



TECHNOLOGY TRANSFER AND LOCAL MANUFACTURING OF PHARMACEUTICALS: THE SOUTH AFRICAN CASE

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“... We believe that in the area of indigenous pharmaceuticals, there are untapped opportunities for economic growth, skills and job creation...” (South African Minister of Science and Technology, 2009)

ABBREVIATIONS AND ACRONYMS

AU – African Union

ARV – Anti – Retroviral

TT – Technology Transfer

R&D – Research and Development

IP – Intellectual Property

LDCs – Least Developing Countries

OTC – Over the Counter

APIs – Active Pharmaceutical Ingredients

TB – Tuberculosis

WHO – World Health Organization

SSA – Sub – Saharan Africa

DTI (the) – Department of Trade and Industry

SADP – South African Drug Action Programme

MCC – Medicines Control Council

IMPP – Interchangeable Multi – source Pharmaceutical Products

NDP – National Drug Policy

INN – International Non – proprietary Name

MPC – Medicines Pricing Committee

BBEE – Broad – based Black Economic Empowerment

US FDA – US Food and Drug Administration

SADC – Southern African Development Community

1. INTRODUCTION

1.1 Background

Technology transfer (TT) is the process of developing practical applications from the results of scientific research. TT is also the process of converting scientific findings into useful products for society. Thus in a broader sense, TT is anything that increases the capacity of people to benefit economically and/or socially from innovation.

Technology transfer is therefore a complex, long and usually expensive process of research and development (R&D) spanning basic research, applied research and commercial development. Technology transfer affects a society's economic well being both directly and indirectly by resulting in new products, services and jobs. While the debate continues over more specific claims of economic impact, it is generally accepted that TT has been of economic benefit to all countries that have promoted it and have active innovation systems. The success of TT (especially in the US) has attracted interest from several other countries who have changed their laws and policies to allow for better management and transfer of Intellectual Property (IP); in Africa this includes countries like South Africa and Kenya.

A key example of the classic three – tier R&D process involved in most TT can be found in the discovery and development of drugs – the pharmaceutical industry. In this industry, technology transfer refers to the processes that are needed for successful progress from drug discovery to product development to clinical trials to full-scale commercialization, or it is the process by which a developer of technology makes their technology available to a commercial partner that will exploit the technology. The TT being referred to in this note shall focus on the aforementioned regarding local manufacturing of drugs and vaccines for type II and III diseases in South Africa.ⁱ

Technology transfer is a legal concept, in that at the international level, common but differentiated commitments are made by countries to facilitate its flow from the north to the south. TT is equally an economic concept, because TT flows follow investment climates and are determined more by economic considerations – markets, competitiveness and factors of production than anything elseⁱⁱ.

Arguments abound that the right to health is a fundamental human right not a social, cultural and economic right. However, it is widely recognized that for global health needs to be met, there is an obvious need to increase resources for health R&D. Africa, where many developing and least developing countries (LDC) are found is a major target beneficiary of products of health R&D (particularly into types II and III diseases), if not the R&D itself. However, recognizing that “re-invention of the wheel” to deal with the myriad health problems that African countries encounter is not only unnecessary but not the best use of limited resources; transfer of technology then becomes an important driver of health R&D.

Globally, the importance of pharmaceutical TT for developing countries as an important health and economic improvement tool has been recognized at the highest levels, as amply demonstrated in article 66.2 of the trade related aspects of intellectual property

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(TRIPS) agreement and element four of the Global strategy and plan of action on public health, innovation and intellectual property.

1.2 Objectives

The objective of this study is to produce a short policy and solution oriented note on the South African Experience on technology transfer in local manufacturing of drugs and vaccines for types II and III diseases. The note briefly addresses the following:

1. The general socio-political context for local production of pharmaceuticals in South Africa;
2. The general regulatory environment: the enabling regulatory framework, economic and social realities on the ground and institutional set up;
3. Relevant situations where such technology transfer in local production has been successful and where it was not;
4. The main factors, including drivers/incentives and barriers for technology transfer in the South African context;
5. Recommendations of what can be done by home and host countries and firms to increase flow and quality of technology transfer in local manufacturing.

This note is to support the WHO/ICTSD/UNCTAD/TRALAC African dialogue on Technology Transfer and local manufacturing to be held in Cape-Town, South Africa from the 10th – 11th of December 2009.

1.3 Methods

This note is specifically policy and action oriented and not necessarily academic. The preparation of the note was based on simple literature searches and documents provided by the World Health Organization (WHO) coupled with informal interviews held with various stakeholders within South Africa and internationally.

2. PHARMACEUTICAL PRODUCTION IN SOUTH AFRICA

2.1 The Importance of the South African Pharmaceutical Industry

Africa has a consumer market of between four to five billion tablets – capsules (tab – cap)/year considering only attendance to people with HIV/AIDS, Malaria and Tuberculosis (TB) symptoms. Thirty – six percent of this African market is accounted for by South Africa, Nigeria and Tanzania, the only countries having an individual demand enough to use the theoretical installed capacity of a pharmaceutical plant with a single production line for tablets and another one for capsules for HIV/AIDS, Malaria and TB medicines on a single shift (i.e. more than 300 million tab – cap/year) (AU, 2009). The need for pharmaceuticals both within South Africa and the rest of Africa is large and growing. This is especially true given that 30 million Africans are HIV-positive yet only one million are on ARVs; 300 – 500 million cases of malaria occur in Africa each year, but few are treated; and there are annually some two point four million cases of tuberculosis but treatment is sporadic and poorly managed. Urbanization in Africa (such as has occurred in South Africa) and its attendant life style diseases such as

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cardiovascular and diabetic illnesses, further underpin the importance of Africa being self-sufficient in the production of medicines (*Maloney and Segal, 2007*). South Africa has the greatest potential to becoming a strong leader in this area.

2.2 General overview

South Africa has a relatively well-developed pharmaceutical industry, comprising a complex network of manufacturers, distributors and dispensers. Facing numerous challenges regarding the provision of increased access to equitable and cost-effective healthcare, the South African health industry has undergone significant change over the past few years especially in the areas of the structure and funding of the industry. Considering that a number of drugs are soon to lose their patent protection, there is increasing demand for such primary health care level drugs such as generic antibiotics and over – the – counter (OTC) drugs. Over the past few years, there have been a number of mergers and take-overs, as the industry has restructured to meet competitive challenges. Multinational pharmaceutical companies continue to dominate the industry (*Mbendi, 2009*).

Various kinds of local production take place in South Africa, including primary production of chemicals and limited local production of generic active pharmaceutical ingredients (APIs). Despite the presence of over 90 registered pharmaceutical operations in South Africa, the majority of firms are operating only as sales and marketing offices, with R&D and production being undertaken overseas (*Maloney and Segal, 2007*). Locally produced medicines are mostly generic, and the majority of the production facilities are privately owned; accounting for only a small proportion of national requirements (*WHO, 2005*).

2.3 Local Manufacturing and Distribution

Generally in South Africa there is limited local production of generic active ingredients, however drug formulation and last step synthesis is common among the local subsidiaries of multinational drug companies (*Mbendi, 2009*).

A study conducted for the World Bank in 2005 showed that locally owned South African manufacturers sourced thirty nine percent of active ingredients, ninety seven percent of packing materials and forty nine percent of excipients locally. On the other hand, local subsidiaries of multinational drug companies sourced one pint five percent of active ingredients, thirty six percent of packing materials and twenty percent of excipients locally. The non – locally sourced inputs came mainly from India and China, thus overall the value currently added across the pharmaceutical value chain in South Africa is relatively low (*Kaplan and Laing, 2005; Maloney and Segal, 2007*). The 2005 study also found that local producers in South Africa often lack regular strategic planning and tend to focus on prioritization rather than standards and targets. The local subsidiaries of multinational drug companies however generally evaluated their business strategy every five years. In South Africa, it normally takes twenty four to thirty six months for new chemical entities from local manufacturers to be registered. It takes approximately the same amount of time to register the first generic, while for existing products or new indications for existing products it takes about twelve to eighteen months to get registered. These times are up to four times higher than what is considered to be international best practice (*Kaplan and Laing, 2005; Maloney and Segal, 2007*).

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Pharmaceuticals distribution in South Africa occurs through dispensing doctors, pharmacists with wholesale licenses and wholesalers as well as buying groups. Some companies, or groups of companies, have their own distribution systems. Dispensing occurs via both public and private channels (*Mbendi, 2009*). Private local producers have identified problem areas including too many points of sale, theft, several mark – ups along the value chain to pharmacy without much consideration being given to the actual costs and value added. On the other hand, public local producers have been concerned about thefts, poor information regarding drug requirements of local hospitals, untimely payment for stock supplied and lack of exporting infrastructure (*Kaplan and Laing, 2005*).

2.4 Recent Developments and Trends

Since the 1990s, the global pharmaceutical industry has experienced a shift in industry dynamics stemming from both a thinning drug pipeline and rising drug development and production costs. As a result, most companies have been consolidating their production and manufacturing activities through mergers and acquisitions; creating “centres of excellence/expertise” in a few countries characterized by large, low-cost units in logistically well-placed areas attractive to service major markets. Unlike India and China, South Africa has been rather negatively affected by this trend (*Maloney and Segal, 2007*).

South Africa used to have much larger capacity in production, but many of these sites have been closed down and/or rendered obsolete (mainly belonging to multinational R&D – based companies). As of 2007, only ten companies had production factories in South Africa, with another six using local companies for contract manufacturing and packaging, and even this is also on a downward trend. Other reports indicate that over 30 companies have closed over the past 5 years. Owing to their inability to compete against Indian and Chinese imports, local producers have been scaling down to achieve better economies of scale, while local subsidiaries of multinational drug companies have been focusing on fewer areas of expertise (*Kaplan and Laing, 2005; Maloney and Segal, 2007*). These trends suggest that production is generally more efficient overseas than locally. However this results in a heavy dependence on other countries in order to meet South Africa’s drug needs. In 2007, employment stood at about 16,000 people, or about one point three percent of the total manufacturing labour force (*Maloney and Segal, 2007*).

Recent pricing control policies, aimed at improving price equity and distribution, have been blamed by industry as further compounding the already deteriorating drug manufacturing situation. The government’s strong focus on primary health care coupled with the burden of the HIV/AIDS epidemic have led to severe cut-backs in funding for upstream research. This has invariably led to falling skills availability which is additionally unevenly distributed across the health sector. E.g. the number of pharmacy graduates per year from South Africa’s universities dropped from 450 students only a few years ago to 320 in 2007, and only fourteen percent of registered pharmacists work in the public sector (*Maloney and Segal, 2007*). Other factors affecting local production include restrictions from intellectual property rights and patent requirements; wide fluctuations in cost per unit; the high cost of bioequivalence tests for each product (required for

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prequalification by the WHO) and the high cost of active pharmaceutical ingredients (APIs) when purchased in small quantities (*WHO, 2005*). On the whole, at the global level, South Africa's competitiveness as a drug manufacturer has been decreasing.

According to South Africa's department of trade and industry (the DTI), the pharmaceutical industry is the fifth largest industry contributing to South Africa's trade deficit (830 million USD in 2005). The sector experienced weak export growth (two percent in USD terms between 2005 and 2006), and has a demand for skills that are in short supply in the country. The ratio of imported to exported pharmaceuticals ready for retail sale rose from approximately 8:1 in 1998 to 17:1 in 2006. Imports of pharmaceuticals in finished dosage form grew from 1.1 million USD in 2007 to 1.4 million USD in 2008 (a growth of twenty four point nine percent). South Africa has also moved from being a net exporter of medical textiles to a net importer. The overall trade deficit in the healthcare sector, including pharmaceutical, medical devices and medical diagnostics, was more than 3 billion USD in 2007. The country faces a growing reliance on imported pharmaceuticals and medicines, posing a risk to the security of supply, coupled with stagnant exports and a widening production capacity and technology gap for future exports (*Maloney and Segal, 2007; The Citizen, 2009*).

The preceding notwithstanding, South Africa remains by far the largest pharmaceutical producer in Africa and is also the only sub – Saharan African (SSA) country that has a generic manufacturing company with WHO prequalification for some of its anti – retroviral (ARV) products. Compared to other African countries, it also has a relatively well developed long-term strategy that includes the manufacture of active ingredients for its products, thereby aiming to ensure sustainability in production.

3. THE REGULATORY ENVIRONMENT

3.1 Introduction

Improved provision of and access to healthcare are together considered clearly a public policy priority in South Africa by the industry, public sector as well as civil society groups. Pharmaceuticals are a crucial component of this. This is reflected in various aspects of South Africa's legislation and forms the baseline for sometimes even opposing views/approaches adopted by various stakeholders including the local manufacturing industry and civil society organizations. Reinforcing this national commitment, the African Union has now pledged to improve pharmaceutical capacity and provision on the continent (*AU, 2009*).

3.2 South Africa's National Drug Policy & Pricing Regulations

Since 2004 when South Africa moved to become a democratically governed state, there have been many policy developments. An important development was the formulation of the National drug policy which aimed at addressing several issues that included developing an equitable pricing plan for drugs used in the public and private sectors and developing specific strategies to increase the use of generic drugs in South Africa. The policy is legislatively supported by the Medicines and Related Substances Control Act

(101 of 1965). This policy was to follow a clear and logical system for reducing inefficiency and waste and improving efficiency and effectiveness through the development of an adequate pharmaceutical strategies infrastructure and was to be implemented by the South African Drug Action Programme (SADAP), established within the Department of Health (*NDP, 1995*). The main driver for this and other policy shifts was governments desire to increase equity in what was a highly skewed healthcare and pharmaceutical sector (*Maloney and Segal, 2007*). E.g. in 1990 the private sector was responsible for eighty percent of the country's total expenditure on drugs, although sixty to seventy percent of the total volume of pharmaceuticals was consumed in the public sector (*NDP, 1995*). The Medicines Control Council (MCC) is responsible for rationalising drug registration, controlling the registration of practitioners and the licensing of premises, enhancing the inspectorate and laboratory functions, and promoting other quality assurance measures. The MCC plays a prominent role in facilitating the harmonisation of drug regulation and control in Southern Africa (*NDP, 1995*).

As part of the NDP, a sector-wide medicines pricing committee (MPC) exists to monitor and regulate drug prices – including the benchmarking of medicines as part of the pricing regulations of 2004 (*Beaumont and Klink, 2007; Gray, 2009*). The committee is composed of health economists, pharmacoeconomists, representatives from the Department of Finance, the DTI, the procurement unit of the department of health, the department of state expenditure, and consumer representatives. As part of the policy, all drugs at the primary care level are to be supplied free of charge. At the secondary and tertiary levels a fixed affordable co – payment for drugs supplied by the state is levied. Systems of exemption exist. Where the State deems that the retail prices of certain pharmaceuticals are unacceptable and that these pharmaceuticals are essential to the well being of any sector of the population, the state is to make them available to the private sector at acquisition cost plus the transaction costs involved. In order to favour generic drugs and their production in the country, the NDP promotes the use of interchangeable multi – source pharmaceutical products (IMPP), using the international non – proprietary name (INN), or generic name. This is aimed at reducing drug costs and expenditure (*Gray, 2009; NDP, 1995*).

3.3 Perceived Impact of Policies on Local Industry and Society

Although the broad thrust of the South African government to improve health equity via the NDP has been lauded, there has been serious contestation (mainly by the pharmaceutical industry) on the nature, mode of implementation and capacity to implement the policies. The policy and regulatory environment is said to have compounded the earlier mentioned lack of value – adding activities in the local South African drug manufacturing sector. Even though there have been some gains in re – adjusting what was a highly skewed healthcare and pharmaceutical sector, presently some twenty percent of the population is served privately but consumes around 275 USD/capita per year, and eighty percent is served publicly but consumes 15 USD/capita per year (*TAC, 2009; Maloney and Segal, 2007*). Also as earlier alluded to, local drug manufacturers have complained that the process for registration and approval of drugs and clinical trials and licensing producers to carry out manufacturing in South Africa by the MCC has problems regarding clarity, implementation of quality standards and timing

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leading to delays that are up to four times higher than what is considered to be international best practice (*Maloney and Segal, 2007*).

The local manufacturing industry and other stakeholders have described the pricing policies put in place by the MPC as “deeply problematic”, “lacking transparency and economic rationale” in addition to being “methodologically flawed”, especially because based on various benchmarks, generic drugs are to be priced at forty percent of the resulting originator priceⁱⁱⁱ (*Beaumont and Klink, 2007; Maloney and Segal, 2007*). Local industry believes that the pricing policy alienates multinational companies in South Africa, leading them to limit themselves to sales and marketing, and renders segments of the industry economically unviable^{iv}. The situation is said to be even worse for generic manufacturers who claim they are unable to make impact projections since their prices are to be based on the benchmarked originator price. Some within industry and other stakeholders are also concerned that even the social policy goals of government may be damaged by the pricing proposal. This is because pharmaceutical companies often cross-subsidise prices in the public sector with the prices in the private sector which are higher. Thus it is projected that benchmarking in the private sector will lead to a natural increase public in public sector prices to make up for the shortfall (*Maloney and Segal, 2007*). Despite all these concerns, South Africa has already achieved up to a twenty one percent decrease in ex – manufacturer price level for the private market (*SAPTA, 2005*).

3.4 Legislation, Policies, Technology Transfer, TRIPS and HIV/AIDS

Apart from control of medicines pricing, South Africa has various other domestic mechanisms, ranging from the constitutional mandate to progressively realize access to healthcare through the local manufacture of pharmaceuticals, to measures flowing from the 1997 amendments to the Medicines Act, the National Health Act of 2003, the Broad – based Black Economic Empowerment (BBEE) Act to address issues of access and the recently agreed plan to combat HIV/AIDS and in the on-going debates over the Health Charter (*SAPTA, 2005*).

In the face of a looming HIV/AIDS epidemic affecting almost 25 million people in South Africa, in 1997, President Nelson Mandela signed the amended Medicine and Related Substances Control Act (Act 90) in order to create a legal framework within which to promote the availability of more affordable medicines (especially HIV/AIDS – related drugs) via parallel imports and compulsory license. The South African Pharmaceutical Manufacturers' Association, together with 39 multinational pharmaceutical industries opposed this amendment act and filed lawsuits against the government, alleging that the changes in the law violated the trade related aspects of intellectual property (TRIPS) agreement. Strong pressure from access campaigners, civil society and international public opinion led the companies to withdraw their suit in April 2001. This impasse between the public and pharmaceutical companies in South Africa brought the impact of patents on public health to international attention. Subsequently the Doha ministerial declaration of November 14, 2001 (the Declaration) and the World Trade Organization (WTO) general council decision of August 30, 2003 (the Decision) have placed the issue of access to affordable medicines in a new light, requiring appropriate implementation strategies by developing countries to benefit from the TRIPS flexibilities. Despite all these legislative and policy triumphs, accessible and affordable HIV/AIDS medicines still remain a major challenge in SSA including South Africa (*Osewe et al, 2008; Sun, 2002*).

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“South Africa has incorporated the TRIPS flexibilities into its domestic legislation by virtue of the Patents Act of 1978 and its subsequent amendments and the Medicine and Allied Substances Control Amendment Act of 1997, satisfying the requirements for local production. Though the 1997 law may indeed be TRIPS – compliant, it is also TRIPS – plus, offering greater protection for patent owners than required by the TRIPS Agreement. The country also has vibrant provisions in its Competition Act of 1998, which have been used in the past to address the issue of ARV pricing and voluntary licensing for local production” (*Osewe et al., 2008*). “Although South African patent law provides for compulsory licensing, the relevant provisions could be considered TRIPS – plus because they require the agreement of the patentee (or a hearing when such agreement is lacking)” (*Osewe et al., 2008*). The closest that South Africa came to issuing a compulsory license was in a case brought by the AIDS Law Project, a South African civil society organization against two South Africa based multinational pharmaceutical companies. This resulted in the two companies issuing voluntary licenses to Aspen Pharmacare Holdings Limited (a local South African company) and two other generic companies for the local production of generic versions of stavudine, nevirapine, lamivudine, zidovudine, and combinations thereof. The agreement reached further allowed for the export of the drugs manufactured under license in South Africa to any other SSA country, based on a royalty payment of five percent (*Osewe et al, 2008*).

“The South African government’s rollout of ARV’s together with the implementation of various models of voluntary licensing in the field of HIV, are two factors that have increased access to medicines. It is estimated that some 110,000 – 115,000 South African patients can now access ARV’s through products using both the original and voluntary licensed products” (*SAPTA, 2005*). This effect is thought to have been further enhanced by the full implementation of a Single Exit Price on a manufacturer level.

4. EXAMPLES OF “TECHNOLOGY TRANSFER” IN SOUTH AFRICA

I have chosen to place TT in the heading above in quotation marks because most of the arrangements made between the local South African manufacturer and the external do not include actual TT. Rather a license is granted to the local manufacturer whose own responsibility it is to conduct their own "reverse engineering" from scratch and register the product without the benefit of relying on the earlier registration of the originator product among others. Also, most of the ARVs produced by the South African local manufacturers are from imported generic ARV APIs without the involvement of any actual TT.

The only genuine example of comprehensive TT can be found in the first example below – the deal between Eli Lilly and Aspen Pharmacare regarding the manufacture of capreomycin and cycloserive, for the treatment of multiple drug resistant (MDR) TB for the South African and regional markets.

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In the table below, I have tried to describe some of the successful TT activities that have taken place in the South African Pharmaceutical industry. Although most of the TT described was born out of years of contention between brand owners and civil society, there are not many obvious situations where such TT failed. One example however is that of the South African generic drug firm Thembalami Pharmaceuticals. Thembalami was created as a joint venture between the South Africa-based pharmaceutical group Adcock Ingram and India-based generic drug firm Ranbaxy. It is presently known as Ranbaxy and Sonke. The company withdrew its bid to supply the South African government with ARVs licensed from GSK and BI. Ranbaxy voluntarily recalled all of its HIV/AIDS drugs in South Africa because of problems with a research company that conducted studies to determine if the generic drugs offered the same "therapeutic value" as the brand-name versions. A company report to the WHO had highlighted problems with the bioequivalence studies for tablets of the antiretroviral drug Avocomb – which contains the antiretrovirals zidovudine and lamivudine – and subsequent investigations revealed similar problems with other products. At the time, Thembalami was expecting to produce a generic of BI's nevirapine that would have cost 30% to 40% less than the originator brand (*Medlinks, 2004*).

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Technology transfer recipient (s)	Technology Donor(s)	Product	Type of transfer	Details
Aspen Pharmacare	Eli Lilly	Anti – TB drugs	Manufacturing	Lilly is providing both capreomycin and cycloserine at a fraction of their cost to WHO Green Light Committee-approved DOTS – Plus treatment programmes around the world. Lilly has signed a technology transfer agreement with Aspen Pharmacare Holdings, Ltd company in South Africa. In addition to making available the necessary manufacturing know – how, Lilly is providing financial assistance for the purchase of equipment (liophilization equipment, necessary for the freeze – drying step of injectable production) and/or conversion of manufacturing facilities and technical training for various stages in the manufacturing processes. The Lilly MDR – TB Partnership is a uniquely comprehensive initiative with the Green Light Committee of the World Health Organization, the U.S. Department of Health and Human Services’ Centres for Disease Control and Prevention (CDC), Brigham and Women’s Hospital (BWH), an affiliate of Harvard Medical School, the International Council of Nurses (ICN) and Purdue University to increase the number of trained personnel and drugs available to treat the expanding crisis of MDR TB. Lilly has also invested in its own facilities to enable it to double its current production of capreomycin, one of the essential drugs used to treat MDR TB (<i>Grace, 2004</i>).
Aspen Pharmacare Enaleni – Cipla (formerly Cipla – Medpro) Feza Pharmaceuticals	GSK, Boehringer Ingelheim (BI), Bristol Myers Squibb (BMS)	ARVs	Licences for manufacturing	GSK and BI/BMS issued voluntary licenses to Aspen and three other generic companies for the local production of generic versions of stavudine, nevirapine, lamivudine, zidovudine, and combinations thereof. One implication of the new agreement is that the four generics companies will be able to sell the ARVs to governments in sub-Saharan Africa, based on a royalty payment of five percent, thereby getting around access

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Biotech Laboratories				<p>problems exacerbated by the domestic legislation in some of these countries that is in excess of that required by TRIPS (<i>Osewe et al, 2008</i>).</p> <p>Aspen launched its first generic ARVs, stavudine capsules of 20 mg, 30 mg, and 40 mg in August 2003. Aspen is the leading supplier of generic medicines to both the private and public sectors in South Africa. Currently, Aspen has an installed capacity of 5.5 billion for tablets and capsules. It has prequalified all three of its stavudine products with WHO and can therefore supply them under the Global Fund arrangements. The US Food and Drug Administration (FDA) has also tentatively approved its combination pack of lamivudine-zidovudine and nevirapine tablets. Three inspections of Aspen production facilities in 2005 by the FDA, the UK Medicines and Healthcare Products Regulatory Agency and WHO found the plant and processes to be compliant with international standards. As part of its vertical integration program, Aspen has also purchased an API plant in Cape Town, Together with its technology partner Matrix, it intends to begin producing APIs at this plant under a joint venture arrangement called Astrix. According to the management of Aspen, the end – state target market projection of Astrix is to manufacture APIs for supply to manufacturers of ARVs on the entire African continent (<i>Osewe et al, 2004; e – drug, 2004</i>).</p> <p>Enaleni (a generic company incorporated in South Africa in 2003) bought all shares in Cipla – Medpro in December 2005. Cipla – Medpro was one of the first companies to register generic ARVs in South Africa. Enaleni – Cipla is now the third largest manufacturer of generics in SSA and a potential provider of a first line</p>
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				<p>regimen of ARVs. It provides AZT or zidovudine, 3TC or lamivudine, combivar (AZT/3TC combination) as well as nevirapine and d4T or stavudine, and provides a portion of the d4T used for government's ARV rollout (<i>Avafia et al, 2006; AEGiS, 2004</i>).</p> <p>Feza Pharmaceuticals is a joint venture between Creative Outsourcing Solutions International and African Healthcare Solutions and has a licence for the manufacture, import, distribution and sale of ARVs containing AZT or 3TC. To date, however, Feza has not been selling the said ARVs in the South African market (<i>Avafia et al, 2006</i>).</p>
Ranbaxy and Sonke (formerly Thembalami)	Merck & Co. (MRK)/MSD (Pty) Ltd	ARV	License to manufacture	<p>Merck & Co., Inc., (the parent company of MSD (Pty) Ltd. South Africa) signed an agreement to grant a non-exclusive patent license for the manufacture and sale of a generic version of efavirenz to Ranbaxy (at the time Thembalami Pharmaceuticals (Pty) Ltd., a local South African pharmaceutical company). This license covers South Africa and other countries in the Southern African Development Community (SADC), and will apply to both the public and private sectors in these countries (<i>Avafia et al, 2006</i>).</p> <p>Ranbaxy previously operated under the name Thembalami Pharmaceuticals which was a joint venture between Ranbaxy and Adcock Ingram. In February 2006, Ranbaxy was entered into a joint venture agreement with Community Investment Holdings (CIH) to establish Sonke pharmaceuticals, whose mandate is to market and to distribute ARVs manufactured by Ranbaxy (<i>BioSpace, 2004</i>).</p>
Aspen Pharmacare	Gilead Sciences	ARV	License to Manufacture	<p>Aspen entered into a nonexclusive agreement with Gilead to produce the antiretroviral drugs Viread and Truvada. Aspen will have exclusive distribution rights</p>

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				for the drugs in Africa under the terms of the deal. Gilead will provide Aspen with the ingredients and technology to make Viread and Truvada – which is a combination of Viread and Emtriva, known generically as emtricitabine, and Aspen will seek licensing approval in African countries where the drugs are not already registered (<i>Avafia et al, 2006; The body, 2005; IFPMA, 2009</i>).
Adcock Ingram	Baxter	Large Volume Parenterals	Manufacturing	Adcock Ingram Critical Care, is South Africa's largest supplier of hospital and critical-care products, blood systems and accessories as well as products used for renal dialysis and transplant medication has a 60 year relationship with US-based Baxter International. Adcock Ingram is licensed in South Africa to produce a range of large-volume parenterals under license from Baxter. This included elements of technology transfer and the licensor's quality supervision (<i>Adcock Ingram, 2009</i>).
Adcock Ingram Aspen Pharmacare	Merck & Co. (MRK)/MSD (Pty) Ltd	ARVs	License to manufacture	In July 2006 Aspen obtained a voluntary licence from MSD for efavirenz. South Africa's second largest generic manufacturer, Adcock Ingram, obtained voluntary licence from MSD for Efavirenz in 2004, but production did not start until 2007. Currently Aspen and Adcock have voluntary licences for over 20 ARVs, made from generic ARV APIs (<i>Kudlinski, 2009</i>).

5. FACTORS INFLUENCING TECHNOLOGY TRANSFER IN SOUTH AFRICA

5.1 Drivers/Incentives for Technology Transfer

- i. Good business and manufacturing practices: Aspen took good advantage of the voluntary license offered by GSK, BI and BMS to successfully develop into and sustain a viable local ARV manufacturing company. It did so despite competition from already established producers and the need to source APIs from China and India who were themselves competitors. The company's success is primarily the result of its adoption of good business and manufacturing practices, particularly in the areas of product identification and formulation technology.
- ii. Potential for competitive pricing: Aspen balances cost to remain competitive by having higher private sector prices and very low public sector prices. E.g. as of 2008, the stavudine, lamivudine, and nevirapine combination costs about 44 USD per patient per month in the private sector, but less than 15 USD per patient for the same ARVs sold to the state which are procured in very large quantities.
- iii. Strategic planning: Aspen outsources all its formulation technology requirements. At the strategic level, therefore, it could be said that Aspen's approach to local production is based on the concept of viable trade in its product identification and competitive advantage in its formulation technology plan. This has created an enabling environment for vertical integration, with prospects for higher capacity utilization and eventual lowering of production costs (*Osewe et al, 2008*).
- iv. Strong economy, environment and civil society: South Africa has a larger and more robust economy compared to other African countries together with a large market for ARVs. The country also has very strong, organized and well informed civil society movement to influence public policy on TT and ARV pricing in addition to the investor-friendly nature of its domestic legislation. All these factors contributed to the success of companies like Aspen in benefiting from TT. For TT to be successful there needs to be a supportive business and scientific environment in the recipient country that is conducive to such arrangements. That environment should include skilled workers, economic and political stability, IP protection, a supportive regulatory environment, market size and potential, and a well-developed national infrastructure of natural resources and transport.
- v. Transparent and efficient regulation: Contentious issues such as benchmarking of prices and policies such as single exit pricing, if not approached expediently, have the potential to discourage TT to local producers. Generic firms maintain they are a commodity industry operating on a model based on high volume and low value; if that value is cut further, some firms argue that their already thin margins will get squeezed and their model will be rendered unviable in South Africa. Because pharmaceuticals are necessarily a highly regulated industry, the regulatory function must be efficient and transparent for TT to be economically viable.

- vi. Opportunities for contingency supply: Multinational pharmaceutical companies are inclined to transfer technology to local manufacturers with the potential to receive when they foresee an inability to meet time scales and volume demands from large procurers such as the WHO or UNICEF. Eli Lilly chose to transfer technology to Aspen for the production of cycloserine and capreomycin in good part because they needed a well positioned partner to manufacture more cheaply and to deliver faster to developing countries, otherwise they were going to have difficulty meeting WHO demand projections. Aspen had the vacant capacity to be "upgraded" to a contingency supplier.
- vii. Public/investor pressure and corporate Image: Patent holders are sometimes coerced into engaging in TT in response to public and/or investor pressure to meet an urgent need. GSK and BI chose to offer voluntary licenses to four South African local manufacturers and withdrew a court case in response to piling public pressure and the risk of severely damaging an already tainted corporate image. It is also known that Calpers, the world's largest pension fund and a GSK shareholder was instrumental in getting GSK to explore licensing deals with generic ARV manufacturers in South Africa, fearing a backlash in the West.
- viii. Access to new machinery, training, know-how and business partnerships: This makes the prospect of TT very desirable to local pharmaceutical manufacturers since the technology, equipment etc could be applied profitably beyond the initial purpose. This was the case in the Eli Lilly – Aspen Pharmacare TT.

5.2 Barriers/disincentives to Technology Transfer

- i. Lack of efficiency: Aspen's main weakness is a high conversion cost when compared with that of India. Its production processes therefore require further automation to improve efficiency and lower costs in that sphere, which could then trickle down into even lower pricing for its products.
- ii. Focussing on the low end: Except in South Africa, local production of pharmaceuticals in SSA has been mainly confined to low – end production of medicines in final dosage forms from imported APIs, rather than high-end production involving the manufacture of APIs. If Africa is to emerge as being self – sufficient in drug production, there is the need for substantial investments into the manufacture of APIs.
- iii. Low market share: Some local manufacturers are importing APIs in relatively small quantities at rather high prices, based on a few pending ARV orders. Local producers also face significant challenges in meeting international quality standards and capturing a critical market share. Greater market share would increase the volume of APIs purchased to the levels needed to obtain better negotiated prices, resulting in lower prices of the ARVs produced (*Osewe et al, 2008*).
- iv. Cost of prequalification: The cost of bioequivalence testing for each product, necessary for the acquisition of WHO prequalification appears to be far beyond

the budgets of most local manufacturers of ARVs and therefore contributes to their inability to attain WHO prequalification for their products. There is benefit in meeting international standards since it opens up the opportunity for trading across not only the rest of Africa but the entire world (including supplying under the Global Fund arrangements), as evidenced by South African local manufacturers like Aspen and Adcock Ingram. The AU and regional economic groupings such as SADC, COMESA, EAC and ECOWAS could further explore funding mechanisms and lead negotiations for promising local manufacturers to hurdle this challenge.

- v. Labour Issues: The pharmaceuticals sector demands relatively skilled labour. A shortage of this is a disincentive to TT. High labour turnover and absenteeism owing to unattractive conditions of service are other negative contributors. The number of pharmacy graduates per year from South Africa's universities dropped from 450 students only a few years ago to 320 in 2007, and only fourteen percent of registered pharmacists work in the public sector (*Maloney and Segal, 2007*).

6. LESSONS LEARNT AND RECOMMENDATIONS

- i. Commitment and collaboration: High-level political commitment (financial and structural support) is required for TT for local production to be successful. This means alignment and communication across departments on a common vision on the role pharmaceuticals are to play in South Africa's industrial and social policies.
- ii. Form strategic partnerships: Like some South African local pharmaceutical companies, others in Africa should seek to form strategic partnerships with well – established pharmaceutical companies through win-win voluntary licensing agreements, joint ventures and other mutually beneficial TT arrangements to enhance sustainable local production in the medium and long terms.
- iii. Provide technical assistance: Like South Africa has been able to do, regional IP organisations should provide technical assistance to their member countries by commissioning special studies to examine the national patent laws and already existing agreements to ensure the inclusion of provisions that maximize the benefits of the TRIPS flexibilities and promote affordable access to medicines for types II and III diseases.
- iv. Countries require support from TRALAC – like organizations in the development of simple administrative structures and IP regimes addressing patent life, compulsory licensing, parallel importing, and data exclusivity all especially related to medicines for types II and III diseases and the drafting of appropriate provisions that empower national drug regulatory authorities in their reliance on, and use of, data for the registration of generics.
- v. Development partners such as the World Bank, WTO, and WHO should be encouraged to support programs that seek to provide simple guidelines and

technical assistance to local pharmaceutical manufacturing companies on the requirements for WHO prequalification and how to avoid delays associated with the application process.

- vi. Focus on sustainability: Regardless of whether South Africa, or any other developing country, can take advantage of technology transfer to locally produce pharmaceuticals, its sustainability depends in large part upon the relative competitiveness of the local manufacturing industry as well as the impact of external factors (overall national health policy, investment incentives etc) (*Kaplan and Laing, 2005*). Presently, the DTI scores pharmaceutical investments among the highest in qualifying for government support (*The DTI, 2008*).
- vii. Take advantage of global trends: The global trend of multinational pharmaceutical companies to consolidate to create large, low-cost units in logistically well-placed areas attractive to service major markets can either be a blessing or a curse. Some South African subsidiaries of multinationals are closing because they believe the country does not offer an attractive enough package to serve as a base for consolidation. R&D based companies may be incentivized to engage in TT with local manufacturers developing as part of the larger trend towards outsourcing non-core activities such that overall production is more cost effective.
- viii. Harmonization: Regulatory authorities in different African countries tend to enforce manufacturing standards at different levels leading to the possibility that for similar standards, the cost of compliance can be significantly different between countries. This does not promote TT across the region.
- ix. Build innovative capacity: Given the severe disease burden in South Africa investment in developing competitive capability in clinical trials could stimulate growth in the R&D – based segment of the pharmaceuticals value chain; otherwise described as “building innovative capacity”. This will also result in inward transfer of knowledge and technology, since trials carried out to international standards will demand extensive monitoring and also augment the critical mass of skilled personnel needed to engage in TT for local production. This investment may come in the form of tax incentives, grants and facilitated linkages with universities and research institutions. In South Africa, the DTI offers attractive incentives to investors in pharmaceuticals (*the DTI, 2008*).
- x. Recognize levels of interdependence: The inter-dependence between industrial policy and healthcare policy when it comes to pharmaceuticals must be clearly assessed and considered in planning for TT. For example, where social goals in healthcare are to be achieved through measures which affect the regulatory and IPR determinants, consideration needs to be given to the economic or investment impacts on TT to the local pharmaceutical industry.
- xi. Be realistic: While never losing sight of the need to seek out the good of their citizens in securing a TT deal for local production, African governments must be constantly aware that companies are also under significant pressure to increase earnings, for which reason they assess TT deals in the same way as they would a commercial

deal, i.e. whether the deal has the potential to earn a reasonable return for the company (in cash or In kind) (*Grace, 2004*).

ENDNOTES

ⁱ The definitions of Type I, II and III diseases, are as referred to by the Commission on Macroeconomics and Health and as further elaborated in the CIPIH report:

- *Type I diseases* are incident in both rich and poor countries, with large numbers of vulnerable populations in each.
- *Type II diseases* are incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries.
- *Type III diseases* are those that are overwhelmingly or exclusively incident in developing countries.

ⁱⁱ With permission from HAI Africa

ⁱⁱⁱ The current pricing proposal in South Africa mandates benchmarking originator drug prices in South Africa against a basket of four comparator countries (Australia, Canada, New Zealand and Spain), and choosing the lowest price of the five countries as the drug price in South Africa. Achieving a suitable benchmarking methodology in South Africa is complicated in that market realities are different from those in proposed benchmark countries including additional transformation requirements (such as those in the Broad Based Black Economic Empowerment system).

^{iv} South African multinational pharmaceutical companies estimate losses of 35% of their South African revenues with the pricing proposal.

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