

The Scientific Crusade for Affordable Medicines

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It is beyond dispute that we are in the midst of a global health crisis. Millions of people around the world, the majority of them living in developing countries, are dying because they lack access to life-saving medications for diseases like AIDS, tuberculosis, and malaria. Cost is a tremendous factor in this crisis.

Two thirds of the value of medicines produced globally is accounted for by companies in five major countries, UK, US, Japan, Germany and France. Large volume markets of lower priced medicines exist in the highly competitive markets of China and India. For the period 1985 to 1999, the share of low income countries in the world dropped from 3.9% to 2.6%, and that of middle income countries dropped from 7% to 4.5%. The share of high income countries increased from 89.1% to 92.2%. (World Medicines Situation, 2004)

The transnational pharmaceutical industry has been going through a period of unprecedented restructuring, most evidently mergers between different companies, driven mainly by cost-cutting measures on Research and Development, production and various other reasons. The mega-mergers for example, Glaxo Wellcome with Smith- Kline Beecham resulting in GlaxoSmithKline, the Hoechst Marion, and Roussel became Rhone-Poulenc Rhorer became Aventis. Aventis with Sanofi became Sanofi-Aventis. These have led to market concentration and reorientation of the global pharmaceutical environment. The global pharmaceutical industry is colossal in size. The industry is characterized by high -value, mainly patented products and low value largely off-patent multi-source products. There is also clustering of manufacturing, outsourcing opportunities and multipurpose facilities

A number of medicines that were patent -protected, have come off-patent. For the period 1997 to 2007, 38 drugs that account for 20% of the global pharmaceutical market by value will come off patent. There has been a changing legislative environment, TRIPS flexibilities (Trade Related Aspects of Intellectual Property Rights), with impact on the generic market. In some countries there has been the removal of tariffs on finished pharmaceutical products.

A critical issue in generic manufacturing is access to Active Pharmaceutical Ingredients (API) and the global market for generic API's is estimated at \$6 billion growing at 8-10 % annually. The critical mass of sales level of API is essential. Both patented and non-patented medicines rely on outsourcing API production. The manufacture of chemicals is not just limited to pharmaceuticals but includes the dyes and other industrial agents, pesticides etc.

From a production point of view, the manufacturing of pharmaceuticals and related products can be classified based on the following:

- Bulk manufacture of synthetic organic chemicals--chemical process
- Pharmaceutical excipient manufacturing
- Bulk manufacture of antibiotics, through fermentation, synthesis through culture of micro-organisms (biological process)
- Preparation of biological and biotechnologically derived products
- Preparation of human and animal derived blood products
- Production of naturally occurring or vegetable sources (alkaloids, insulins, hormones)
- Processing of bulk medicines into finished forms (various dosage forms)
- Production of sterile products (small and large volume parenterals)

There is high level of differentiation, in terms of formulation types, delivery systems, timed released applications. This is of relevance to the initiatives that are underway to promote local production of essential medicines to improve and facilitate access.

The development and manufacture of medicines must be aimed at improving public health and well-being, thereby contributing to economic growth. There should be an alignment of profitability goals of industry and the society's need for improved access, and affordable healthcare.

In 1999 an estimated 1.2 billion people survived on less than one dollar per day, and nearly 2.8 billion on less than two dollars per day. About 90 percent of them live in South or East Asia or Sub-Saharan Africa. As the economic gap between Industrialized and Low Income Countries (LICs) widen, so too is the health gap between rich and poor. This is particularly evident in relation to the HIV/AIDS, tuberculosis and malaria epidemics in Africa. For too long we have accepted the access gap as a fact of life. Twenty eight million people have already died from AIDS and, if things stay as they are, by 2020 the number of deaths will be close to 100 million. Average life span by 2010 will be 27 years in Botswana and Mozambique and in the low 30's in many of their neighboring countries-level not seen since the end of the Nineteenth Century.

Life-saving combination antiretroviral therapy for HIV/AIDS is available-but not to all. During 2001, in high-income countries, 500,000 persons took ARVs and fewer than 25,000 died; in Sub-Saharan Africa, fewer than 30,000 persons took ARVs and 2.2 million die. This huge gap in care has been called a crime against humanity and a holocaust of the poor. It is certainly making us realize that we need to put an end to the global apartheid of poverty and health.

Thailand's Experience in Local ARV Production: a Long-term Solution in Implementing Successful ARV Programmes

HIV/AIDS Situation in Thailand

About 600,000 people are infected with HIV in Thailand, out of a population of 65 million. It is estimated that 2 % of men and 1 % of women are currently living with HIV. There are 20,000 new AIDS and HIV infected patients each year. As a result of successful prevention campaign, the incidence of newly HIV infected has stabilized. Now, Thailand is moving into a more "mature" phase of the epidemic. More and more people are showing symptoms and requiring care. The health care system in Thailand has sufficient resources to treat many common opportunistic infections.

Thailand has experience with antiretroviral therapy since 1988 but the experience has been mixed because of the involved costs and initial poor implementation of treatment in clinical practices.

The Government Pharmaceutical Organization

Government Pharmaceutical Organization (GPO) is a state enterprise under Ministry of Public Health. Its function is to manufacture and supply pharmaceuticals and other medical products to support health services activities of Ministry of Public Health throughout the country.

GPO manufactures more than 300 items of pharmaceuticals especially drugs in the National List of Essential Drugs including biological products. Total number of employee is 2,200 and annual sale volume is about USD 100 million. GPO spends about 2 % of the sale to research and development.

GPO realizes that one of the factors that is critical for access to antiretroviral drug is affordable prices. Drugs should be available at affordable prices so that they fall within the financial reach of health services and individual in need.

The Research and Development Institute of GPO performs basic, applied and pilot scale research which is essential not only to develop new pharmaceutical products but also to compliment and improve existing technologies.

This unit has been working on the formulation development and bioequivalence studies of HIV/AIDS-related drugs since 1992. Thailand is the first developing country to make generic ARV available in 1995.

The first generic ARV drug was AZT, in 1995, which GPO sold to Ministry of Public Health to prevent mother-to-child transmission.

In 2001, a fixed-dose generic combination drug known as GPO-VIR was invented, which contains either 30 or 40 mg of stavudine, 150 mg of lamivudine and 200 mg of nevirapine.

This fixed-dose combination has simplified treatment; -increased patient compliance reduced the emergence of drug resistance HIV, and lowered the price.

At the time, patients receiving this regimen took 6 pills a day at a cost of about 85 USD a month for generic drugs and 474 USD for original drugs.

Production of GPO-VIR began in April 2002. Patients take two pills a day at a cost of 27 USD a month, or 324 USD a year. GPO-VIR is now used by about three quarters of the more than 100,000 people being treated for HIV infection in Thailand.

GPO's Generic Production

Manufacturing of any generic product is possible only after bioequivalence study. All production phases take into consideration the ever more stringent Good Manufacturing Practice (GMP) on manufacturing and quality assurance. GPO now manufactures 11 types of antiretroviral medication in more than 25 dosage forms, with sufficient production for 100,000 patients. Increased production is planned, as well as a new production facility with improved quality standard.

Attempts to reduce the price from 5 to more than 20 times of its original price depending on the sources of raw materials is now possible due to GPO's generic production of these drugs.

Thailand will achieve the goal of improving affordability through the increase of local production where the costs are lower and quality can be maintained. In 2002 Thai government has established a policy of universal coverage for antiretroviral treatment and also offered to supply drugs to 30,000 patients in Cambodia, Laos and Vietnam.

The Africa Mission: Transfer of Pharmaceutical Technology

World medicine production is on the increase but it is concentrated in a few industrialized countries. Despite the growth observed over the years, studies indicate that Africa's share of world medicine production continues to decline. Low-income countries (including in Africa) account for about 3% of global output and over 90% of the medicines used in the African Region are imported.

It is estimated that about half the population in the African Region lack regular access to essential medicines. In the context of constantly changing socio-economic environment, globalization of trade and patents, increasing health care costs and medicine prices, the demand for essential medicines remains largely unmet in the African region. The increasing incidence of HIV/AIDS has exacerbated the problem of access to essential medicines.

An assessment of local production of medicines that was carried out by WHO/AFRO indicated that out of the 46 countries in the Region, 37 have pharmaceutical industries; 34 have secondary level production (production of finished dosage forms) and 25 have tertiary production (limited to packaging or repackaging). Some countries have both secondary and tertiary production, whereas 9 countries such as Botswana, Chad, Congo, Equatorial Guinea, Gambia, Guinea, Guinea Bissau, Mauritania and Sao Tome and Principe, have no pharmaceutical industries. The majority of production facilities are privately-owned and locally-produced medicines are mostly generic which satisfy only a small proportion of national requirements.

Major constraints in the production of essential medicines in the Region included inadequate resources (human and financial), increasing costs, underutilization of capacities, tough competition from imported medicines and inability to meet GMP requirements.

The Problem of HIV/ AIDS, Tuberculosis and Malaria in Africa

Africa's 785 million people continue to suffer from a huge burden of preventable and treatable disease due to HIV/AIDS, tuberculosis (TB), and Malaria. These diseases cause incalculable human suffering with devastating human and economic impacts.

Although there is no cure for HIV infection, antiretroviral drugs (ARVs) can dramatically reduce HIV-related morbidity and mortality and improve quality of life. The progress that has been made in the global response to AIDS is real-but inadequate. An estimated 1.3 million people throughout the world are now using antiretroviral medications for HIV infection in low and middle-income countries, representing 20 % of the 6.5 million estimated to need it. Scale-up in Africa, the continent hardest hit by the HIV epidemic, has been most dramatic, rising from 160,000 at the end of 2003 to 810,000 by the end of 2005.

One of the possibilities of increasing access to ARVs is transfer of technology for domestic production. Experiences so far indicate that technology transfer is not widely applied to the African continent. Enabling factors for building local manufacturing capacity through technology transfer are local technical expertise, incentives for mutual technical cooperation, and "warming up" of the local market.

For instance, in Tanzania, of the 33 million people living in that country, an estimated two million people are living with HIV/AIDS. By 2010, AIDS is expected to increase the death rate in Tanzania by more than 50 %, and life expectancy will drop from 65 to 37 years. Nine percent of Tanzania's active labor forces were HIV-positive in the year 2005. Each year in Tanzania, approximately 50,000 to 60,000 children are born HIV-positive. Some 170,000 Tanzanians living with HIV/AIDS are children under the age 15 and younger.

Currently only one third of the sub-Saharan African countries have capacities for secondary manufacturing. Very often when they do have capacities, they are not in full good manufacturing practices. Today's best available fixed-dose combination of stavudine, lamivudine and nevirapine for which local production capacities are not available in Tanzania. In order to reduce the morbidity and mortality rates among the Tanzania population, the local production of HIV/AIDS-related drugs would provide a long-term solution.

Tanzania Pharmaceutical Industries (TPI), a pharmaceutical manufacturing company, 40 % owned by the government, 60 % by private entrepreneurs, has teamed up to manufacture artemisinin-based antimalarial drugs at affordable prices. Because Tanzania is one of the countries hardest hit by HIV/AIDS, Tanzania has decided to start manufacturing life prolonging drugs for AIDS patients. Since the country has an acute shortage of highly qualified technical and industrial pharmacist, TPI has entered into an agreement with experts from Thailand who have agreed to cooperate and transfer knowledge and know-how and all the necessary information to support the production of pharmaceuticals and in particular antimalarials, antiretrovirals and anti-TB drugs.

Producing Affordable drugs to treat Malaria:

The increase in malaria disease burden in Africa is of great concern nationally and internationally. An estimated 300-500 million new cases of malaria and an estimated 1.5-2.7 million deaths occur each year. The highest mortality (more than 90 %) occurs in children less than 5 years old in Africa. *Plasmodium falciparum* malaria is associated with severe morbidity and mortality, and in the absence of early diagnosis and effective treatment, it may be fatal.

The top condition for which patients are admitted to the hospitals in most African countries is malaria and it is one of the commonest causes of death in the medical wards.

Most of artemisinin-based antimalarial drugs available in private pharmacies in African countries, are imported, and are unaffordable to the population as prices are too high. It is, therefore, necessary to manufacture them locally or have simple formulation produced in the countries for poor malaria patients.

Tanzania spends 3.4 % of its Gross National Product on malaria. Each year the fight against malaria costs the country USD 100 million. Thirty percent of the people who go to clinics have malaria. Twenty five percent of the children who die in hospitals, die of malaria.

The Tanzania project focused on the development and implementation of newly formulated antimalarials (Artesunate) with Tanzania Pharmaceutical Industries (TPI) including:

1. The technical backup for TPI in areas of production and system development, such as standard operating procedures
2. The formulation of finished dosage forms
3. Quality improvement and quality assurance

The newly developed drug name Thaitanzunate was launched officially by Tanzanian Minister of Health in September 2003. The cost of treatment for adults is 0.80 USD. Paediatric dry syrup formulation has been manufactured in May 2004.

Action Medeor, the German NGO supporting this project, acts as partner and responsible for the technology transfer and for non-profit procurement in Tanzania

The recommendation in Guidelines for the Treatment of Malaria by WHO in 2006, is to use artesunate or artemisinin suppositories only as pre-referral treatment and to refer the patients to a facility where complete parenteral treatment with artesunate, quinine or artemether can be instituted.

Since manufacturing facility is not available or ready for production of antimalarial drugs in tablet form in Burkina Faso, Gambia and Senegal and the use of artesunate suppository is within WHO guideline, the production of artesunate suppository production was carried out in selected hospitals. Priority is given to countries where quality control laboratory is available. In other words, artesunate suppository is a life-saving drug against malaria that does not require manufacturing facilities for its preparation and could be administered conveniently and expeditiously by the hospital to malaria infected patients.

Training of personnel on artesunate suppositories production at Centre Hospitalier National Pediatrique, Charles De Gaulle, Ouagadougou, Burkina Faso; Royal Victoria Teaching Hospital (RVTH), Banjul, The Gambia; Centre Hospitalier Aristide Le Dantec, Dakar, Sénégal and Usine Malienne De Produits Pharmaceutiques (UMPP), Bamako, Mali have been successfully completed. Quality control of the products has been conducted, most of which comply with specifications.

The pharmaceutical plant in Gabon is ready for the technology transfer project of Royal Thai Government related to the production of fixed-dose combination of antiretroviral and antimalarial drugs provided that HPLC is available for quality control of manufactured products.

The objective of the project has been successfully achieved whereby technology transfer on local production of affordable antimalarials has been simultaneously implemented in all of the five West African countries vis-a-vis the varied needs and local conditions of available facilities with approval of the concerned health authorities.

Transfer of Technology in the Local Production of Antimalarial Drugs in Mali

The Royal Thai Embassy in Dakar has an intention to continue the Embassy's 2006 Project on the transfer of technology in the local production of antimalarial drugs in West African countries. Thus, the principal objective of 2007 project is to increase the manufacturing capabilities of the Malien factory (UMPP) in Mali in order to produce antimalarial drugs on an industrial scale for local market and regional consumption.

Local production of essential drugs deemed by the government of Mali as a priority and crucial contribution not only to the improvement of healthcare but also to the social and economic well-beings of its population.

The personnel of U.M.P.P now masters all the production techniques. They are highly capable of manufacturing artesunate 50 mg tablets and amodiaquine 153 mg tablets as well as a fixed-dose combination of AS/AQ. In other words, U.M.P.P is the first factory in the whole of the African continent that possesses the know-how to manufacture these two antimalarial drugs at an industrial scale, and in particular the fixed-dose of AS/AQ.

The implementation of this phase of the project owes its success to a very large extent to the competence, dedication, efforts and discipline of the personnel of U.M.P.P which is the greatest strength of the factory. Despite the factory's lack of modern facilities and degraded infrastructure, its personnel's contribution to the functioning of the factory is clearly illustrated in the good maintenance of the existing, albeit, old machines and their diligent operation of their designated responsibilities. Furthermore, the personnel of the U.M.P.P demonstrated the ability to utilize the available resources and develop their skills to adapt to the constrained circumstances in order to overcome the challenges and difficulties of production. This factor tremendously helps to overcome many challenges facing the implementation of the project and gives hope and aspiration for U.M.P.P to realize their objective of producing the first high quality co-blistered artesunate and amodiaquine tablets and also fixed-dose combination of AS/AQ in West Africa that is accessible for all.

It is expected that U.M.P.P. will greatly contribute to the realization of the country's National Health Policy Objectives of making available to all Maliens, essential pharmaceutical products of quality at a price that individual and the community can afford whenever it is needed.

Local Production of Essential Medicines in East Africa (Tanzania, Zambia, Ethiopia and Uganda)

In Tanzania, an agreement was reached on the Memorandum of Understanding between Berlin Pharmaceuticals of Thailand and Tanzania Pharmaceuticals Industries (TPI) to co-operate and exchange knowledge, know-how and support each other on the procurement, distribution, sale and production of essential pharmaceuticals over a period of five years. During this period at least five products would be manufactured.

In Ethiopia, Bethlehem Pharmaceuticals takes into consideration the priority diseases which at present afflict the population of the country such as HIV/AIDS, malaria and tuberculosis, has indicated its

readiness to manufacture quality and effective drugs for the three diseases and satisfy the demand of the country at affordable prices.

In Ethiopian Ministerial Council meeting in November 2006, pharmaceutical sector is one of four sectors that Ethiopian government has aimed to support and promote efficient local pharmaceutical production. In the course of the implementation of this policy, utmost effort has been made to ensure that local production is being encouraged, emphasized and revitalized.

Conclusion

There are technical and human resources gaps that need to be filled up via technology transfer. Creation of local good manufacturing site capable of receiving the technology transfer represents the best viable and long-term sustainable option for greater access to medicines in African countries. It will also represent the focal point of knowledge and skill oriented society and for a transition into value added manufacturing.

To improve access to essential drugs, the stimulation of local manufacturing of essential drugs provide a win-win solution to all involved parties and most importantly it represents a viable and sustainable means of tackling the problem at its source.
