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Review

Production of antiretroviral drugs in middle- and low-income countries

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This review outlines the main issues concerning the production of antiretroviral (ARV) drugs in middle- and low-income countries and the relevant political, legal and technical requirements for supporting such production. The requirements for efficient local production, including the manufacture of generic and branded products and public demand, have been considered from economic, market and socio-political perspectives. A steady and consistent government policy is crucial to success. Additional crucial factors in establishing local production are adequate infrastructure, qualified human resources in technical and managerial areas, and production–distribution logistics systems. The creation or strengthening of a national drug regulatory agency is a basic requirement. Production of ARVs relies on the structure of the international market for active pharmaceutical ingredients (APIs), which are highly monopolized for inclusion in branded or patented drugs, or are concentrated in a few Asian generic companies. Countries seeking to begin local production must develop strategies to overcome the various barriers. For instance, sub-Saharan African countries may benefit from developing multilateral health agreements with neighbouring countries. Such agreements are recommended and should be complemented by technology transfers, especially for the manufacture of APIs. Achieving a production level that is sustainable in the long term is crucial to maintaining patients' access to ARVs.

Introduction

Many authors in recent decades have discussed whether local production facilitates access to essential drugs, such as antiretroviral (ARV) medicines. Some argue that local ARV production is essential to making the medicines available [1]. Despite the complexity of producing these drugs, given the relative lack of infrastructure and human resources in many countries, local ARV manufacturing has been successfully implemented in several middle- and low-income countries in recent years [2]. The difficulties involved in local production can be at least partially overcome and local production is feasible [2,3]. The most important factor in fostering ARV production in low- and middle-income countries is the genuine willingness of their governments to support the establishment of such an industry (Table 1).

Due, in part, to the recent deterioration of the global economic situation, it is increasingly difficult to obtain international aid for countries of low or middle income. For example, low-income Tanzania is likely to experience challenges in its fight against HIV as reductions in funding from major donors, such as Canada, Denmark and the United States, are not made up for by funding from local sources. Fatma Mrisho, the Executive Chairperson of the Tanzania Commission for AIDS (TACAIDS), stated: '*As we are talking now, I have just met representatives from CIDA and DANIDA – both of whom have confirmed to me that they will no longer contribute to the National Multi-Sectoral Strategic Framework (NMSF) – with effect from 2015. We, as a nation, need to get prompt replacement for the funding, failure of which all the achievements made in the fight against HIV and AIDS for more than 20 years will experience a heavy blow… The US President's Emergency Plan for AIDS Relief (PEPFAR)… has been a leading financier of HIV/AIDS interventions in the country, is also reducing funding*' [4].

Therefore, it is important that countries seek the autonomy to ensure access to essential medicines and

Table 1. Actions by which governments can promote and support local pharmaceutical production

Define clear and supportive government health and industrial policy priorities for the production of ARVs and APIs, including drugs under patent.
Introduce fiscal relief, incentives and subsidies for a defined period of time for both new and existing generic pharmaceutical and pharmochemical industries to guarantee increased market participation by these manufacturers.
Obtain international support, mainly from partners such as the WHO, UNITAID and others, to accelerate international prequalification for already established manufacturers.
Train pharmaceutical personnel in all production steps, quality control, storage and distribution of APIs and finished formulations with guaranteed quality assurance.
Garner participation from the private sector in the key strategies set by the government.
Build partnerships through South-South collaboration for technology transfer.

API, active pharmaceutical ingredient; ARV, antiretroviral.

health care for their populations. Nations must establish strategic industrial policies that may include partnerships with both neighbouring and more distant countries for technology transfer. Countries must also create or strengthen regulatory frameworks to adapt to a reality in which the state is responsible for the health of its population on the basis of an understanding that a healthy population is a primary condition for a free and sovereign nation. As an example of such an approach, the Brazilian Federal Constitution states: (article 2) '*Health is a fundamental human right; the State must provide the conditions essential to its full realization*'; (paragraph 1) '*It is the State's duty to ensure health through the formulation and implementation of economic and social policies aimed at reducing the risks of diseases and other hazards and to establish conditions that ensure universal and equal access to actions and services for its promotion, protection and recovery*' [5].

Potential government roles in industrial processes

Any industrial process involves economic and social factors. The economic factors include those that attract private or public investment within the context of an existing marketplace. Additional factors in the case of drugs include, for example, a product's expected lifespan in the local market, position in the world market and international price (which may be influenced by factors other than patent protection), as well as the optimal time for the product to enter the market. The 'social return' reflects the government's motivation in promoting the production of goods and services that reduce the country's dependence on external imports. The most important social return in the case of pharmaceutical production is the accumulation of technological knowledge and capacity to produce drugs, which fosters additional expansion of knowledge and innovation in companies and research institutions, and ultimately results in income generation and increased local employment in the medium and long terms.

Local production of drugs can have advantageous effects on a country's balance of payments by reducing imports and increasing exports, and can potentially reduce drug prices. These potential effects provide incentives for countries to attract capital to invest in producing medicines once they have reduced the financial risk of doing so. Over time, countries engaging in pharmaceutical production must devote significant attention to the restrictions imposed by intellectual property rights, quality assurance and the necessary overall infrastructure. Since the advent of Trade-Related Aspects of Intellectual Property Rights (TRIPS), no country has been able to guarantee its citizens access to essential medicines mainly due to patent rights, which impose a monopoly situation that is only partially balanced by the flexibilities of TRIPS: '*the Doha Declaration reaffirmed countries' right to use TRIPS safeguards such as compulsory licenses or parallel importation to overcome patent barriers to promote access to medicines, and guided countries in their use*' [6]. In low- and middle-income countries, local production is optimal wherever large volumes of ARVs are needed and economies of scale may be achieved. Otherwise, such countries should look to establish regional agreements to accomplish local production. What, then, are the factors that can guarantee sustainable and effective production of high-quality ARVs in low- and middle-income countries?

The development and manufacture of medicines must aim to improve public health and well-being, thereby contributing to economic development. Industry can and should be profitable in alignment with society's needs for affordable health care and improved access to medicines. Factors that undermine the production of affordable, high-quality and essential medicines include: weak national public policy, lack of adequate working capital, monetary inflation, high costs of production inputs, lack of adequate objective information on sources and prices of pharmaceutical starting materials, and a scarcity of human resources. However, well-established local production of essential medicines and

ARVs increases technological competence and skill; it also creates spin-off industries, such as accessories for the pharmaceutical industry, including wrapping materials, packaging and disposable materials, among others. These effects of local production can all result in new commercial activities that can add to overall development.

Production and formulation of active pharmaceutical ingredients

The most complex and costly component in drug formulations is the production of active pharmaceutical ingredients (APIs) [7]. Any country that aspires to be less dependent on the international market must establish a strategic plan, set priorities and realize that reducing costs and improving efficiency will reduce API prices. Reducing dependence on the international market will require countries to define their priorities on the use of APIs and to decide whether to produce APIs for first- or second-line drugs, as this decision will determine cost savings and added value. The price structure for an API will depend on where it is manufactured, while several other factors can also influence the impact of the API price on the overall price of the formulated product (Table 2).

These different scenarios, to some extent, explain the wide variation among prices of medicines supplied by different companies in the world market, as can be observed, for instance, with efavirenz (which ranges from 200 to 600 USD/kg) and tenofovir (from 385 to 725 USD/kg) [8]. The final ARV price is also affected by the concentration of the API in the tablet or capsule; for example, the cost of efavirenz in 600 mg tablets may account for up to 93% of the total cost of production, whereas in the 50 mg tablets – a formulation to treat children – this proportion drops to 50%. Hence, more expensive APIs will have a greater proportional impact on the cost of production and consequently on the final ARV price. In fact, API prices above 100 USD/kg will result in an average of 80% of the manufacturing costs. Direct manufacturing costs largely depend on the API prices, and prices ranging from 55% to 99% are actually available. Therefore, data on the cost of antiretroviral drug production may provide benchmarks for purchasers to negotiate lower prices and support sustainable business models. Indirect inputs, such as salaries, equipment costs and scale of production will also impact, but at a lesser extent, the final ARV costs. The ability to achieve price reductions in line with production costs will have critical implications for sustainable treatment for HIV/AIDS in the developing world. Reducing a drug's price is currently possible for many antiretrovirals as demonstrated by some studies elsewhere [9].

Requirements for ARV production

The existence of a national drug regulatory agency (NDRA) is essential to ensure the quality of pharmaceutical products on the market. A country seeking to produce medicines must have its industrial plant(s) inspected and approved by an NDRA. At the same time, the NDRA must recognize its responsibility to inspect all industrial plants and rigorously evaluate applications submitted by manufacturers to register the medicines they intend to produce (Table 3). NDRA authorization must be required to establish an industrial factory in accordance with international standards for factory design and all legal environmental requirements [10,11]. The priorities established by the NDRA in approving installation of factories, certifying Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP), and testing bioequivalence will determine whether patients have early access to these medicines (Table 3).

Table 2. Various production scenarios that affect ARV prices

Factories producing both APIs and finished formulations
Companies that are both pharmochemical and pharmaceutical, like a number of Indian pharmaceutical manufacturers, produce both APIs and finished drugs. The API price has less impact on the price of the finished product when the API is manufactured by the same company that produces the finished product (that is, vertical integration) rather than purchased from an outside entity.
Factories that depend on buying APIs from an international supplier
The impact of the API price on the price of the finished product will depend on the policies of the country importing the API. If this country provides subsidies to the pharmaceutical industry for importing raw materials for manufacturing priority medicines, the finished product should be available at a lower price.
Factories in countries with local producers of APIs
If API manufacturers are present in a given country, it is easier for producers of the finished formulations (that is, medicines) located in that country to negotiate lower prices for the APIs than if the producers of the medicines were purchasing the APIs from companies abroad. Thus, the impact of API price on the finished formulation will be lower than the impact of API price on the same finished formulation produced in countries where local API producers are not present.

API, active pharmaceutical ingredient; ARV, antiretroviral.

The costs of bioequivalence tests are high and must be subsidized by governments or through international loans. These costs may vary among countries because they depend on existing internal support, such as laboratorial infrastructure and technical capability. If such support is lacking in a country, the necessary tests can be performed abroad. Of course, this approach deeply affects pricing. For example, financial constraints, lack of expertise and the absence of national guidelines on bioequivalence tests have been recognized as major issues in Kenya [12]. In Brazil, the costs of ARV bioequivalence tests range from 100,000 to 300,000 USD, essentially depending on the test length and the quantity of volunteers or patients needed; such costs also reflect the tests' clinical pre-conditions and any formulation proofs that include either new molecules or new associations created between known drugs. Table 4 describes some of the infrastructure requirements for factories to produce ARVs.

The primary argument for local production of ARVs is essentially the existence of demand and the ARV market clearly reflects this tendency. Far from contracting or remaining constant, the global market continues to expand. The main force driving this trend is that the need for ARVs is changing dramatically with the gradual incorporation of recent therapeutic advances. For instance, while the 2010 WHO guidelines recommended the start of antiretroviral therapy (ART) when an individual's $CD4^+$ T-cell count decreased below 350 cells/mm^3, the 2013 WHO guidelines recommend middle- and lower-income countries initiate treatment in adults living with HIV when their $CD4^+$ T-cell count is 500 cells/mm^3 or lower. Furthermore, the treatment of HIV-infected children is advised to start as early as possible. Widespread adoption of these recommendations obviously requires an increase in the availability of ART worldwide. At the end of 2012, close to 10 million people were receiving ART in low- and middle-income countries. However, over 16 million other people who are eligible for ART under the new 2013 guidelines do not have access to ARV drugs [13].

Production and marketing strategies must take these changing conditions into account. However, rationalizing the production of ARVs in terms of availability and access may require fundamental changes to the production of branded and patented products. The companies that produce branded and patented ARVs tend to market their drugs primarily in high-income countries because these companies often have profitable monopolies in such countries. These companies' commercial strategies include transferring licenses and policing prices, as well as making specific investments (Table 5).

In the areas of generic APIs, active intermediates and generic ARVs, India and China are the most important suppliers. As producers, Indian and Chinese companies aim chiefly to expand their sales in national and international markets and essentially behave similarly to other companies, with export strategies, global funding politics and product innovation that also includes new pharmaceutical formulations. The main strategies of Indian and Chinese producers of generic ARVs are summarized in Table 6.

Local production of ARV medicines: advantages and obstacles

There are a number of examples of successful local ARV production in developing countries that have been able to establish and consolidate their positions despite

Table 3. Key responsibilities of an NDRA

Periodic inspection of the industrial process to certify GMP and GLP in factories.
Registration of medicines by evaluating applications, with particular attention to issues concerning formulation development, stability studies, quality control and, in the case of generic drugs, all studies regarding bioequivalence.
Promotion of health inspections at ports, airports and other entry points of imported medicines, raw materials and other related materials.
Establishment of specific rules and regulations for post-market surveillance.

GLP, Good Laboratory Practices; GMP, Good Manufacturing Practices; NDRA, national drug regulatory agency.

Table 4. Infrastructure requirements for factories that produce ARVs

Availability of pure water, stable electricity and gas supplies, and an adequate system for medicine transport.
Development of human resources consisting of skilled professionals and technicians with expertise in pharmaceutical development, quality control, quality assurance, manufacturing processes, regulatory affairs and engineering for pharmaceutical industries.
Establishment of a diversified portfolio including other medicines to guarantee the sustainability and availability of products for which demand is low. Ideally, this portfolio would be achieved through collaborative agreements with productive neighbouring countries.

ARV, antiretroviral.

the persistence of certain obstacles. In Latin America, companies in Brazil, Argentina and Cuba are currently able to satisfy their internal ARV demand. In Asia, India and China are successful local producers, and Thailand has consolidated the production of ARVs through government pharmaceutical organizations (GPOs) to meet their national demand. In Africa, the main argument against local production is the impossibility of producing ARVs that are cheaper than those produced in India or China. However, the South African Minister of Science and Technology declared in 2009 '*…we believe that in the area of indigenous pharmaceuticals, there are untapped opportunities for economic growth, skills and job creation…*' [14].

In sub-Saharan Africa, countries with consolidated local ARV production have clearly confirmed the importance of local production to afford local populations increased access to ARVs. Although Aspen Pharmacare is the largest ARV manufacturer in South Africa, there are other private companies that also intend to produce ARVs. In Ghana, the most important manufacturer is Danadams, a private company born from a joint venture between Ghana Dapong and the Chinese Adams Pharmaceutical. In Uganda, the most important manufacturer is the importer Quality Chemicals, which produces ARV medicines locally in association with the Indian pharmaceutical company Cipla. In Nigeria, the most important manufacturer is Nigeria-German Chemicals PLC. Suppliers in Zimbabwe and Kenya are Varichem Pharmaceuticals and Universal Corporation, respectively. Presently, only Aspen Pharmacare, Varichem Pharmaceuticals, Universal Corporation and Quality Chemicals are pre-qualified by the WHO as suppliers of certain specific products. ARVs in Africa are also currently produced in Kenya, the Democratic Republic of the Congo, Tanzania and Zambia.

Fortunately, most of the countries listed in Table 7 have NDRAs, although these agencies could be more efficient. In some countries, registering a new generic formulation takes approximately 24 months [14], and certification of ARVs could and should be recognized on an international and not only a national basis. In most cases, production is primarily geared to supplying the demands of the various ministries of health. Sub-Saharan countries that intend to begin local ARV production should consider doing so at a regional level, using already existing international agreements. This strategy would make ARVs available to citizens of countries that do not by themselves meet the minimal criteria for local production due to lack of infrastructure, roads, energy, water, demand, human resources, and/or financial and government commitment. Such a broad goal could be adequately supported through the involvement of various African economic organizations, such as the Economic Community of West African States (ECOWAS), the Economic Community of Central African States (ECCAS), the West African Economic and Monetary Union (WAEMU), the Common Market for Eastern and Southern Africa (COMESA) and the Southern African Development Community (SADC). Some of these entities have already expressed interest in taking such an approach. However, applying this political strategy would not exempt the countries involved from fulfilling the following two requirements: firstly, as countries that receive medicines, they must strengthen their regulatory capacities and quality

Table 5. Marketing strategies used by branded ARV companies

Offering voluntary licenses with technology transfer to markets with high demand for products.
Creating generic subsidiary pharmaceutical research and development companies, such as ViiV Healthcare, a global specialist HIV company established by GlaxoSmithKline and Pfizer in 2009 to deliver advances in treatment and care for people living with HIV. The Japanese company Shionogi joined ViiV Healthcare in 2012, with a focus on both national and international markets, to sell patented drugs.
Establishing tiered pricing using various criteria. As a result of this approach, some countries pay two, three and four times more than other countries with the same income levels.

ARV, antiretroviral.

Table 6. Marketing strategies used by generic ARV companies

Export APIs to countries that have already established local production, such as Brazil.
Establish a merger or joint venture with a local manufacturer, such as Danadams Company in Ghana.
Develop fixed-dose combinations of ARVs and off-patent drugs.
Set lower prices for generic ARVs to respond to global initiatives.
Build new facilities for producing ARVs using external funds; one example of this approach is a factory in Mozambique that was financed by Brazil.

API, active pharmaceutical ingredient; ARV, antiretroviral.

Table 7. Current local production of ARVs by region: advantages and obstacles

Local production	Advantages	Obstacles
Latin America[a]	Strengthened local skills in pharmaceutical development and production Reduced ARV prices Consolidated certification of NDRA by international organization: Argentina (ANMAT) South–South collaboration in technology development Established strategies for partnership for the development of production (PDP): Brazil Sustainability of ARV production due to guaranteed government market	Low API production due to international dependence on intermediate supply Delays in NDRA registration of medicines Difficulties in chain of distribution of medicines in rural areas: Brazil High prices of patented drugs even when voluntary licenses are established
Asia[b]	Existing high market demand for APIs and intermediate molecules: China and India Production of high volume of generic ARVs to meet international demand under umbrella of international funders: China and India Promotion of joint ventures with local manufacturers in different regions: China and India Fostering of pre-qualified products by the WHO and FDA: China and India Strengthened local skills in pharmaceutical development and production: Thailand, China and India Reduced ARV prices: Thailand, China and India South–South collaboration in technology: Thailand and China Fostering of sustainability of ARV production due to guaranteed government market: Thailand	Lack of API production: Thailand Little research and development for innovative drugs: India and China High prices of bioequivalence tests: Thailand High prices of patented drugs even when voluntary licenses are established
Africa[c]	Reduced ARV prices: after Varichem Pharmaceuticals began local production, monthly treatment cost per patient decreased from 30 USD–50 USD to 15 USD in Nigeria Reduced ARV prices: Aspen Pharmacare has been responsible for satisfying high demand for ARVs in South Africa, and with some government subsidies, its prices are highly competitive with those of generic Indian companies Reduced ARV prices: in Ghana, Danadams' prices are reported to be extremely competitive[d] Local manufacturing would prevent shortage of ARVs at country level: Ghana Significant industry ties to national health, police and other government entities, facilitating strategic approach to national AIDS treatment programmes Strengthened local skills in pharmaceutical development and production Improved controls over medicines with regard to storage, distribution and quality Increased understanding of patent law and its restrictions on access to medicines Increased regional integration and health-care capacity	Importation of generic ARVs from China and India High prices of bioequivalence tests, delaying registration and prequalification Patented drugs Lack of legislation for universal access (as is found in Brazil) to ARVs and giving governments authority to authorize local production Tiered pricing by branded companies High prices of imported APIs because Africa has so far been highly dependent on raw materials

[a]Refers to Brazil, Argentina and Cuba. [b]Refers to China, India and Thailand. [c]Refers to South Africa, Uganda, Nigeria and Ghana. [d]According to Sarah Perkins, Faculty of Law at the University of Toronto (Toronto, Canada), *'If Danadams could afford the bioequivalence tests to obtain WHO approval; it could be supplying even more of the country's drug needs at prices on a par with or lower than those from India*' [10]. API, active pharmaceutical ingredient; ARV, antiretroviral; NDRA, national drug regulatory agency.

control to ensure the safety of drugs available in the local market; secondly, they must establish a common strategy to test bioavailability to resolve logistical challenges to acquiring APIs and ARVs, ensure product quality and competitive pricing, and establish mechanisms to export and distribute products to other African countries. South-South Technology Transfer Programs can play an important role in expanding ARV production within the sub-Saharan region. Policies and strategies used by some developing countries, such as India, Brazil, China, Cuba and Thailand, could be the bases for Memoranda of Understanding that include provisions for African manufacturers' acquiring expertise in ARV re-engineering, industrial plants outfitted to be adequate for GMP, GLP and Good Clinical Practices, bioequivalence tests, and other relevant technologies.

In this way, it seems feasible that such countries could meet their demand for ARVs through regionalized ARV production.

Conclusions

Initiating production of ARVs or any other essential drugs depends fundamentally on governments' commitments to the notion that health is a human right and duty of the State. Despite innumerable barriers, implementing local production of ARVs is feasible in middle- and low-income countries, as has already been shown in some Asian, South American and African countries. Public investment to develop infrastructure, regulations, suitable human resources and logistics are key to creating a favourable environment for such production. Fair business agreements among governments and branded and generic API producers will also help. Industrial policies may be synergized by developing regional partnerships among neighbouring countries and fostering international technology transfer at several levels to increase countries' expertise in API manufacture and formulation of final products. In this context, partnerships for product development may be very successful. Creating or strengthening NDRAs is equally crucial to guarantee the success of ARV portfolios and the availability of high-quality medicines to patients. Furthermore, the political issues involved in support for local production of ARVs may serve as a template for nations facing other public health challenges, such as the need for medicines to treat hepatitis C and neglected infectious diseases.

Disclosure statement

The authors declare no competing interests.

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