body of researchers presented in the Literature Review, the findings of this dissertation suggest that the protection of patents influences the type of technology transfer arrangement entered by firms in developing countries. However, it also demonstrates that patent compliance is a necessary, but insufficient condition for the transfer of technology. State-ownership of domestic firms is also an influencing factor. Although the negative association between state ownership and ARV licensing may not be surprising, it does bring some of the most interesting implications. This is because the causation of the relationship between state ownership and technology transfer is not entirely clear.
As noted in the discussion of the multi-country analysis in Chapter 4, the difficulty these institutions (patent holders and state-owned firms) have collaborating with one another makes their relationship important to address. This study was not able to determine from which side unwillingness to enter voluntary licenses derived: that of patent holders or that of state-owned firms and their governments. Poor collaboration may be the result of ideological differences about the role of IP in public health and how much governments should intervene in the pharmaceutical industry. Even though the research-based industry has no direct government involvement in developed countries, they do tend to have very close ties with their home country government. PhRMA is an extremely powerful lobby group within the United States, and many policies are in place to foster the industry’s growth: IP protection, subsidies, tax incentives, and drug development grants, as seen in the Patent Act, Orphan Drug Act, Bayh-Dole Act, and others.

Also, discussed in Chapter 4, the dynamics of the relationship between governments and its pharmaceutical industry raise questions about the influence governments have on industry action, in terms of licensing and use of TRIPS flexibilities. Given the state-ownership of some domestic firms in developing countries and the close ties of patent holders with their governments in developed countries, issues over collaboration may run into the broader political regimes of the respective countries and their bilateral relations. For example, the disparate political ideologies of the neoconservative Bush Administration in the United States and Thailand’s military regime in 2007 may have affected the poor interaction of patent holders, Merck & Co. and Abbott Laboratories, with the Thai Government Pharmaceutical Organization at the time Thailand issued its compulsory licenses for the ARVs efavirenz and lopinavir/ritonavir. The obstacles to
collaboration are important to understand in order to determine appropriate policy responses and strategies to ensure long-term ARV affordability in developing countries in spite of political relations.

Importantly, the research findings also indicate that, even though patent compliance was positively associated with voluntary licensing, many of these licenses may not have been issued readily, as the case of South Africa points. The political environment, including pressure by civil society in South Africa, threats of compulsory licenses in Kenya, and patent reviews in India, have influenced patent holders to issue some of these licenses. In addition, the majority of licenses have been issued to firms in only two countries: South Africa and India. Of the total number of manufacturing initiatives, few achieved WHO prequalification by December 2008. Again, only firms in South Africa, India, and one firm for one ARV in China have received this WHO accreditation. This reinforces questions in the literature about domestic manufacturers’ capacity to produce low-cost and quality assured ARVs.

Finally, out of the 321 ARV manufacturing initiatives found in the multi-country analysis, only 27 initiatives were in LDCs. Only three LDC firms, one in Tanzania, Ethiopia and Bangladesh were issued voluntary licenses under corporate social responsibility programs by Hofmann-La Roche. This stresses the poor use of Article 66.2 and the 30 August Decision of the General Council under the TRIPS Agreement, which call on developed countries to provide incentives to the pharmaceutical industry to supply technology to build manufacturing bases in LDCs. The study results also reaffirm the concern outlined in Paragraph 6 of the Doha Declaration about the
capacity of developing countries and LDCs to manufacture their own ARVs during public health crises.

Also discussed earlier in this chapter, both case studies clearly point to the important role international NGOs and civil society organizations played in facilitating the transfer of technology. This was particularly the case in South Africa, where poor leadership from and policy coherence within the Mbeki Administration forced civil society, through TAC, to fight for the right to affordable treatment through the country’s judicial system. Engagement by civil society organizations in drug access issues has important implications for both developing countries and LDCs. Within developing countries, strong grassroots civil society movements should use their political power to shift government policy, through lobbying and legislative measures, if the appropriate framework is in place. In LDCs, where grassroots civil society movements may not be organized or powerful, international organizations have been able to assist with human resource training, the diffusion of new technology, and build capacity within the country.

Kirton and Cooper (2009) highlight the important implications of civil society movements. They suggest that civil society and media in developing countries provide a level of capacity that government cannot fulfil. They emphasize that states are no longer the dominant actors in health governance and call on all actors, including grassroots organizations, NGOs, private firms, multinational actors, and international institutions, to shape governance at the global level. Therefore, to effectively manage health crises, Dal, Sunderland and Drager (2009) argue that policy convergence, through health diplomacy, must be achieved at the domestic and global
level, between health and trade policies. Competing actors must reconcile their differences to avoid global health risks, particularly those that might result from the international trade agreements, such as the TRIPS Agreement.

Furthermore, developing countries and LDCs should assess their perceptions of what constitutes technology transfer and whether their perceptions are in line with those of patent holders. Depending on the perspectives of each WTO member country, technology may or may not be best transferred through a license. Similar to their fight within WTO to use compulsory licensing to meet public health needs resulting in the Doha Declaration and 30 August Decision, developing counties should push for concrete measures of technology transfer to their countries. These measures should be based on identifiable outcomes that LDCs find most appropriate for their situations.

Moreover, developed countries should be held accountable for their efforts to incentivize the pharmaceutical industry to transfer technology to LDCs under Article 66.2 of the TRIPS Agreement as well as the 30 August Decision. Though developed countries must submit reports every 3 years to WTO on their technology transfer activities, it is not clear how these reports are assessed or whether there are any consequences for inadequate country efforts. There are also no requirements under WTO to ensure that the technology transfer initiatives that do take place in LDCs are long-term, sustainable, and use technologies suitable for the conditions in each respective country.
Similarly, there is no assurance that donor financing for specific development projects will actually cover the cost of meeting the proposed outcomes or that the bulk of financing will remain within LDCs. These challenges were evident in the European Commission’s US$6 million grant provided to Action Medeor to assist TPI with the construction of a WHO accredited ARV plant. Questions often surround how much funding is channelled back to donor countries by outsourcing foreign contractors and consultants to implement these projects.

By other accounts in Uganda and South Africa (discussed in Chapters 2 and 3), a US$6 million budget seems small for what is required of an internationally accredited ARV manufacturing facility. Even if the plant is completed, this budget does not cover the costs associated with WHO prequalification of the ARVs. This is not only a timely, expensive procedure that requires skilled human resources, but it is essential for donor procurement, which makes WHO prequalification critical to the success of the ARV manufacturing initiative. Whether the European Union intends to report this grant as a project to WTO under Article 66.2 of the TRIPS Agreement is unclear. Nevertheless, the Tanzanian ARV manufacturing initiative highlights the limitation of short-term donor grants to transfer technology effectively and complete projects’ intended outcomes.

The challenge of attracting technology transfer has implications for LDCs with limited resources and those developing countries with state-owned firms. Developing country and LDC governments should be particularly cautious when revising patent legislation to conform to TRIPS standards. Early TRIPS compliance should not be sought in the hopes that an increased transfer of pharmaceutical technology from patent holders will result. Both developing countries
and LDCs should ensure that appropriate provisions are in place to allow flexible use of their patent legislation, including narrowing the scope of patentability, using parallel importation, and issuing of compulsory licenses (whether for domestic production or importation by a third-party).

**TRIPS, ARV Manufacturing and ARV Affordability**

**Research Contribution: Does Domestic Production Increase ARV Affordability?**

Case studies in Tanzania and South Africa indicate that domestic production of ARVs cannot reduce prices substantially beyond those imported from large-scale generic firms, such as those found in India. In Tanzania, Tanzania Pharmaceutical Industries (TPI) was unable to meet the quality assurance standards required of donor-financed tenders in order to gain market access. In addition, TPI’s minimal production capacity and inability to manufacture active pharmaceutical ingredients (APIs) made economies of scale impossible and, thereby, price ARV reduction difficult. In South Africa, Aspen has met international quality standards for a number of ARVs and, with its production capacity, can reduce ARV prices from patent holders. However, restricted competition in the South African market (as a result of patent compliance) keeps Aspen’s ARV prices higher than those found in neighbouring countries whose products derive, predominantly, from generic Indian manufacturers.

The cases in Tanzania and South Africa addressed two important issues when discussing the ability of local manufacturing initiatives to produce affordable ARVs. The first issue is the capacity of firms to manufacture its own APIs or gain significant market share to reduce price and compete with international high-volume, low-cost generic drug firms, such those in India. The second issue is the ability of firms to achieve international quality standards (such as WHO
prequalification and FDA approval) to meet both domestic and international tender requirements necessary of lucrative donor-financed tenders. These two issues, and their implications, were explored in an article commission by the journal *Eurohealth* and reprinted here with permission (Wilson, et al., 2008b). Generally, as indicated in the literature (Bennett, Quick, & Velásquez, 1997; Kaplan, et al., 2003; Kaplan & Laing, 2005), domestic drug production initiatives in Sub-Saharan African countries, such as Tanzania, are difficult to implement and sustain.

Manufacturing is not the only means to achieve more affordable ARVs, nor is it the only issue when considering ARV access. Both case studies noted scarce human resources, not only to assist with the development of the pharmaceutical industry’s manufacturing and innovative capacity, but to care for patients. Availability of health personnel, such as physicians, nurses, and pharmacists, is crucial to ensure that affordable drugs are received and administered properly by those in need. These access issues need to be considered further in conjunction with affordability initiatives, to ensure a comprehensive approach to drug access.

*The Price is Right: Promoting local production for ARVs in Sub-Saharan Africa*
By Kinsley Wilson, Jillian Clare Cohen-Kohler, and Alan Whiteside

To increase access to antiretroviral drugs (ARVs) for treating AIDS in the developing world, donor countries and multilateral agencies have developed a variety of initiatives. In 2008, the European Commission and European countries provided over 60% (or US$1.89 billion) of the Global Fund to Fight HIV/AIDS, Malaria and Tuberculosis budget. With these sustained pledges, Global Fund supported programmes project to treat 1.8 million HIV-infected patients over a five year period (Global Fund, 2008). To equitably access this treatment, the World Health Organisation (WHO) emphasizes a drug’s rational selection and use, sustainable
financing, affordable pricing, while also maintaining reliable health and supply systems (WHO, 2004b). For ARV treatment, a notable challenge has been affordability. This is why the promotion of local production has the potential to address the critical issue of ensuring sustainable ARV supply.

One of the barriers to ARV price in high prevalence HIV/AIDS countries is the World Trade Organisation’s Agreement on the Trade Related Aspects of Intellectual Property (TRIPS). In exchange for international trade liberalisation, TRIPS requires 20 years of pharmaceutical patent protection. This provides a market monopoly for patent holding drug companies and enables them to set their prices freely. ARV prices are often out of reach for developing and least-developed countries. In 2000, when few generic drugs were available, the lowest price triple combination ARV treatment was US$10,439 (MSF, 2007).

Since TRIPS took effect in 1995, international organisations, such as Médecins Sans Frontières (MSF), have encouraged developing and least-developed countries to exercise flexibilities in the agreement and subsequent Doha Declaration in order to increase ARV access. Compulsory licensing authorises government use of a patent under public health crises or national emergency. A transition period allows developing and least-developed countries until 2006 and 2016, respectively, to implement pharmaceutical patents in domestic legislation. Both enable the domestic manufacture of generic ARVs.

Brazil and Thailand have been noteworthy in their efforts to reduce the prices of patent holding drug firms. In both countries, compulsory licensing threats initiated significant price negotiations
with multinationals. This, along with generic production of ARVs that were not patented domestically prior to TRIPS, facilitated a more affordable treatment scale-up. India also made use of the TRIPS Agreement’s 2006 developing country transition period. By waiting to enforce product patents in its domestic legislation, India fostered and expanded its generic drug industry. Following these initiatives, a number of Sub-Saharan African countries with substantial populations of infected people (South Africa, Zimbabwe, Zambia, Tanzania, Uganda, Kenya, and Ethiopia) are reported to be trying to manufacture ARVs domestically.

Generic production is able to lower the cost of drugs, since it does not have to carry the large research and development (R&D) costs of the drug discovery process. Within the WHO framework, local manufacture is assumed to predominantly impact the affordability of drugs. This in turn improves the cost-effectiveness of ARV therapy; frees resources to increase treatment numbers; and strengthens other access components. The link between domestic production and access, however, relies on two conditions:

- that these medicines can be manufactured more cheaply than they can be imported; and
- they will meet WHO prequalification standards required for donor financing.

Donors have become involved in local production capacity-building. The development of local capacity has been assisted by the European Commission, which in 2003 established a health line grant for domestic drug manufacturing. The priority area specifically includes “technology transfer, leading to local production of affordable key pharmaceuticals and commodities in prevention, treatment and care of HIV/AIDS, malaria and tuberculosis” and offered to finance proposals of up to €5 million. At present, we are aware of only one example of this grant
accessed for ARV production. In November 2006, a German non-government organization, Action Medeor, partnered with a Tanzanian manufacturer, Tanzania Pharmaceutical Industries, was successfully awarded this budget for the construction of a new ARV plant.

Arising from these efforts, the question is: can local ARV production increase treatment access cost-effectively? The European Commission grant may suggest that domestic production should deliver more affordable treatment, but as we show this may not be the case, as the perennial debate of whether it is financially more attractive to “make” or “buy” still seems to rest on the latter. This article will discuss the ability of Sub-Saharan African countries to produce first-line ARV products at a competitive price and quality while considering some emerging issues concerning the production of second-line therapies.

**Competitive Pricing**

With efforts from AIDS advocates and international organisations, such as the William J. Clinton Foundation and MSF, India’s generic firms paved the way for dramatic ARV price reduction and now act as the major suppliers for developing countries. This occurred concurrently with the development of domestic manufacture in Brazil and Thailand, while, in South Africa, the excessive pricing complaint brought before the Competition Commission led to the first voluntary ARV licenses under reasonable royalty terms in a developing country.

Since 2000, first-line therapy prices have plummeted from over US$10,000 (€6,700) per patient per year for patented products to under $100 (€67) per patient per year for the leading triple therapy lamivudine, stavudine, and nevirapine (3TC+d4T+NVP) (MSF, 2007). This price
reduction coupled with increases in multilateral and bilateral aid enabled WHO’s “3 by 5” Initiative to scale-up treatment numbers significantly. At the end of 2006, an estimated 1.3 million people in Sub-Saharan Africa were receiving ARVs, equalling 28% coverage, up from 100,000 individuals or 2% coverage at the launch of the 2003 initiative (UNAIDS, 2007).

While there is no doubt that generic competition stimulates the reduction of drug prices and increases affordability, the debate over domestic manufacturing in developing countries remains polarised. Advocates argue domestic production increases access to essential medicines; strengthens long-term health security, self-sufficiency, employment; and saves foreign exchange (African Union, 2007). However, research contends that a local manufacturing industry is often not a viable alternative for developing countries and does not necessarily reduce prices over imported drugs (Kaplan & Laing, 2005).

The South African National Economic Development and Labour Council found that 80% of a manufacturer’s profits on a generic drug will be captured within eighteen months of the originator drug coming off patent (Maloney and Myburgh, 2007). Therefore, unless a generic manufacturer is one of the first to enter, the ARV market essentially becomes commodity-based and price is the distinguishing factor among products. WHO recommends, and donors require, international competitive tenders to ensure the lowest cost ARVs are procured. Here, razor-thin margins and large volumes are required to remain competitive. The WHO promotes the “rule-of-five” which states that five bids on a tender engage enough competition to ensure the lowest generic price (WHO, 1999). Competition facilitates greater affordability by pushing prices down
to marginal costs, but it is difficult for new manufacturers to match the price of longstanding firms.

Currently, six generic manufacturers produce a leading WHO prequalified treatment regime 3TC+d4T+NVP. The most sophisticated generic drug industry in Sub-Saharan Africa is in South Africa. The country’s leading ARV manufacturer, Aspen Pharmacare, currently produces its regime at a quoted price of US$158 (€106) per person per year (JCFMS, 2008). A least-developing country manufacturer has yet to announce a price publicly. Comparatively, the listed median transaction price in 2007 was US$92 (€61) and US$91 (€62) per patient per year in low-income and middle-income countries, respectively (WHO, 2008b). Even though tendered prices often differ from the estimated and listed prices, the disparity between Aspen’s treatment cost and the median price is noteworthy.

Therefore, within the access framework, the question facing Sub-Saharan African countries is whether they can make ARVs inexpensively and justify their manufacture over their import. They have limited resources and manufacturers lack vertical integration which limits their capacity and keeps production costs high. The skilled labour necessary to develop and formulate ARVs is sparse in Sub-Saharan Africa compared with industrialised countries (where drug discovery most commonly occurs) and the emerging economies of India and China (where generic industry flourishes). As an example, researchers employed in R&D per million population amount to an average of 2,538 individuals across EU member countries, 708 individuals in China, 119 in India, 307 in South Africa, and less than 51 in any other reporting Sub-Saharan African country (UNDP, 2008). Therefore, the sheer size of China and India’s skilled human resource population magnifies the industry’s development potential and reduces
labour costs compared with Sub-Saharan African countries with the possible exception of South Africa.

Most crucial to ARV production is the level of manufacturing capacity. The capacity to synthesise or extract active pharmaceutical ingredients (APIs) needed to formulate ARVs is the key to drug costs: APIs are volume dependent and comprise 55 to 99% of the manufacturers’ cost (Pinheiro, et al., 2006). Without the technology to manufacture APIs, they must be imported from producing countries, such as India and China. As a result, the fight for market share is fierce as large and vertically integrated API producing generic firms are positioned with lower costs and greater economies of scale. In order to compete, a Sub-Saharan African manufacturer needs to be assured an expanded national and/or regional market to generate the larger volumes necessary to reduce the contracted price of APIs. This is difficult in the public tender system where quantities are generally determined once the tender is awarded, but pricing is required upfront.

Quality Matters

By the end of 2007, programmes supported by the Global Fund reported that 1.1 million individuals in Sub-Saharan Africa were receiving treatment (UNAIDS, 2007). These and other donors, especially European governments, the United States President’s Emergency Plan for AIDS Relief, and development agencies, play a critical role in ARV market entry as they largely finance procurement in Sub-Saharan Africa. With donor financing, ARVs must meet a minimum quality threshold in international competitive tenders: WHO prequalification.
The WHO prequalification programme was introduced in 2001 to assist developing countries without stringent drug regulatory authorities (DRAs) to assess the quality of ARVs on the international market. The programme publishes a list of certified products and manufacturers that meet quality and safety standards to facilitate the public procurement process. Tenders financed with donor aid limit eligibility to WHO prequalified manufacturers and products. In Africa, only Aspen Pharmacare has achieved WHO prequalification for a triple therapy regime.

Donors and developing countries alike appreciate WHO prequalification as it streamlines regulation and quality assurance where there are limited resources to assess ARVs independently. However, it has come under some scrutiny. DRAs striving to achieve national recognition for their capacity suggest that their ability and authority to evaluate product and manufacturer standards is undermined by the programme. For manufacturers, achieving WHO prequalification is a rigorous process requiring a large upfront investment and strong technical and development resources that are often lacking in Sub-Saharan Africa. The costs associated with the completion and submission of a product dossier can be over US$200,000 (€134,000) and the review process can last up to 24 months. These upfront costs are difficult for a small local manufacturer to bear. As the eligibility criterion disqualifies local manufacturers from donor-financed tenders, these products are unable to compete in most public tenders.

Without meeting WHO prequalification requirements, local industry can only compete in tenders supported by domestic financing where unless specified by the tender board, only local DRA approval is required. This occurs, for example, within the Ministries of Health of countries like Brazil and Thailand where government financing procures ARVs from their state-owned
enterprises. However, it is a challenge to convince Sub-Saharan African country governments who have much larger populations on ARVs and who rely heavily on donor aid to finance their own ARV procurement programmes entirely. This is particularly the case if there are questions of ARV price and quality.

The Next Generation

Currently, a significant number of first-line generics are on the market. Eleven WHO prequalified generic manufacturers produce a range of first-line ARV products. The issue of affordable supply; therefore, is now being directed toward second-line regimes. These ARV regimes are crucial for HIV/AIDS patients who have failed or are resistant to first-line therapy. As with first-line ARVs, there is opportunity for generic competition to reduce prices and increase affordability. Second-line regimes, however, change many of the ARV market characteristics as there is a smaller market size, higher development costs, and less competition than their first-line counterparts.

Currently, around 4% of adults and 1% of children are on second-line treatment in low- and middle-income countries or approximately 180,000 individuals in 2008. With such small demand a large generic market does not yet exist for second-line treatments. As ARV resistance is estimated at a rate of 3% a year (WHO, 2007a), alternative first- and second-line regimes will become a larger portion of ARV procurement. Important to the second-line regime is a newer class of drugs, protease inhibitors, of which many are protected under patents (patents are currently pending in India for WHO’s priority recommended lopinavir/ritonavir and atazanavir). As a result, these ARVs are procured primarily by patent holding pharmaceutical firms and can
be priced 10 to 20 times greater than first-line ARVs. Prices for the few generic second-line
drugs available are also quite variable. Research found generic prices for second-line regimes
were often greater than those of patented products with median prices ranging from US$948 to
US$4,245 (€635 to €2844) against US$865 to US$2,577 (€580 to €1727), respectively (Waning,
2007). As these prices consume a substantial proportion of donor and government budgets,
advocates call for these prices to be reduced further.

This is difficult with few second-line generics currently on the market. A few patent holding
drug firms have contracted non-exclusive licenses for second-line ARVs to Indian and South
African manufacturers (such as Bristol Myers Squibb’s atazanavir to Emcure Pharmaceuticals
and Aspen Pharmacare). Efforts are also underway in Thailand to import as well as produce
generic versions of Abbott’s lopinavir/ritonavir and Merck & Co.’s alternative first-line ARV
efavirenz under compulsory licenses issued in 2007 and 2006, respectively. However, both the
European Commissioner for Trade and the Office of the United States Trade Representative
(USTR) emphasised their deep concern over the process of compulsory licensing to the Thai
Ministry of Commerce. As a result, Thailand was placed on the Priority Watch List of the annual
USTR Special 301 trade report. This international trade pressure to enforce patents stalls generic
ARV market entry and contradicts the intention of the European Commission grant to support
manufacture of generic ARVs. However, it is unlikely that this trend will stop as the imposition
of TRIPS-plus standards on countries is now a core strategy of the research-based
pharmaceutical industry, primarily through the imposition of new standards under bilateral and
regional trade agreements.
Market entry also lags for many second-line products because of small volumes, pending patent status (in India), time for development, increased technological complexity and its associated costs, as well as DRA and WHO prequalification application processes and delays. What these licenses and other generic production efforts will mean for price reduction has yet to be determined. There is concern that the multiple voluntary licenses may make it increasingly difficult for advocates to suggest there is a lack of competition in the marketplace in order to negotiate further price reductions.

The issue of second-line ARVs, therefore, encourages least-developed countries to utilise their 2016 transition period and manufacture these drugs, such as current efforts underway in Tanzania. Yet, like first-line regimes, their ability to do so remains in question. In Tanzania, second-line drugs are not tendered publicly, but financed, procured, and supplied by PEPFAR. Market penetration is limited without FDA approval or WHO Prequalification.

The Way Forward?

In order to maximise ARV treatment access through affordable pricing tenders must seek the lowest cost quality drugs available. This is typically the system in place in Sub-Sahara African countries as donors stipulate international competitive tenders to procure ARVs. Success of local manufacturers then relies on the capacity of the firm to achieve two necessary components of donor-financed tenders: international quality standards and economies of scale to lower price. The targeted financial support from the European Commission has resulted in only one grant of which we are aware and its position on the use of TRIPS safeguards to promote generic manufacturing appears contradictory. We believe that local manufacture in Sub-Saharan Africa,
under current constraints, is difficult to achieve successfully. It is not presently in the interest of patients, governments, donors or drug companies.

Consideration has and should be taken to develop regional cooperation among DRAs and manufactures to shorten the time to market authorisation and to pool procurement volumes to increase economies of scale, respectively. Politically, however, an initiative of this type seems unlikely. Manufacturing is not solely an issue of access, but also economic development. It must address issues of financing, technology, employment, self-sufficiency, and revenue requiring policies that are difficult for a region to agree upon.

Additionally, of particular note to donor countries is that financing drug procurement and encouraging local production efforts fails to address many other critical components of the WHO access framework that prevent affordable medicines from reaching patients. Increased donor attention should address shortages of human resources, patient adherence, and sustainability of pledged donor financing. While increasing the number of people receiving treatment is a short-term goal that provides impressive statistics, it neither addresses sustainability nor does it improve poorly performing health system and poor health infrastructure that limit the availability of treatment and basic care.

**Implications of Research Findings**

Research findings from the case studies of ARV manufacturers in Tanzania and South Africa indicate that their ARV prices are not likely reduced substantially from large-scale generic
importers, such as those found in India. These case studies raise a number of policy implications pertinent at both the domestic and regional levels.

One of the most surprising findings of this research was the poor communication between and within government ministries, drug firms, various agencies and organizations about the technology transfer and local manufacturing initiatives occurring within countries. Even though the Tanzanian government holds 40% ownership in TPI, many informants across ministries were unaware of the manufacturing initiative. Most notably, this included informants at Commission on Science and Technology (COSTECH), whose very role it is to monitor, evaluate, and assist with any technology entering the country, as well as informants at the Ministry of Trade and Industry (MoIT), where a representative currently sits on TPI’s Board of Directors. This poor communication extended to international institutions and bilateral agencies, such as UNIDO, PEPFAR and the World Bank. The implications here are clear: Comprehensive multi-sector strategies to foster local industry are impossible to implement if communication among key stakeholders is not effective.

The need for multi-sector comprehensive strategies is not only a domestic issue, but a regional one as well. The multi-country analysis found a number of manufacturing initiatives for ARVs underway in the Sub-Saharan African region alone. For example, a number of firms in Ethiopia, Tanzania, Uganda, Kenya, Zimbabwe, Zambia, Mozambique, Democratic Republic of Congo, South Africa, and possibly other countries, have at some stage been developing or manufacturing ARVs. A number of these firms, in addition to manufacturing for their local populations, hope to expand regionally. Many of these countries have close political, economic, and trade relations
and are members of regional communities, including the East African Community (EAC), the Common Market for Eastern and Southern Africa (COMESA) and the Southern African Development Community (SADC). Yet, many of the individuals involved with domestic ARV manufacturing initiatives are not aware of one another (with the exception of ongoing initiatives in South Africa and Kenya).

Poor communication and coordination stresses the need for domestic and regional situation analyses by manufacturers when considering ARV development (even if firms do not intend to export regionally). Analyses of this type afford manufacturers with a complete understanding of the opportunities and constraints within the potential market, including their potential competitors. Furthermore, with a number of ARV initiatives underway in Sub-Saharan Africa, there is opportunity for collaboration and capacity building among firms and countries. Countries looking to use local manufacturing as a means to increase ARV access must also firmly grasp its capacity and capability to do so, based on the domestic conditions presented within this dissertation and diagrammed in Figure 7. Simple, but often overlooked, situation analyses must be completed prior to entering any manufacturing initiative.

A sustainable response to local ARV manufacturing addresses opportunities holistically across advocates, government, donors, and industry. This includes a multi-sector strategy that ties industrial, education, and science and technology policies together to foster a manufacturing environment with the necessary incentives, skilled human resources and capacity for long-term viability. Sub-Saharan African countries, and their domestic drug firms, should have an understanding of the ability of manufacturers not only to finance, develop, and produce ARVs
that meet international quality accreditation, but, importantly, their ability to compete on the open international market. This ensures that countries’ populations receive quality ARVs at the most affordable prices.

There is stiff competition in the domestic ARV markets of LDCs, which can import generics from abroad. Many of India’s generic drug firms are vertically integrated and have high-volume capacity. Here, economies of scale enable the production of generic drugs that are currently the lowest priced in the world. In addition, many Indian firms have achieved WHO prequalification and FDA approval, whereas only Aspen (in South Africa) has been accredited out of all Sub-Saharan African manufacturers. Given that international quality approved ARVs can be manufactured in high volumes at low cost, Sub-Saharan African manufacturers find it difficult to compete even in their own markets.

This dissertation highlights the fact that domestic ARV production is not the solution for each African nation. Therefore, when considering local manufacturing initiatives in developing countries and LDCs, question surrounds each country’s motivation. Is the primary objective to meet health or development goals? Indicated by the case studies of Tanzania and South Africa, reconciling these two objectives is challenging. Obviously, governments in Sub-Saharan Africa should be interested in addressing the high burden of HIV/AIDS by procuring the lowest priced ARVs for their populations; however, Sub-Saharan African governments also have other interests, such as improving infrastructure, self-sufficiency, fostering technological and economic development and generating employment. This is reinforced by Kaplan and Laing
(2005) who note that local production is most often addressed in terms of industrial development rather than health policy issues, such as drug affordability.

Health and industrial interests may or may not conflict with each other. Understanding these priorities may help Sub-Saharan African governments appropriately address drug manufacturing. For example, developing a domestic pharmaceutical industry aiming to generate employment may not be the adequate response. A pharmaceutical firm requires labours that are skilled and semi-skilled. In both Tanzania and South Africa, where unskilled labour unemployment is high and retaining skilled workers is difficult, recruiting the necessary skilled human resources is a challenge.

Government resources should effectively address priority outcomes. To achieve ARV access, are there other HIV/AIDS programs or health initiatives that may produce the desired outcomes more cost-effectively than local ARV manufacturing? Developing countries and LDCs must consider other strategies to increase ARV affordability and ARV access more generally. Cost-reduction strategies can include price negotiations with patent holders, bulk procurement, parallel importation, and competitive tenders. To improve treatment access, attention should focus on improving the number of health professionals able to assist with ARV scale-up, to monitor treatment adherence, and to provide basic care.

If achieving sustainable access to low-cost ARVs is the primary objective and sole constraint of local manufacturing, the most efficient effort is regional cooperation in manufacturing, procurement, and harmonization of DRAs. This would ease entry barriers of ARVs into
neighbouring countries and allow firms to enter the market quickly. Prices would be reduced based on pooled resources and large-scale efficiencies. Recently, the African Union (2008) identified opportunities for regional ARV manufacturing. Pursuant to the Assembly Decision 55 during the Abuja Summit in 2005, the African Union mandated the development of a *Pharmaceutical Manufacturing Plan for Africa*. Currently, a technical committee is studying the implications of regional pharmaceutical production, based on six priority areas: mapping; situation analysis and compilation of findings; manufacturing agenda; intellectual property issues; political, geographical and economic considerations; and financing (African Union, 2008). This plan aims to utilize the 2016 transition period of LDCs under the TRIPS Agreement to develop a variety of drug manufacturing initiatives.

Regional initiatives of this type, however, face a number of serious constraints. The harmonization of either procurement or DRAs is unlikely, and the success of regional manufacturing is questionable. In exchange for production efficiencies, an inter-government agency could create bureaucratic inefficiencies, where achieving consensus among participating countries would be difficult. Here, national interest and politics are large obstacles to drug access. The process of deciding where manufacturing plants and regional DRAs should be located is highly political, involving numerous actors and lobby groups across ministries, governments, and industries. Regionalization of DRAs would come at the cost of a country’s perceived threat to health security and self-sufficiency, disabling autonomy in product registration and evaluation. Consolidation could see a loss of employment, human resource capacity, and income generation in certain countries. Some LDCs may also feel pressure to abide by stipulations required by more dominant Sub-Saharan Africa countries, such as South Africa.
For example, IP protection varies by country. Regional manufacturing, procurement, and DRA agencies would have to come to consensus on the adequate level of patent enforcement, while also considering current obligations under the TRIPS Agreement and other trade agreements.

When firms compete in the ARV market, WHO prequalification or FDA approval is essential. A number of issues surrounding WHO prequalification were discussed in the *Eurohealth* article. The WHO Prequalification Programme developed an internationally recognized quality standard to assist authorities and organizations that did not have the technical capacity to assess ARV quality themselves. WHO prequalification is a standard requirement in tenders financed by the Global Fund, many bilateral donors, and even by many governments. International quality standards are important. They ensure that only ARVs of good quality reach patients.

These international quality standards, which were intended to streamline drug approvals, however, create unnecessary duplication and delay drug availability. Currently, ARVs must be approved both by WHO and registered by the local DRA in the country of procurement. Both procedures can be lengthy; in some cases the registration process can take over 2 years, as seen in South Africa. It is also necessary, but costly, to compile appropriate quality assurance and bioequivalence data. These costs compound when the application and dossier requirements for each DRA approval differ. Accreditation also became further complicated when PEPFAR announced that it would only finance the procurement of FDA approved products, noting that FDA quality standards are higher than WHO. PEPFAR’s large and unilateral efforts control a substantial proportion of ARV procurement in Sub-Saharan Africa. As a result, manufacturers already WHO prequalified and approved by local DRAs must also register with the FDA in order
to be eligible for PEPFAR procurement. Although the process was simplified with WHO fast-tracking prequalification for products registered by stringent DRAs (such as FDA, Health Canada, etc), it has caused confusion among procurement officials and manufacturers alike. Aspen faced this problem when its products were denied entry into a number of Sub-Saharan African countries, because, even though they were FDA approved, they lacked local DRA registration and WHO prequalification. The supply constraints resulting from these instances can be avoided with appropriate cooperation among DRAs.

As mentioned previously, DRA harmonization within Sub-Saharan Africa is unlikely. However, some type of cooperation should be pursued among DRAs and international regulatory bodies, to ensure timely drug availability on the market, while also enabling countries to maintain their sovereign interests. This could include streamlining applications across countries to simplify the registration process, fast-tracking applications already approved by neighbouring DRAs, and granting immediate approval to products accredited by stringent DRAs, such as WHO and FDA. Also, efforts to exchange information and increase technical capacity among authorities, as well as joint R&D initiatives, may strengthen respective DRAs, enhance human resource training, and foster the manufacturing capabilities of domestic firms.

Finally, manufacturing costs is not the only factor that can influence treatment price. A government’s tender specifications can have a direct impact on ARV treatment price. The most common mechanism for government tenders to ensure cost reduction is through international competitive bidding. Allowing multiple generic manufacturers to bid on a tender increases competition and drives down price. This effect is highlighted when comparing the case studies in
Tanzania and South Africa. International competitive bidding was seen in Tanzania, reducing ARVs prices significantly beyond what the domestic manufacturer, TPI, could achieve. However, restricted competition in South Africa (due to patent compliance) kept Aspen’s prices higher than neighbouring countries for alternative first-line ARVs.

In addition to competitive bidding, another tender specification can have profound impact on treatment cost: triple fixed-dose combinations (FDCs). Combining three ARVs into one pill not only eases treatment for patients, it decreases the total cost of triple therapy. The FDC 3TC+d4t+NVP was procured in national tenders in Tanzania; however, in South Africa, no triple FDC was tendered. In South Africa, patent enforcement does not preclude the tender of this FDC because no restrictions were placed on combining the products licensed from GSK, BI, and BMS. This policy choice by the South Africa government to omit first-line triple FDCs from tender, left the total treatment cost for first-line therapy significantly higher than those countries that do tender FDCs. Therefore, it is important for developing country governments to understand that it is not just manufacturing costs that affect ARV price. Tender specifications, such as competitive bidding and product combinations, also have an important role to play to ensure the lowest cost, good quality ARVs are procured.

**Limitations of the Research**

Many limitations of the collection and analysis of data were discussed in Chapter 1. There were practical and country-specific limitations to the research. In practical terms, this research was limited by time and funding. In some cases, telephone interviews were used to supplement key-informant interviews. In each country case, there was a limit on the number of potential
documents and informants that were available. This was affected by bureaucratic obstacles, unavailability of informants, or unwillingness to disclose information, the last of which was most noticeable in terms of accessing the terms and conditions of the technology transfer arrangements.

Prior to this research, cases of technology transfer for the local manufacture of ARVs in Tanzania and South Africa had little empirical research. Therefore, an in-depth understanding of the events in each case was imperative. As this dissertation conducted a small-\(n\) comparative case study, the results have limited generalizability, or external validity. Nevertheless, this research did develop a common conceptual framework for these cases (Figure 7). This framework modelled the important factors that lead to technology transfer arrangements and the affordable production of ARVs. This fills a gap in the literature on ARV manufacturing and adds a new framework to propel further investigation in the area. Importantly, the study findings note key policy implications for developing countries and LDCs that are considering ARV manufacturing as a means to increase access.

Some of the limitations of the small-\(n\) comparative case study in Tanzania and South Africa were minimized by the large-\(n\) multi-country analysis performed across 25 developing countries and LDCs. This enabled the dissertation to test its case study findings of two factors that influence the transfer of technology: TRIPS-compliant patents and firm ownership. With the results of the multi-county analysis, this dissertation is generalizable across developing countries for these two variables (patent compliance and firm ownership). This multi-country analysis, however, had a number of limitations that were described in Chapter 4. For example, this study only tested two
of the variables that emerged from the comparative case study research. Not enough information was available across countries to test other variables: manufacturing capacity, political environment, ARV market characteristics, and the impact of civil society. The multi-country analysis also did not test variables that, although they did not emerge from the case studies, may have also been influential, such as cultural relations.

Finally, the multi-country analysis only tested the first theoretical research question: Does the protection of intellectual property lead to an increase in technology transfer? It did not address the second theoretical research question: Does the local production of ARVs increase drug affordability? This second research question, however, was discussed more thoroughly and generally within Sub-Saharan Africa in the article commissioned by the journal *Eurohealth*. There are many factors to consider when discussing the local manufacture of ARVs and all could not be addressed in this dissertation. This field requires greater attention among academics and this research offers a number of recommendations for future research to follow.

**Recommendations for Future Research**

Given the research findings and experiences of the comparative case study and multi-country analysis, a variety of avenues for future research should be explored. Currently, there is a dearth of case study research on developing countries and LDCs that have entered technology transfer arrangements to manufacture ARVs locally. This gap needs to be filled.

First, the case study findings from this dissertation should be tested, both in single and small-\(n\) cases studies as well as across large datasets. This research should not only be limited to Sub-
Saharan Africa and ARVs, but include all developing countries and LDCs that are using the transfer of technology to manufacture essential medicines to decrease prices and increase drug access.

There could even be a simple, but important, precursor to this: a database that identifies which countries have attempted to manufacture ARVs, their level of manufacturing capacity, the type of technology transfer arrangement through which this is occurring, and their achievements. Many researchers and organizations focus only on initiatives that attain a marked level of achievement (such as WHO prequalification, FDA approval, compulsory licensing), or those that supply the majority of the market. This is most common in countries such as India, South Africa, Brazil, China, and Thailand. However, there are many ongoing initiatives in LDCs that have gained no attention, most likely as they have not achieved any measurable level of success. This does not mean, though, that these LDC cases lack important empirical findings for researchers, the international community, and LDC governments.

Many interesting implications can be drawn simply from understanding which technology transfer arrangements and manufacturing initiatives are ongoing, which have products that are registered locally, and which have been terminated or delayed. This descriptive information alone is important to understand how many developing countries are undertaking these large ARV manufacturing initiatives. As these initiatives develop, it is important to understand what events cause their progress or setbacks. Obviously, to address this issue, success and failure among the local manufacturing industry should be better defined. Can an industry produce affordable ARVs and be sustainable without WHO prequalification and/or an export market?
What are the minimum market requirements and policy incentives needed to ensure a viable industry? More case studies are needed to understand the conditions that contributed to the development of ARV manufacturing initiatives as well as their success/failure to derive appropriate policy recommendations in a broad context, particularly as they relate to the use of TRIPS flexibilities for public health imperatives.

To give an appropriate perspective on developing countries undertaking local manufacturing initiatives and the “make-or-buy” debate, these case studies should be compared with case studies of countries that also have a high burden of disease, but have chosen to import drugs as the preferred means to increase access. The latter case studies can be a result of the use of the country’s TRIPS transition period to import generic drugs from abroad or through a compulsory license to import under the 30 August Decision of the General Council. An understanding of the differences and similarities in these countries’ policy environments, pharmaceutical markets, firm dynamics, and manufacturing capacity could provide valuable information that could confirm or negate some of the findings from this dissertation.

Also, as discussed in Chapter 4, how and by whom patent enforcement is measured in developing and LDCs is not well understood in the literature. Research should be conducted on the various means through which patents can be enforced by domestic firms and governments as well as patent holders and their home country governments. How the level of enforcement, in addition to patent protection, impacts the transfer of technology to developing country is an important topic to investigate. For developing countries that are already obliged to protect
patents under the TRIPS Agreement, this research could provide a valuable understanding of the policy options available to them as well as the potential impact on drug access.

Additionally, the meaning of technology transfer in the literature and across stakeholders differs. Given its relevance under the TRIPS Agreement and the 30 August Decision of the General Council, it is imperative to understand how LDCs, developing and developed countries, and industry each define technology transfer and how they perceive it to be implemented under Articles 7 and 66.2 of the TRIPS Agreement. It should also be investigated how technology transfer could be implemented most effectively. This would be interesting to explore using the case of a current technology transfer initiative to understand whether firms’ goals and objectives are in alignment and are being met.

Although it may be too early for conclusive results, research should begin to investigate countries that changed their patent regime between 1995 and 2005 and how governments and industry feel this impacted the flow of ARV technology to their firms, domestic pharmaceutical industry strategy, and drug access. This should be examined in countries such as India, Brazil, and Thailand, using for important second-line ARVs that are under patent. While some of these analyses may have begun, the impact of this transition should be explored also in the context of LDCs that import these medicines. Consideration should be given to how this transition impacts LDC drug affordability as well as the development of technology transfer initiatives.

Currently, technology transfer initiatives under voluntary licenses for second-line ARVs are underway in LDCs, such as Tanzania, Ethiopia, and Bangladesh, under Roche’s corporate social
responsibility program. From the vantage point of the patent holder, it is important to understand why these particular countries and firms were chosen. It also raises two questions: What is the level of technical assistance brought to these firms? How do corporate social responsibility technology transfer initiatives differ from other voluntary licenses?

Discussed in Chapter 4, an additional topic to explore is the relationship between government and state-owned pharmaceutical firms. Of specific interest is the likelihood of governments with state-owned firms to issue a compulsory license and develop local ARV manufacturing initiatives compared to those governments with private domestic drug firms. What are the dynamics between these institutions (governments and pharmaceutical firms) and how do they facilitate or inhibit this process? The level of government support, in terms of subsidies, tax credits, and public investments funds to both state and private firms, should be investigated to understand how this support may affect firm and government strategies, including the development of local manufacturing and technology transfer initiatives. Similarly, the relationship between state-owned firms in developing countries and the research-based pharmaceutical industry should be explored. How does this relationship compare to that of the research-based industry with private firms in developing countries? Do patent holder and domestic firm negotiation strategies differ based on domestic firm ownership?

The case study of Tanzania revealed the tension that local DRAs felt as a result of donor WHO prequalification and FDA approval requirements, over and above local accreditation. Both cases in Tanzania and South Africa also revealed the challenge faced by local manufacturers to access neighbouring markets due to individual DRA requirements in each country. The relationship
among DRAs and the power struggles between them should be researched to analyze their impact on drug access. This could include an assessment of the various attempts to harmonize DRAs, either regionally or internationally, and how the political environment and relations between countries help or hinder this formation. Similarly, research could also confront the difficulty in Sub-Saharan Africa to pool ARV procurement, which could reduce costs by increasing scale.

Additional gaps were found within both case studies on tender processes for ARVs. In particular, the decision making behind firm and ARV product eligibility, the influence of donors on tender specifications, and the relationship of tender boards with their local DRAs and local drug firms need further investigation. Case studies of Tanzania and South Africa highlighted discrepancies in the tender processes and alluded to a lack of transparency. These issues are important to explore and have serious consequences for drug price, sustainability of local manufacturing initiatives, and government accountability in drug provision.

Finally, this dissertation examined drug access through one of its components: affordability. Affordability has received prominent attention internationally because of the role the TRIPS Agreement, developed countries, and the research-based pharmaceutical industry play in keeping ARV prices high. Since ratification of the TRIPS Agreement, priority in drug access has turned to domestic ARV manufacturing as the necessary and appropriate drug access response. The findings of this dissertation, however, reinforce that many Sub-Saharan African countries cannot develop viable ARV manufacturing industries that reduce prices greater than those offered by foreign importers. ARV manufacturing should be left to countries that have the appropriate IP
framework, technical capacity to produce APIs, low-cost skilled labour, and economies of scale to ensure the largest price reductions. Importantly, there are a number of components that contribute to ARV access that have been overlooked and require additional examination. Specifically noted from key-informant interviews are challenges of health human resources to dispense and treat patients with ARVs, the quality of ARVs, the quantification of ARV volumes, as well as the necessary infrastructure and supply chain management to deliver ARVs in a timely and quality-assured manner. These components of ARV access need be considered in conjunction with price to ensure the most effective response is used, enabling affordable and sustainable ARV treatment for those most in need. Manufacturing is not the sole drug access solution for any country, regardless of capacity or development level.
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Appendix A: WHO Treatment Guidelines for First- and Second-Line ARVs

First-Line ARV Treatment

*First-line* treatment is the initial triple therapy ARV regimen used by patients starting treatment.

In 2003, WHO (2003) guidelines recommend two classes of ARVs for initial treatment. Treatment includes two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) as the preferential treatment. In resource limited settings, this includes one thymidine-analogue NRTI (i.e., d4T or AZT), combined with 3TC (WHO, 2007a).

First-line treatment regimens in developing countries include combinations of:

- d4T or AZT
- +
- 3TC
- +
- NVP or EFV

In accordance with WHO guidelines, AZT or d4T, combined with 3TC and an NNRTI, are the predominant first-line regimens in most countries and covers 95% of those on treatment (WHO, 2007a). EFV is not to be used in women who are of child bearing age or are pregnant.

When discussing first-line treatment *failure*, the term is defined either clinically, and/or immunologically, and/or virologically. Failure denotes loss of treatment efficacy and triggers a switch of the entire regimen. Single drug substitutions of an individual ARV (generally found in the same class) for reasons of toxicity, drug-drug interaction or intolerance does not require an entire regimen change and, as such, the patient technically remains on first-line treatment (WHO, 2007a).
Alternative-First Line ARV Treatment

More recently, WHO (2006a) revised its treatment guidelines to include an improved first-line treatment regimen. This regimen is similar to the initial first-line treatment recommendation of two NRTIs and one NNRTI, but changes the thymidine nucleoside analogue (d4T or AZT) for a nucleotide (TDF):

\[
\begin{align*}
\text{TDF} & + 3\text{TC or FTC} \\
& + \text{NVP or EFV}
\end{align*}
\]

TDF is gaining preference for first-line treatment due to its low toxicity profile and its increased availability in developing countries (WHO, 2007a). The Clinton Foundation HIV/AIDS Initiative (CHAI) forecasted a shift to TDF in both first-line and second-line treatment and suggests that, by 2010, TDF will become the dominant first-line NRTI for new patients in low- and middle-income countries (WHO, 2007a). However, using TDF in the first-line regimen increases cost substantially. MSF (2007) notes that this switch in regimen will increase treatment costs from US$99 per person per year (pppy) for d4T+3TC+NVP, to US$339 for TDF+FTC+EFV, and US$426 for TDF+3TC+NVP based on the negotiated prices of the Clinton Foundation.

Second-Line ARV Treatment

Second-line treatment is the subsequent regimen used after first-line treatment has failed. WHO (2007a) guidelines recommend the use of two NRTI drugs in combination with a ritonavir-boosted protease inhibitor (PI). In second-line treatment, WHO (2007a) suggests that those NRTIs not used in first-line therapy are used as the NRTI components in second-line therapy, with non-thymidine based NRTIs preferred (i.e. ABC, ddi, TDF).
TDF+3TC
or
ABC+ddI
+
LPV/r or ATV/r

These regimens are given the highest priority among current second-line options recommended by WHO (when thymidine analogue NRTIs [d4T or AZT] are used in first-line therapy). In December 2006, an estimated 2% of the ARV treatment population was on second-line treatment (40,000 individuals). The majority of second-line treatment patients reside in Brazil (WHO, 2007a). In 2007, the cost of second-line regimens in low- and middle-income countries varied from $US1,000 to $US2,500 per person per year (WHO, 2006c). Given the average switch rate of 3% per year, the WHO estimates that, by 2010, 90% of the cost of treatment will be put toward second-line regimens (WHO, 2006c). This is unless price reductions can be achieved.

If TDF is used as the improved first-line treatment regimen, second-line recommendations changes to include:

AZT+3TC
+
LPV/r or ATV/r

CHAI has forecasted the consolidation of PIs around LPV/r or ATV/r. Though LPV/r currently dominates the market in low- and middle-income countries, they predict a shift towards ATV/r. This will occur once a single daily fixed-dose combination of ATV/r is available and affordable. CHAI estimates that ATV/r could see as much as a 40% price decrease over LPV/r. This is because ATV requires less active pharmaceutical ingredients per dose than does LPV (CHAI, 2006). Among second-line ARV drugs, generic forms of TDF, TDF+3TC, TDF+FTC, ABC,
3TC, ddI, SQV, IDV, NFV and LPV/r are currently available. WHO (2007a) notes that many of these products, such as, TDF and its combinations, ddI enteric-coated capsules, and LPV/r, have been submitted to WHO and United States Food and Drug Administration for quality accreditation, but have yet to be approved. However, their purchase is available through UNITAID or Global Fund financing under the quality category c(i) (see Appendix G for a description of procurement categories).

Sources: WHO (2006,a,c, and 2007a).
### Appendix B: Developing and Least-Developed Country Members of the World Trade Organization

#### Least-Developed Country Members

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#### Developing Country Members

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Appendix C: TRIPS Transition Periods for Pharmaceutical Patent Implementation

Three pharmaceutical patent transition periods exist under the World Trade Organization’s (WTO) Agreement on the Trade-Related Aspects of Intellectual Property (TRIPS). These transition periods are in place to allow governments of WTO developing and least-developed countries time to implement pharmaceutical product and process patents into domestic legislation.

During the first patent exemption period, the TRIPS Agreement does not require pharmaceutical process or product patent protection for those drugs that were in the pipeline\(^{54}\) at the time the TRIPS Agreement came into force. This means that only drugs for which a patent application was filed from January 1, 1995 onward were not included under the TRIPS Agreement’s patent obligations. Drugs that were in development, but not yet on the market, did not require protection under the TRIPS Agreement.

Brazil illustrates the use of the first exemption period in the TRIPS Agreement. The country created its patent law in 1996 to become fully TRIPS compliant, and patent protection for pharmaceuticals was introduced on May 14, 1997. In doing so, Brazil retained the ability to manufacture a number of ARVs that had been patented in developed countries prior to the introduction of the TRIPS Agreement. This included the key ARVs in the first-line regimen, 3TC+d4T+NVP. Currently, 7 of 18 ARVs used in Brazil’s treatment guidelines are not under patent and can be manufactured domestically (Nunn, et al., 2007). Brazil did not fully utilize this transitional provision, however, and introduced standards beyond that required of the TRIPS

\(^{54}\) Pipeline pharmaceutical products are those for which a patent exists, but the drug has not yet entered the market.
Agreement (commonly referred to as TRIPS-plus provisions). Between May 15, 1996 and May 15, 1997, it was possible to register a pre-existing foreign patent or pending application in Brazil to obtain pipeline patent protection. Nevertheless, Brazil’s partial use of the pre-1995 provision is important in the global context because this transition period was not available for many developing countries that implemented patent law prior to the TRIPS Agreement. For example, South Africa’s Patents Act protected both product and process patents before the country ratified the TRIPS Agreement and most ARVs were already patented in the country. Unlike Brazil, no ARV products in South Africa could be manufactured domestically unless authorized to do so by the patent holder or government issued a compulsory license.

The second transition period in the TRIPS Agreement gave developing countries until January 1, 2000 to apply TRIPS standards to both product and process patents. Further, developing countries that had not legislated product patents prior to the TRIPS Agreement were given until January 1, 2005 for their introduction. Because most developing countries already provided product patent protection, this 2005 transition period only applied to a few countries. It should be stated that Brazil, as a developing country without patent legislation prior to 1996, technically could have been granted this extended transition time. Facing extreme pressure from the United States that included threats of bilateral trade sanctions, it complied early in 1996.

The most notable country that made use of the 2005 transition was India. Since 1970, India only protected process patents; it became TRIPS compliant in April 2006 after its revised Patent Act was passed by Parliament in March 2005. Using the 2005 transition period to evade product

55 Some of the countries that notified the WTO of their intent to use the transition period mailbox system were: Argentina, Brazil, India, Egypt, Morocco, Turkey, Kuwait, Pakistan, Tunisia, United Arab Emirates, Paraguay, and Uruguay.
patent protection, India was able to reverse engineer many ARVs that were patented in developed and developing countries. Reverse engineering allows manufacturers to examine the product and find new ways to manufacture it so that it does not infringe the process patent in place. The ability and capacity of these Indian generic firms to develop these processes led to substantial growth of the generic ARV market. As a result, India manufacturers have an array of first-line and some second-line generic ARVs, and are the largest provider of ARVs to developing countries.

The third and final transition period under the TRIPS Agreement is specific to LDCs. Initially, under the agreement, LDCs were required to amend their patent legislation by January 1, 2006, but pursuant to the Doha Declaration this deadline was extended to 2016. Most LDCs in Sub-Saharan Africa have been making use of the transition period. It allows these countries to import generic ARVs from any producing country, such as India. There are also a number of countries, such as the United Republic of Tanzania (Tanzania), Zimbabwe, and Uganda among others, that are developing their own national manufacturing initiatives.
Appendix D: Intellectual Property, Innovation, and Developing Countries

Intellectual Property (IP) and Innovation

Considered the mainstay of the drug discovery process, the research-based pharmaceutical industry (hereafter called the patent holding pharmaceutical industry) argues that patents are necessary to recoup the fixed and sunk costs of bringing a new drug to market. The industry claims that it takes on high risk in its efforts to produce new drug compounds. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), the percentage of sales that went to R&D in 2007 was 18.7% (PhRMA, 2008); however, the actual cost of R&D for pharmaceutical innovation is difficult to establish and remains unknown. The pharmaceutical industry remains extremely guarded about their actual costs, allocation of expenditure and profits. Dimasi and Grabowski (2007) estimate that the cost to develop a drug, from discovery through product registration in 2006 was US$1.3 billion. Researchers estimate that this process takes from 10 to 15 years to complete and that these sunk costs do not guarantee a successful outcome (DiMasi, 2001; DiMasi, Hansen & Grabowski, 2003; Dickson & Gagnon, 2004). PhRMA (2008) also claims that only one of every 10,000 potential medicines makes it through the R&D process and enters the market. Of those that do reach the market, only a few generate an appropriate return on investment (Schweitzer, 1997). To recoup their R&D costs and profit from their “high-risk” investments, patent holders sell their product at monopoly prices during the patent period.

The costing figures of the patent holding pharmaceutical companies, however, remain highly disputed. Gagnon and Lexchin (2008) found that pharmaceutical firms spend almost twice as much on promotion as they do on R&D. Firms often include promotion and advertising
expenditure as part of their R&D costs. Similarly, the high rates of return on investment these drugs provide counter PhRMA’s argument. Critics note that, in 2002, ten Fortune 500 pharmaceutical companies’ profits (US$35.9 billion) were greater than the profits of all other companies combined ($33.7 billion) (Angell, 2004). The pharmaceutical industry’s profit (14.3% of sales) was also far above the median for all industries (4.6%) (Angell, 2004).

Pharmaceutical industry profits are also compounded by large public investment in R&D. Research records large subsidies and transfers the industry acquires from government for new drug development (Scherer, 1993). For example, the Orphan Drug Act was passed in 1983 by the United States Congress to provide incentives, through tax reductions and marketing exclusivity for 7 years post-approval to motivate industry to invest in drugs for rare diseases that afflict fewer than 200,000 individuals in the United States. Provisions also included tax credits for clinical testing and simplified approval by the United States Food and Drug Administration (FDA).

Finally, the value or innovativeness of new drug products on the market is often criticized. Often new products are not necessarily new chemical entities, but combinations and duplicates of drugs already developed, called me-too drugs (Davis, 1992). These are primarily developed for, and sold in, high income markets. These me-too drugs will be further addressed in the following section.

In response to the debate over the appropriateness of patents, scholars Hollis (2005) and Pogge (2007), among others, call for a change in the way that innovation in the pharmaceutical industry
is rewarded. They suggest a new system based on the value or benefit a product brings to a particular need. For example, attempting to bring together investor incentives and social health objectives, Hollis (2005) proposed a system where new drugs are rewarded based on the “incremental therapeutic benefits” (p. 25) of the innovation. In this system the reward is paid directly to the innovator, followed by a competitive bid for the product license. Theoretically, this proposal would appropriately direct health innovation and benefit areas where drug discovery is most needed and most cost-effective, while avoiding many marketing and advertising costs that have limited social benefit.

A number of practical implementation issues, however, challenge the proposal for a new pharmaceutical innovation system. This new system would require an overhaul of current IP legislation that is in the process of being harmonized across WTO members. Questions remain over the value of a pharmaceutical invention and the appropriate monetary compensation. For example, who pays the reward and how much is paid? Hollis (2005) notes that these payments could amount to 3% of the United States government’s annual federal budget. It would be difficult to convince many other governments to implement this system. Similarly, drugs may have varying benefits in countries with different disease profiles, and it may prove a challenge to provide incentives to invent drugs for neglected diseases of countries with very little to contribute to the proposed fund. Finally, bureaucratic inefficiencies and negative political interference may result from a public managed innovation fund. Although these issues are addressed by Hollis (2005), enough uncertainty remains to probe other models that could be implemented within the current IP innovation framework that would require minimal
modification and also benefit pharmaceutical innovation in neglected diseases predominantly affecting developing countries.

Developing Country Markets and Innovation

When considering what constitutes a pharmaceutical market, it is necessary to distinguish treatment demand from need. In order for individuals to demand a product, they must not only need treatment, but have some level of purchasing power. Unlike most developed countries, the majority of pharmaceutical expenditure in developing countries is through individual out-of-pocket payments. Payments range anywhere from 50% to 90% of the drug cost and they consume a large portion of health expenditure (Quick, 2003). These out-of-pocket payments by low-income individuals can be double those of the richest 10% of the population (Govindaraj, Reich, & Cohen, 2000). This is compounded by the fact that, due to their low income level, the purchasing power of those most in need of essential medicines is low.

The impact purchasing power has on demand is revealed by an economic survey in countries of the Organization for Economic Cooperation and Development. The survey found that consumers’ demand for drugs tends to be sensitive to price and that there is a good correlation between expenditure on pharmaceuticals and income levels (Jacobzone, 2000). It is not surprising, then, that the generally low-income level of individuals in developing countries, with the added burden of paying for drugs out-of-pocket, makes their population even more sensitive to price (Kumar, 2004; Chaudhuri, et al., 2003). This suggests that it is not their willingness to pay, or their need, but their ability to pay that affects demand (Hollis, 2004).
As far as multinational patent holding drug firms are concerned, low-income populations do not make up part of the market for a drug, given that they cannot pay the high prices necessary to contribute to the return on investment of patent holders (Orbinski, 2003). This also extends to governments that operate with small per capita health expenditure; they cannot afford the price of patented medicines. In response, patent holders maximize profits by targeting and selling to the highest income groups in the private sector (Love & Hubbard, 2004). Govindaraj, Reich, and Cohen (2000) found that, even though developing countries make up approximately 85% of the world’s population, they account for 20% of global pharmaceutical sales.

The effects of pharmaceutical patents are then controversial in developing countries which are not considered a valuable pharmaceutical market. In response to high prices, the patent holding pharmaceutical industry and supporters of the TRIPS Agreement focus mostly on the benefits gained from the agreement’s implementation in developing countries, rather than the impact the TRIPS Agreement may have on drug prices (Pécoul, et al., 1999). Patent protection claims to generate incentives for pharmaceutical firms to invest in foreign direct investment (FDI) and R&D for new drugs to treat diseases in developing countries (Pécoul, et al., 1999). Herein is the paradox: they are not part of what the research-based industry considers a market and they do not contribute to the R&D incentives of the manufacturer even if they do protect patents (Hollis, 2004). North America, Europe and Japan together represent 80% of the global pharmaceutical market and Africa only 1%; therefore, pharmaceutical R&D does not respond to Sub-Saharan African markets (Sterckx, 2004). Even developing countries that do purchase patented medicines are not benefited with investment in treatments predominantly afflicting their region.
The patent system is inefficient in the case of developing countries, because companies’ R&D respond to the incentives provided by wealthy markets and consumers by investing in lifestyle and me-too drugs. For example, Troullier and colleagues (2002) demonstrated that, of 1393 new chemical entities with market authorization between 1975 and 1999, only 13 (0.9%) were designed to combat tropical diseases and three to treat tuberculosis (which together cause 11.4% of global disease burden). More recently, Chirac and Torreele (2006) expanded Troullier and colleagues’ database to the year 2004 and determined that only four out of 1556 new chemical entities were for treating neglected diseases (including malaria and leishmaniasis). This highlights the imbalance and bias of innovation in favour of high-income countries. Infectious and parasitic diseases make up approximately one-third of the world’s disease burden (Troullier, et al., 2002), but less than 5% of the US$70 billion spent on R&D was allocated to these tropical diseases (Orbinski, 2003). The lack of R&D in tropical diseases suggests that market incentives, as a result of patents, are ineffective in countries where market prospects are poor or do not exist (Troullier, et al., 2002). Although developed country governments can influence R&D priorities, they generally favour drugs with commercial application and not those that treat diseases in countries that lack purchasing power (Pécoul, 2004).

The development of ARVs for the treatment of HIV/AIDS is a unique case of what was once considered a neglected disease. Neglected diseases are life threatening or extremely disabling illnesses for which treatment options do not exist. They are generally tropical infections that tend to be endemic in low-income countries that affect millions, but are often overlooked by the multinational patent holding industry for lack of market potential (WHO, 2008a). In the 1980s, the United States and European countries were experiencing an increase in HIV prevalence rates.
Fears of the virus reaching epidemic proportions in developed countries spurred heavy investment into R&D. Many of the first ARVs approved in the United States were discovered under public financing. For example, zidovudine (AZT) was first synthesized as a treatment for cancer in 1964, under a grant by the United States National Institutes of Health, but was abandoned after it was proven ineffective in mice. In 1985, researchers at Burroughs Wellcome (now GlaxoSmitKline) found evidence that it could be used in the treatment of ARV, and a patent was granted. Similarly, didanosine was discovered by a PhD student at Arizona State University in 1988 and was modified at the National Cancer Institute which awarded a 10 year exclusive license to Bristol Myers Squibb (BMS) to market the drug. This caused alarm for two reasons. First, much of the cost of R&D for HIV/AIDS treatment was borne by the United States government through its agencies and funding mechanisms and not by pharmaceutical industry. This takes away much of the sunk costs and high risk that need to be rewarded with patents. Second, some of these drugs had already been discovered and were patented again for a new use once they were found effective in HIV/AIDS treatment. With these patents came high prices out of reach for most individuals in developing countries.
Appendix E: Information Letter and Consent Form

UNIVERSITY OF TORONTO  
Leslie Dan Faculty of Pharmacy

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<tr>
<th>Investigator: Kinsley Wilson, PhD Candidate</th>
<th>Local Collaborator: Olipa Ngassapa, PhD</th>
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<td>University of Toronto</td>
<td>Muhimbili University College of Health Sciences</td>
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<td>Email: [enter address]</td>
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<td>Tel: [enter local number]</td>
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<tr>
<th>Supervisor: Dr. Jillian Clare Cohen, PhD</th>
<th>Local Collaborator: Timothy Quinlan, PhD</th>
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<td>University of Toronto</td>
<td>University of KwaZulu-Natal</td>
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INFORMATION LETTER:
The transfer of technology to developing countries for the local production of ARVs: A comparative case study

You are invited to participate in an interview for a multi-site project as part of a PhD thesis. For this study, approximately 20 participants in each Tanzania and South Africa will be recruited for interview. Your eligibility has been based on your knowledge and understanding of your firm’s role in the transfer of technology for the local manufacture of ARVs and the process through which the technology is being transferred. Therefore, the purpose of this study is to identify the factors that have led to the technology transfer arrangements for the local production of ARVs in Tanzania and South Africa as well as the process of technology transfer that is being utilized by these arrangements.

The interviews will last approximately one hour and be located in a setting of your choice. Questions will be based on your knowledge of the above mentioned events. Participation in this study is voluntary and at any point you do not wish to answer a question or wish to terminate the interview you may do so with no adverse consequences. There will be no compensation for your participation in this study.

This study has been reviewed and received ethics clearance through the Research Ethics Board (REB) at the University of Toronto, Canada, as well as at the University of KwaZulu-Natal, South Africa, and the Muhimbili University College of Health Science at the University of Dar-es-Salaam, Tanzania. This study is funded by the Social Science Humanities Research Council of Canada as well as the International Development Research Centre. The investigators may be reached anytime if questions or problems arise. There are no conflicts of interest on the part of the researchers, their institutions or the sponsors.

The level of confidentiality of your personal information and any direct quotations is your choice. Complete confidentiality of all individual information will be provided at your request in the consent form. If you have questions about your rights as a research participant, please contact Jill Parsons, Health Sciences Ethics Review Officer, Ethics Review Office, University of Toronto, at telephone [enter number] or by email: [enter email].
CONSENT FORM

The transfer of technology to developing countries for the local production of ARVs: A comparative case study

To: [Enter Participant’s Name]

Thank you for taking the time to be part of this study. The key-informant interview you are about to participate in will last for approximately one hour. If at any point in this interview you do not wish to answer a question or want to terminate the interview, you are free to do so at no consequence.

This interview seeks your knowledge about the involvement of your organization/government in the development of the technology transfer arrangements for the local production of antiretrovirals in your country as well as the process of technology transfer undergone to enable their production. It is also asked that you kindly consent to having the interview audio-recorded. Should you choose not to be audio-recorded; the researcher will instead take notes with your permission.

The level of confidentiality of all personal information and direct quotations is your choice. Should you choose complete confidentiality, all information and opinions will be kept strictly confidential and will not be made available, except in coded form, to anyone who is not part of the research team unless required by law. Therefore, any risks to the individuals being interviewed or observed will be minimal as their information will be kept strictly confidential and will be coded on a Master Code List. The master list linking your name to the code number will be accessible only to the research team (including the researcher, research assistant and investigators and collaborators).

Digital versions of the recordings as well as the typed transcripts will be placed on a password protected flash drive. The transcripts and recordings will be locked in a filing cabinet within the Leslie Dan Faculty of Pharmacy, University of Toronto as well as at the Health Economic and HIV/AIDS Research Division at the University of KwaZulu-Natal, South Africa, and the Muhimbili University College of Health Sciences at the University of Dar-es-Salaam, Tanzania. These recorded interviews will be destroyed after transcription is complete and verified. For
purposes of verification, the transcripts will be kept for six years from the completion date of the study, after which point, they will be destroyed.

While there are no known significant risks to your participation, potential risks may be a degree of personal risk in having your or your organization’s views exposed. This may include possible criticism from the public, your peers or superiors. Further, foreseeable risks may also include emotional risk, such as feeling uncomfortable, anxious or upset by questions asked during the interview process. It is possible that these risks can be mitigated by keeping your personal information strictly confidential should you choose. However, as a participant you will have the benefit of knowing that the information you provide will assist to develop a best-practice guideline as well as a benchmark for technology transfer of essential medicines to developing countries. This information will also assist to identify the needs and opportunities for further research in this area. Aggregate results from this study will be published as part of the investigator’s doctoral dissertation as well as be submitted for publication in peer-reviewed journals. Direct quotations from your interview may be used without any reference to your name. Information about the study results can be retrieved upon telephone/email contact with the primary investigator.

Your cooperation is also asked to be available for follow-up contact if further questions arise and to review, as a member check, any direct quotations or information related to your identity in final documents prior to publication in order ensure the validity of the study. Finally, you are being given a copy of this informed consent to keep for your own records.

As a participant to this interview, I consent to (please check one):

Permission to have this interview audio-recorded and notes taken by the interviewer
Permission to have this interview audio-recorded only
Permission only to have notes taken by the interviewer during the interview

I also consent to the following (please check one):

Permission to identify participant and use direct quotations in published material
Permission to use direct quotations while maintaining anonymity in published material
Complete anonymity without the use of direct quotations in any published material

I _______________ (please print name) am aware of the above stated information as well as the information provided in the informational letter. I consent to participating in this interview, a potential follow-up interview, and to provide a member check of the case study report. I also acknowledge receiving a copy of this consent form.

Signature:__________________________  Date:______________________

If you have questions about your rights as a research participant, please contact: Jill Parsons, Health Sciences Ethics Review Officer, Ethics Review Office, University of Toronto, at telephone [enter number] or by email: [enter email] [local Ethics Review Committee representative] who can be reached at [contact information].
Appendix F: Semi-Structured Interview Guide

Background

What is the current context in your country with regard to HIV/AIDS and ARV drug access? What led to the decision to locally produce patented ARVs?

Factors Influencing Technology Transfer Arrangements

What led to the development of the current TT arrangement? What are the most important factors that shaped the transfer arrangement? How have national policies in place affected the development of the transfer arrangements? How have international policies affected the development of the transfer arrangements? How has the manufacturing and technological capacity of the recipient firm affected the development of the transfer arrangements? How would you compare your country’s situation with those of others in your region?

Process of Technology Transfer

How much communication is there between supplier and recipients firms? What are the terms or conditions of the transfer arrangement? What is/was the duration of the transfer arrangement? What have been the processes involved in the transfer of technology? What type of knowledge was/is exchanged during the transfer (for example, technical, informational, managerial, training, etc)? How was knowledge exchanged during the transfer? What are the end goals of the transfer arrangement? What was the greatest obstacle in the transfer arrangement? What are the most important elements of effective technology transfer? How would you compare this arrangement with other possible technology transfer arrangements in your region?

Contextual

How would you define technology? How would you define technology transfer?
Appendix G: Guidelines for ARV Procurement under Global Fund Financing

The Global Fund Quality Assurance policy sets out guidelines for procuring ARVs in fund recipient countries. These guidelines classify ARVs and their manufacturers. The classes are based on the level of quality assurance a product and its manufacturer has achieved:

**Class A** – WHO Prequalification.

**Class B** – Stringent drug regulatory authority (DRA) approval, such as the United States FDA.

**Class Ci** – Good Manufacturing Practices (GMP) certificate from a stringent DRA or WHO Prequalification Programme letter confirming GMP compliance of manufacturing site and proof of ARV dossier submission to DRA or WHO Prequalification Programme.

**Class Cii** – GMP certificate from stringent DRA or WHO Prequalification Programme letter only.

If there are two or more class A or B manufacturers available for any given ARV and the ARV is available from these manufacturers (i.e., sufficient quantity of finished product can be supplied within 90 days from date of order), then the product *must* be procured from these manufacturers.

For example, tenofovir has three Class A/B manufacturers that are FDA approved and placed on the WHO Prequalification list: Gilead Sciences, Aspen Pharmacare, and Matrix Laboratories. In December 2008, there were four additional manufacturers awaiting WHO prequalification evaluation for their generic versions of tenofovir. Until their prequalification, these versions of tenofovir fall under Class Ci of the Global Fund guidelines (WHO, 2008c).
If there is only one or no equivalent pharmaceutical product that meets Class A/B standards, or if the Principal Recipient (i.e., ARV procurement officer in developing countries) determines that the product is unavailable, then funds may be used to procure Class Ci and Class Cii ARVs, in order of priority. If the Principal Recipient intends to buy pharmaceutical products under Option Ci and Cii, he/she must notify, in writing, the Fund Portfolio Manager at the Global Fund Secretariat and seek approval.