changes be implemented. This has to go hand in hand with a focus on improving data quality and a gradual implementation of the more refined risk adjustment mechanism. Everyone involved in data collection and reporting needs to understand how data is to be used and how it can contribute to the better functioning of the system.

In addition, patients should also begin to share information on their experiences within the health care system, especially if in switching health plans, they have experienced problems accessing care or have been denied care altogether. Their inputs are essential. Finally, providers should clearly state to their patients if they cannot provide appropriate care as a result of inappropriate incentives from HICs. Disclosing all this information would help raise public awareness about the gravity and importance of these issues. It would also help encourage HICs to reduce their risk selection activities and facilitate demands on policy makers to implement an appropriate, fair and viable redistribution mechanism.

The Price is Right?
Promoting local production for ARVs in Sub-Saharan Africa

Kinsley Wilson, Jillian Cohen-Köhler and Alan Whiteside

Summary: Affordability is a key concern of European donors who finance antiretroviral drugs (ARVs) to treat AIDS in Sub-Saharan African countries. In country manufacture of ARV drugs could favourably affect ARV access through increased affordability; however, generics are a volume based market, relying on economies of scale. The ability of Sub-Saharan African countries to reduce their prices below large-scale manufacturers in India is challenging. Additionally, these medicines must meet WHO prequalification standards. While the cost of second-line ARVs remains a concern, donors should focus resources on other components ARV access, such as the supply of human resources for health, health infrastructure and issues of sustainable financing.

Keywords: ARV drugs, Access to medicines, Developing countries, Generic manufacture, Donor financing

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% (about €1.19 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.1 To equitably access this treatment, the World Health Organization (WHO) emphasises a drug’s rational selection and use, sustainable financing and affordable pricing, while also maintaining reliable health and supply systems.2 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 Organization’s Agreement on the Trade Related Aspects of Intellectual Property (TRIPS). In exchange for international trade liberalisation, TRIPS requires twenty 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 (€11,326).3

Since TRIPS took effect in 1995, international organisations, such as Médecins Sans Frontières (MSF), have encouraged both developing and the 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

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health crises or a 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 scale up in treatment. 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 have an impact on 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, the authors are aware of only one example of this grant accessed for ARV production. In November 2006, a German non-governmental organisation, 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 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). 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.

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 and employment while also saving foreign exchange. However, research contends that a local manufacturing industry is often not a viable alternative for developing countries and does not necessarily reduce prices compared to imported drugs.

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. 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.

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. A least-developing country manufacturer has yet to announce a price publicly. Comparatively, the listed median transaction price in 2007 was US$92 (€62) and US$91 (€61) per patient per year in low income and middle income countries, respectively. 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 to industrialised
countries (where drug discovery most commonly occurs) and the emerging economies of India and China (where the 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 States, 708 individuals in China, 119 in India, 307 in South Africa, and less than 51 in any other reporting Sub-Saharan African country. Therefore, the sheer size of China and India’s skilled human resource population magnifies the industry’s development potential and reduces labour costs compared to 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. 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 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
At the end of 2007, programmes supported by the Global Fund reported that 1.1 million individuals in Sub-Saharan Africa were receiving treatment. These and other donors, especially European governments, the United States President’s Emergency Plan for AIDS Relief (PEPFAR), 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 twenty-four 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 an 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, approximating to 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, 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 ten to twenty times greater than first-line ARVs. Prices for the few generic second-line drugs available are also quite variable. Generic prices for second-line regimes are often greater than those of patented products with median prices ranging from US$948 to US$4,245 (€635 to €2,844) against US$865 to US$2,577 (€580 to €1,727), respectively. 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 Sharpe and Dohme’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 US Food and Drug Administration 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-Saharan African countries as donors stipulate international competitive tenders to procure ARVs. The 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, the governments of their countries, donors or drug companies.

Consideration has and should be taken to develop regional cooperation among DRAs and manufacturers 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 the fragmented health system and poor health infrastructure that limit the availability of treatment and basic care.

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