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Antiretrovirals and developing countries

Report by the Secretariat

1. In May 2004, the Executive Board at its 114th session noted the report on the manufacture of antiretroviral agents in developing countries and challenges for the future which suggested issues to be taken into account in assessing the economic feasibility and sustainability of local pharmaceutical production of quality medicines in developing countries.¹
2. The present document highlights recent developments, with a focus on intellectual property rights and relevant provisions in international trade agreements that also affect the feasibility and economic sustainability of local pharmaceutical production. It also gives an update on WHO's activities to support local production of high-quality antiretroviral agents.
3. Promoting and sustaining local capacity for manufacturing pharmaceuticals raises a complex mix of health, social and economic considerations. Policy-makers have to assess the feasibility and economic sustainability of local production in the light of social and health objectives. Arguments to start or maintain local production capacity may also include the possibility to make use of compulsory licensing of priority medicines, in compliance with the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). In view of the HIV/AIDS crisis, ensuring access to treatment and care – including affordable, high-quality medicines – has become the greatest priority. Indeed, access to high-quality medicines is central to the progressive realization of the highest attainable standard of health.²

RECENT DEVELOPMENTS

4. The Doha Declaration on the TRIPS Agreement and Public Health reflects WTO Members' appreciation of the correct balance between patent protection and provision of incentives for drug development and access to medicines. Its fundamental tenet is that the TRIPS agreement "can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all." It confirms the right of WTO Members to use flexibilities allowed by the TRIPS agreement, such as compulsory licences and parallel imports. In the case of countries not able to make effective use of compulsory licensing owing to the lack of domestic manufacturing capacity the Decision on the implementation of paragraph 6 of

¹ See document EB114/2004/REC/1, summary record of the fourth meeting.

² See United Nations Committee on Economic, Social and Cultural Rights, substantive issues arising in the implementation of the International Covenant on Economics, Social and Cultural Rights, General Comment 14 (document E/C.12/2000/4, paragraph 43): The right to the highest attainable standard of health.

the Doha Declaration, adopted by the General Council of WTO on 30 August 2003,¹ provided a legal solution to this problem.

5. A recent study of 11 Latin America and Caribbean countries' national legislation on intellectual property rights and several individual country studies found that most countries had not used the full range of TRIPS flexibilities as affirmed in the Doha Declaration.² However, there are also signs of increasing willingness to use those flexibilities. In 2002, Zimbabwe declared a "Period of emergency" that enabled a local producer to produce antiretroviral agents under compulsory licence. In 2003 the Government of Malaysia used the "Rights of Government" provision in the national patent law to allow the import of generic antiretroviral agents from India for use in public hospitals. In 2004 Mozambique and Zambia both issued compulsory licences for local production of antiretroviral agents. It should be noted that in all but the Malaysian case, the TRIPS flexibilities were used in order to enable antiretroviral agents to be produced locally, and their use did not relate to the decision on the implementation of paragraph 6 of the Doha Declaration.

6. In South Africa and recently Kenya, voluntary licences have been agreed between local manufacturers and the innovator companies or patent holders for the production of antiretroviral agents. National legislation in both countries incorporated some of the TRIPS flexibilities and there seemed to be sufficient political impetus for their use. However, voluntary licensing, especially if it is agreed in face of possible compulsory licensing, does not automatically result in the transfer of technology. In the absence of transfer of technology the development, testing and registration of adequate formulations for high-quality medicines require considerable technological skills and will usually take time.

7. In the case of the WTO General Council's Decision of 30 August 2003, which adopted a system to enable the import and export of medicines produced under compulsory licence, some prospective exporting countries have initiated the process of amending national laws to enable export by generic manufacturers, as most national laws do not allow the supply of export markets under compulsory licences. In particular, Canada and Norway have undertaken such changes, while steps are being taken in the European Union, India and Switzerland. There has yet, however, to be a notification of the intention to use the system. One concern has been whether the complex legal solution would provide sufficient economic incentive for generic manufacturers to view the system adopted as a viable mechanism for production and export under compulsory licence. A public-health-oriented interpretation and implementation of the Decision would require, inter alia, simple and speedy legal procedures and a wide choice of potential suppliers of quality generic medicines.³

8. It will also be important to analyse the implications of the end of the transition period at 1 January 2005 allowed under the TRIPS agreement, which delays the application of patents, on local production and supply of generic antiretroviral agents. From 2005 onwards, production of generic versions of new patented medicines will depend on several factors such as, whether there will be effective use of TRIPS-compliant public health safeguards, whether generic manufacturers will be

¹ WTO, Implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health, Decision of the General Council of 30 August 2003, WT/L/540, 1 September 2003.

² Oliveira MA, Bermudez JAZ, Costa Chaves G, Velásquez G. Has the implementation of the TRIPS Agreement in Latin America and the Caribbean produced intellectual property legislation that favours public health? *Bulletin of the World Health Organization*, 2004, **82**(11):815-821.

³ Statement by WHO to the WTO Council for Trade-Related Aspects of Intellectual Property Rights, 21 September 2004 [available at http://www.who.int/medicines/organization/ood/trips_med].

persuaded of the economic feasibility and viability of producing still-patented medicines under compulsory licence, and whether there will be increased cooperation between generic producers and research-based industry.

9. The use of the TRIPS flexibilities may also be affected by bilateral or subregional free-trade agreements that include provisions beyond the requirements of TRIPS agreement (“TRIPS-plus” provisions) which may have implications for the feasibility of production of generics. Some examples of TRIPS-plus provisions are: the extension of patent terms beyond 20 years as compensation for unreasonable delays in patent grant or marketing approval; restriction on the use of compulsory licences; extended periods of data exclusivity; and prevention of national drug regulatory authorities from granting marketing approval for generic products without the consent or acquiescence of the patent holder. Concerns about such TRIPS-plus provisions were acknowledged in resolution WHA57.14, adopted by the Health Assembly in May 2004, which urged Members States, *inter alia*, “to take into account in bilateral trade agreements the flexibilities contained in the Agreement on Trade-related Aspects of intellectual Property Rights and recognized by the declaration on the TRIPS Agreement and Public Health adopted by the WTO Ministerial Conference (Doha, 2001)”.

RECENT SECRETARIAT ACTIVITIES TO PROMOTE LOCAL PRODUCTION WITH ASSURED QUALITY

10. The Secretariat’s activities to support local manufacture of essential medicines, including antiretroviral agents, focus on two technical areas: assistance to Member States in making optimal use of the flexibilities in the TRIPS agreement and the Decision on implementing paragraph 6 of the Doha Declaration, and assistance in promoting the quality of locally produced medicines.

11. Technical support in the area of intellectual property rights has included the production and dissemination of policy documents on the practical implications of international trade agreements, in order to increase awareness and technical capacity. The Secretariat has participated in regional training courses organized by WTO. National training courses have been held and individualized technical support has been given to Member States in adapting their national legislation and in preparing for international, regional or bilateral trade negotiations.

12. Ensuring the quality of locally produced essential medicines has also been a constant concern. Based on the mandate derived from its Constitution, WHO’s Secretariat has been preparing norms and standards on technical areas such as good manufacturing practices, stability and bioequivalence. International Pharmacopoeia monographs for essential antiretroviral agents have been prepared and an extensive international training programme on good manufacturing practices, aimed at both national regulatory agencies and manufacturers, has been in operation for some years. In addition, many technical support and training programmes (for example, on good manufacturing practices and quality assurance of antiretroviral agents) and global and regional networks exist to strengthen national drug regulatory capacity. The prequalification project (see below) has created excellent on-the-job training opportunities for assessors and inspectors from national drug regulatory authorities.

13. The continuing problems with the quality of essential medicines circulating in developing countries and increased complexity of assessing the quality of new essential medicines for high-priority diseases, such as HIV/AIDS and malaria, have lead to a unified approach by bodies in the United Nations system, through the prequalification project of WHO, UNICEF, UNFPA, and UNAIDS, with the support of the world Bank. WHO’s secretariat provides this service to facilitate access to medicines that meet unified standards for quality, safety and efficacy for treatment of

HIV/AIDS, malaria and tuberculosis. The main objective of the project is to ensure that medicines purchased by its partners are of good quality, safe and effective. Because of its transparency, the project now also provides indirect support to national regulatory agencies, nongovernmental organizations and local manufacturers by offering an independent assessment of the products' compliance with international standards for quality, safety and efficacy. In May 2004, the Health Assembly, in resolution WHA57.14, requested the strengthening of the prequalification project.

14. Since June 2004, several generic antiretroviral medicines have been removed from the list due to noncompliance with international standards at the contract research organizations hired by the manufacturers to conduct bioequivalence studies on the products. Two have subsequently been restored to the list after scientific assessment and inspections, and others await submission of new bioequivalence data. Although the delisting of products has caused some difficulties in countries and programmes relying on these medicines, it also demonstrates the high standards been applied. In the longer term, these actions will ensure that safe, effective and affordable medicines are made available to people who might otherwise have access only to substandard products or no access at all.

15. The production of essential medicines, including antiretroviral agents, has also been supported through the publication of information on the sources and prices of active pharmaceutical ingredients. Work is under way to link this information to WHO's activities in order to promote the quality of pharmaceutical raw materials, such as including the latter in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, and inspecting manufacturers of active pharmaceutical ingredients within the framework of the prequalification project.

FUTURE WHO ACTIVITIES

16. The Secretariat intends to continue its global, regional and country activities to promote the use of the available TRIPS flexibilities and support the implementation of the WTO Decision on the implementation of paragraph 6 of the Doha Declaration. The Secretariat will also continue to monitor the impact of international trade agreements on access to essential medicines and transfer of technology. At the same time, the development of relevant norms and standards, technical support to national drug regulatory authorities to ensure the quality of antiretroviral agents, the prequalification project, and activities to promote the quality of active pharmaceutical ingredients and finished-dosage-form antiretroviral agents will be continued and strengthened.

ACTION BY THE EXECUTIVE BOARD

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

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