WORLD HEALTH ORGANIZATION

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Manufacture of antiretrovirals in developing countries and challenges for the future

Report by the Secretariat

1. Globalization is affecting pharmaceutical industries, influencing national drug policies and shaping national pharmaceutical sectors. Pharmaceuticals account for an increasingly important part of health-care expenditure in both developed and developing countries and almost all governments are battling to contain the associated costs. Managing health emergencies such as HIV/AIDS requires complementary international and national actions in order that those in need receive treatment. The HIV/AIDS pandemic has brought to light unacceptable differences in access to life-saving medicines, including antiretroviral agents.

2. The complex process of pharmaceutical production can be classified into three linked activities: manufacture of active pharmaceutical ingredients and intermediates; production of finished dosage forms from active pharmaceutical ingredients and excipients; and final packaging of finished dosage forms or repackaging of bulk finished products. The whole process requires special technologies, reliable supplies of high-quality raw materials, and dependable provision of top-quality water, electricity, gas and other utilities. It also needs sufficient human resources with specialist knowledge, such as experts in pharmaceutical development, quality assurance and regulatory processes. Even for generic drugs, some research and development is necessary for the manufacture of high-quality products, and the expenses and time incurred are often underestimated. Pharmaceutical plants need a huge initial capital outlay and take many years to construct; they tend to be located in countries with a good infrastructure, reliable utilities and access to technical expertise.

3. Policy decisions about whether to import essential medicines from reputable sources or to promote local manufacture should be based on a careful situation analysis and a critical appraisal of the feasibility of domestic production. When such a choice is made, the most important objective should be delivery of high-quality essential medicines to the people who need them, at prices that they and the community can afford.

MAKE OR BUY?

4. Many countries are interested in building or maintaining local manufacturing capacity and increasing self-reliance. There may be a complex mixture of health and economic arguments to consider. A country may hope to provide a regular supply of low-cost medicines to public health programmes, through government-owned manufacture of medicines rather than privately-owned local suppliers or overseas suppliers. Some countries consider that government-owned medicine-manufacturing plants may help to reduce foreign-exchange needs, provide employment, improve the

balance of trade and the expansion of exports, and contribute to industrial development and transfer of technology.

5. However, there are significant issues in establishing and maintaining a viable and competitive industry. Nearly all the production cost lies in the primary manufacture of active ingredients, and the opportunity for smaller local manufacturers to cut costs in this area is limited. High quality requires financial resources and small production volumes may not create enough revenue for investing in, ensuring and maintaining quality. A country with manufacturing facilities capable of converting bulk active ingredients imported at high cost into finished products may not impact patients' access to needed medicines.

6. In a recent study,[1] commissioned by the World Bank, countries were divided into three categories:

(a) a first group of large countries, such as Brazil, China and India, with well-developed generic-manufacturing industries and potential for innovation, sufficiently robust manufacturing standards and a production infrastructure to provide medicines for exports with internationally competitive prices and quality;

(b) a second group of countries, such as Egypt, Mexico, South Africa and Thailand, with generic industries that may or may not become internationally competitive, depending on numerous country-specific factors;

(c) a third group of smaller countries, some of which already have domestic production capacity but lack quality control or the human resources to meet demands for technical expertise.

7. Although the World Bank study recognizes that data are insufficient, it suggests that a critical level of industrial and socioeconomic development and human and technical resources must be reached before any indigenous industry can survive.

8. The study makes it clear that a country should base any decision on government involvement in pharmaceutical production on a thorough analysis of the feasibility and economic sustainability of any proposal. Particular attention should be paid to the real costs (including those of highly qualified technical and commercial staff, imported equipment, spare parts and raw materials), the quality and prices with which the locally produced medicines will compete, and the nature and size of the domestic market.

9. An update of WHO's guidelines for developing national drug policies considers that production of medicines and vaccines is, in general, best left to the private sector.[2] The role of a country should move from government ownership or direct management of pharmaceutical production towards effective regulation and inspection of medicines produced by the private sector. Government may promote the quality of locally-produced medicines, and thereby strengthen industrial capacity, by strengthening its regulatory agency and by arranging for training in good manufacturing practices.

[1] Kaplan WA, Laing RO, Waning B, Levision L, Foster S. Is local production of pharmaceuticals a way to improve pharmaceutical access in developing and transitional countries? Setting a research agenda. Available at http://www1.worldbank.org/hnp/hsd/documents/LOCALPRODUCTION.pdf.

[2] *How to develop and implement a national drug policy*, Geneva, World Health Organization, 2001, p.44.

LOCAL PRODUCTION OF ANTIRETROVIRAL AGENTS

10. Most of the general principles mentioned above apply equally to the local production of antiretroviral agents, although product formulation and technical production are often complicated, legal and patent issues abound, and international competition is increasing. Little experience with local product development, quality assurance and manufacture, lack of effective regulatory oversight, and limited resources may complicate the situation in countries striving to manufacture antiretrovirals locally. Small countries will have to show that their local production can meet internationally recognized standards for quality assurance and control, and can offer prices that can compete with world market prices. The potential threat that use of low-quality drugs may contribute to the emergence of drug resistance and the eventual inutility of currently effective drugs should also be taken into consideration.

TREATY OBLIGATIONS AND LEGAL ISSUES

11. Countries with existing local manufacturing capacity or envisaging developing such a capacity for antiretrovirals will need to carefully review their treaty obligations and other legal matters in respect of intellectual property rights. For those affected by the Agreement on Trade-Related Aspects of Intellectual Property Rights measures will need to be taken to consider the possibilities offered under the Doha Declaration of 14 November 2001 concerning the TRIPS agreement and Public Health and the WTO General Council Decision of 30 August 2003 concerning paragraph 6 of that Declaration.

ACTIVITIES BY WHO

12. Some of WHO's current activities[1] directly or indirectly support local production. These include:

(a) the formulation, dissemination and promotion of international norms and standards on efficacy, safety and quality,

(b) information exchange systems, training and technical support for regulatory agencies,

(c) training in good manufacturing practices,

(d) support to national medicines control laboratories, and

(e) provision of information on global market prices for active ingredients of essential medicines.

13. In the specific case of antiretroviral agents, the interagency prequalification project undertaken by WHO, UNICEF, UNFPA and UNAIDS, with the support of the World Bank, provides additional support to medicines manufacturers and national drug regulatory authorities by offering an

[1] WHO Medicines Strategy: framework for action in essential drugs and medicines policy 2004-2007, document WHO/EDM/2004.5, in press.

independent assessment – following rigorous international standards – of products' quality specifications and manufacturing plants.[1] All manufacturers that have applied for prequalification receive feedback about the compliance (or non-compliance) of their products with international standards. WHO is also organizing training courses for national regulatory officials on how to assess quality, safety and efficacy of generic antiretroviral agents. During the three courses organized so far (in the African Region, the Region of the Americas and the South-East Asia Region), regulators participating in prequalification assessment teams have shared their technical experience, including that of common quality failures encountered with individual antiretroviral products. The published list of prequalified products, intended for procurement by bodies in the United Nations system, is increasingly being used in medicines programmes funded by the World Bank and the Global Fund to Fight AIDS, Tuberculosis and Malaria, and can serve as guidance for regulatory authorities with limited resources.

IMPROVING ACCESS TO ANTIRETROVIRAL AGENTS

14. Access to essential medicines, including antiretroviral agents, is based on rational selection, affordable prices, sustainable financing and reliable health systems. These systems include a properly functioning, competent national regulatory authority that can safeguard quality of the antiretroviral agent used. The best prices for such medicines are likely to be obtained as a result of: government commitment to preventing and treating the disease through a strong national AIDS programme; a government policy and legal framework promoting competition between multisource products through full use of safeguards under the Agreement on Trade-Related Aspects of Intellectual Property Rights and other measures legally appropriate to the national setting, such as parallel imports and compulsory licensing; and a well-managed central medicine procurement agency which can obtain economies of scale by pooling demand. Regional cooperation and information sharing between countries and assistance from well-established international procurement organizations with experience of supplying antiretroviral agents may also facilitate effective procurement.

ACTION BY THE EXECUTIVE BOARD

15. The Executive Board is invited to note the report.

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[1] More information is available at htpp//www.who.int/medicines.