

## Assuring access to quality antiretroviral medicines: the WHO Prequalification of Medicines Program and access to HIV treatment

Garantia de acesso a medicamentos antirretrovirais: o programa de pré-qualificação da OMS para medicamentos e acesso à terapia antirretroviral

Garantía de acceso a medicamentos antirretrovirales: el programa de precalificación de la OMS para medicamentos y acceso a terapia antirretroviral

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In 2000, only 1 in a 1,000 people living with HIV in Africa had access to treatment. Highly active antiretroviral (ARV) treatment was available in wealthy countries and had changed AIDS from a death sentence into a manageable chronic disease. But the drugs (ARVs) were available only from originator companies, who controlled the patents. They produced small quantities carrying paralyzing price tags – US\$10,000 to US\$15,000 per person per year.

When in early 2000 the world turned its long overdue attention to the HIV/AIDS crisis in the developing world it had to find a solution for the high cost of antiretroviral medicines. Producers of generic versions of ARVs mostly from India offered the drugs at lower prices but controversies broke out over patents on ARVs following the introduction of new global rules on intellectual property by the World Trade Organization (WTO) in 1995. These new WTO rules had introduced tighter patent requirements for medicines. Medicine patents largely restricted procurement agencies such as the United Nations Children's Fund (UNICEF), the International Dispensary Association, and NGOs like Doctors Without Borders (MSF) from distributing generic ARVs made in India. In 2001 the WTO adopted the *Doha Declaration on TRIPS and Public Health* reaffirming the right of countries to take action to overcome patent barriers

to access of medicines. The declaration provided much needed flexibility with regards to patents in the procurement of generic ARVs.

Another important issue was the quality assurance of ARVs, which were relatively new compounds. Most regulators in generic drug manufacturing countries – India, South Africa, and China – and in potential recipient countries had no experience with these “new” products, including the fixed-dose combinations (FDCs).

In response to this situation and to assist United Nations agencies and countries in the procurement of quality medicines, in 2001, the World Health Organization (WHO) established the Prequalification of Medicines Program (PQP) <sup>1</sup>. The Program initially focused on medicines for HIV, tuberculosis and malaria. In the last 13 years the program has been essential in the efforts to scale up treatment of people living with HIV.

FDCs ARVs were an important innovation in HIV/AIDS treatment, particularly for resource-poor settings where the “one pill twice a day” regimen would help increase adherence to treatment, reduce the risk of developing resistance, and simplify the supply chain. FDCs were also less costly. Indian firms were the first to produce an FDC of a WHO-recommended first-line combination (GlaxoSmithKline offered a combination of its compounds abacavir, lamivudine and zidovudine in one pill in early 2000 but this was

not a WHO recommended regimen). They could do so because there were no patent barriers in India to putting three compounds of different originator companies together in one pill. The price of the first generic triple combination by Cipla in 2001 was US\$350 and soon dropped to less than US\$140 per person per year. The combination of lamivudine, stavudine, and nevirapine – compounds developed by three different originators – was sold under the name *Triomune*.

The ARVs including the new fixed-dose combination ARVs produced by generic companies in India needed quality assurance. This problem demanded a quick solution as buying the costly originator medicines was not an option. Also the recommended treatments were not available in patient-friendly “one pill twice a day” combination tablets from brand-name companies. WHO PQP took on the task of determining whether the inexpensive and more convenient products from generic suppliers had the same efficacy and safety profile as the originator products.

In 2002, WHO published its first list of 41 approved formulations of ARVs and other medicines. This list opened up a supply of quality assured low cost generic ARVs for global procurement and helped to establish the market for generic ARVs. The Global Fund to fight AIDS, TB and malaria, created in 2002 subsequently adopted a policy that restricts use of the Fund’s immense purchasing power to products approved by stringent regulatory authorities or prequalified by WHO. This became the norm for global health funders and as a result the publicly funded market for medicines for HIV, TB and malaria of unknown quality quickly shrank.

On 1 December 2003, WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) declared the lack of HIV/AIDS treatment to be a global public health emergency. They launched the “3 by 5” campaign, to get 3 million people on antiretroviral treatment (by 2005). The political momentum of the campaign, combined with new funding from governments, the Global Fund, and the the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), and later from UNITAID, allowed countries to begin purchasing HIV/AIDS medicines in large volumes. Yet to optimize buying power and cover all patients needing treatment, the price of the ARVs would have to be lowered drastically.

The triple FDCs, produced only by generic companies, came to symbolize the great savings that generics could achieve. WHO’s prequalification of Cipla’s first generic FDC of three ARVs (three-in-one-pill) in 2003, a ground-breaking move, brought an important innovation to resource poor countries.

The WHO PQP is strict and does not hesitate to delist products when the applicant’s dossiers are not up to standards. This happened for the first time in 2004 when WHO delisted generic ARVs because of irregularities in the paperwork. This delisting sent a clear signal to the industry that the PQP had teeth and that if they wanted to have a share of the rapidly growing ARV market they had to meet internationally agreed quality standards.

In 2004 the U.S. government established its own process for approving ARVs for procurement using PEPFAR money, called the U.S. FDA’s Tentative Approval mechanism. The U.S. government did not want to rely on the WHO PQP but also realized that PEPFAR money would be insufficient if it did not take advantage of the lower priced generic ARVs and buy from U.S. or European drug companies only. While initially the U.S. FDA’s Tentative Approval mechanism was seen as a direct competitor to the WHO program, both agencies today collaborate.

Today the PQP has prequalified over 350 finished products, including 200 for treatment of HIV/AIDS and has expanded its activities to active pharmaceutical ingredients and clinical testing sites. It is estimated that of 10 million people receiving treatment for HIV, 80% are receiving prequalified ARVs. Its importance goes beyond procurement. The Program has raised the bar for quality assurance of medicines. Its standards are recognized and promoted by others, helping to expand quality medicines production. For example Medicines Patent Pool licenses, that offer the possibility of generic production even when a patent exists, require that producers meet the WHO PQP quality standards.

The focus of the PQP has been on treatments of a few diseases primarily HIV, TB, malaria and neglected diseases. However with the growing demand for treatments of non-communicable diseases in low and middle income countries it will be important that the WHO PQP expands into other areas such as cancer.

Today the core work on ARVs of the WHO PQP is financially supported by UNITAID, a financing mechanism supported by Brazil.

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1. ‘t Hoen EF, Hogerzeil HV, Quick JD, Sillo HB. A quiet revolution in global public health: The World Health Organization’s Prequalification of Medicines Programme. *J Public Health Policy* 2014; doi: 10.1057/jphp.2013.53.

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