

PEPFAR  
WATCH

# Medicine Procurement of ARVs and Other Essential Medicines in the U.S. Global AIDS Program

November 2005



## Background

Anti-retroviral drugs can extend life for many years. And the cost of those drugs has dropped from \$12,000 a year to under \$300 a year -- which places a tremendous possibility within our grasp. Ladies and gentlemen, seldom has history offered a greater opportunity to do so much for so many. - President George W. Bush, State of the Union Address (Jan. 28, 2003).

In his 2003 State of the Union address President Bush acknowledged lower-cost antiretrovirals (ARVs) creating an opportunity to increase the reach of treatment access for people living with AIDS. However the price quoted was available only from generic manufactures. Now, almost three years after this speech and two years after the official launch of the President's Emergency Plan for AIDS Relief (PEPFAR), there is still little evidence that the Bush administration is availing itself of low prices offered by generic producers or that generic ARVs approved for use are being procured with US government dollars.<sup>i</sup> This document will review some of the effects of U.S. procurement policies and the U.S. approval process for generic drugs, including fixed-dose combinations (FDCs), for treatment scale-up in PEPFAR programs.

## Concerns

### **A unilateral system risks undermining the WHO multilateral pre-qualification program and is out of sync with national policies and protocols**

National governments, global initiatives (such as the Global Fund to Fight AIDS, TB, and Malaria and the Clinton Foundation), and international organizations providing treatment (such as Doctors Without Borders), rely upon the World Health Organization (WHO) Pre-qualification Project to certify the quality and efficacy of both generic and brand-named drugs. WHO's guidelines for ARV therapy recommends the 3-in-1 fixed-dose combinations for the first-line therapy, which are only available from generic producers, because they are easier to take and manage. Rather than procuring affordable, bio-equivalent generics already pre-qualified by the WHO and being used to treat hundreds of thousands of people living with HIV/AIDS (PLWHAs), Health and Human Services (HHS) gave early signs that it would not purchase WHO pre-qualified generic ARVs, voicing concerns that WHO's process was not as stringent as the Food and Drug Administration (FDA) to assess the quality of drugs, especially where up to 3 different drugs had been combined in a single pill.

On May 16, 2004, in an attempt to deflect the ensuing international criticism challenging the refusal to purchase generic AIDS drugs and FDCs, HHS announced a FDA "Fast Track" process for reviewing generic and brand-name AIDS drugs whether fixed-dose combination (FDC), co-packages, and a process for single doses.<sup>ii</sup> FDA tentative approval clears the product "for consideration for purchase and use outside the United States under the President's Emergency Plan for AIDS Relief" pending approval by the Office of the Global AIDS Coordinator.<sup>iii</sup> These products may not be marketed in the U.S because of existing patents and/or data or marketing exclusivity.

The US FDA approval system for generic AIDS drugs has created needless duplication of the WHO pre-qualification project and new regulatory obstacles to accessing generic drugs. While the impression was given that the U.S. uses "more stringent" standards than WHO, in reality the standards of testing efficacy

and safety do not differ from WHO: both bodies assert that if a generic drug is absorbed by the body in the same way as the innovator drug (bioequivalence is proven), then the safety and efficacy is the same. The difference, however, lies in the numerous regulatory hurdles built into the process by U.S. law for applicants and that applications for the FDA necessitate some tests to be redone rather than accepting dossiers already submitted to WHO or other Stringent Drug Regulatory Authorities (SDRAs) such as in Europe.

The U.S. unilateralist approach which delays timely procurement of low cost, life saving generics in all US global AIDS programs continues to cause problems for PEPFAR. Foremost is the fact that more expensive name-brand drugs results in fewer number of people receiving life-saving treatment. Secondly, the artificial limitation on suppliers results in drug shortages. Thirdly, the parallel procurement and supply management process strains already-strained resources. Fourthly, the move represents a strain on U.S. foreign relations in its move to discredit and circumvent the WHO process, resulting in some countries barring the import or use of drugs approved only by the FDA.<sup>iv</sup>

### **FDA Fast track approvals: Problems and Delays Remain**

It now appears, however, that the "two to six weeks" timetable promised by the Administration was highly misleading. – U.S. Representative Henry Waxman.

Some delays are caused in part by failure to get reference rights from drug companies, or replicate dossiers prepared for European regulatory bodies. In preparing a New Drug Application (NDA) for the FDA, a generic producer must seek the "right of reference" to underlying data used by innovator companies, such as the composition, quality, safety, and efficacy (from animal and clinical trials). In some cases, originator companies have delayed the release of data (and the right to reference the data) to generic manufacturers or demanded conditions tied to release (such as limits on marketing rights). In more than one case, the right of reference to regulatory data used in Europe, to seek approval of a generic drug was refused so bioequivalence tests had to be repeated against the FDA-approved version of the identical product. Compounding such delays is the fact that EU and other SDRA approval, as well as the WHO pre-qualification process, does not automatically inform, or even expedite, U.S. FDA approval.

Also, tentative approval is not permissible during periods of data exclusivity. According to U.S. regulations, a generic drug application cannot be accepted for review by the FDA, even for tentative approval, until the period of data exclusivity of the originator drug has reached its fourth year (out a 5 year period) granted for new chemical entities (NCEs). The period for exclusivity for "new uses" of an originator drug is 3 years. This not only impacts generic versions of individual drugs, but fixed-dose combinations that contain a drug with exclusive status. Second generation drugs, as well as any new drugs, are crucial to AIDS treatment programs as first generation regimens fail. Currently data exclusivity bars application for tentative approval for generic versions of atazanavir, emtricitabine (FTC), tenofovir (TDF), the Truvada, and Epzicom.

### **Even approved generics are not yet procured**

In January 2005, the Government Accountability Office reported only 6 ARV products (all brand name) were available for use in PEPFAR programs for first-line treatment of HIV/AIDS.<sup>v</sup> Since then 12 generic ARVs have received tentative approval from the FDA and should be available for use:

1. Blister pack of lamivudine/zidovudine (3TC 150mg/AZT 300mg) co-formulation tablets with nevirapine 200mg tablets, Aspen Pharmcare (January 24 2005)
2. Lamivudine 150mg, Ranbaxy Laboratories LTD. (May 27 2005)
3. Lamivudine 150mg and 300mg, Aurobindo Pharma LTD. (June 15 2005)
4. Nevirapine (NVP) 200mg, Aurobindo (June 20 2005)
5. Nevirapine 200mg, Ranbaxy (June 20 2005)
6. Efavirenz (EFV) 600mg, Aurobindo (June 24 2005)
7. Stavudine (d4t) 30mg and 40mg, Aurobindo (July 1 2005)

8. Zidovudine/lamivudine combination (300mg/150mg), Aurobindo (July 6 2005)
9. Zidovudine 300mg, Ranbaxy (July 13 2005)
10. Zidovudine 300mg, Roxane Laboratories, Inc. (July 27 2005)
11. Zidovudine 300mg, Aurobindo (August 25 2005)
12. Zidovudine 50 mg/5mL oral solution, Aurobindo (September 8 2008)
13. Lamivudine 10 mg/mL oral solution, Aurobindo (November 4 2005)<sup>vi</sup>

However, there is little evidence that these additional drugs are actually being procured. Furthermore, many facilities are not even aware of the FDA tentative approvals granted for generic drugs, highlighting fundamental problems with transparency and communication from the headquarter level. And although generic ARVs are preferred by developing countries and are often incorporated into national treatment guidelines because of cost and ease of use, adherence and harmonization between PEPFAR and the national guidelines has yet to occur. Because many national AIDS treatment plans rely upon generic ARVs as a cornerstone to scale-up, governments and facilities have attempted negotiating a “wrap around” arrangement where public or private funding is used to purchase generic ARVs and PEPFAR dollars go to drugs where generic equivalents don't yet exist including some second-generation drugs and pediatric formulations.

### **Drug Shortages Due to Limited Suppliers Have a Freeze-Effect on AIDS Treatment**

Relying on single-source suppliers can and does result in shortages and stockouts. This year major U.S. media outlets reported on shortages of GlaxoSmithKline's Epivir (known as lamivudine or 3TC), Merck's Sustiva (known as efavirenz), and Bristol Myers Squibb's ZERIT (known as stavudine or d4t) leaving PEPFAR-funded programs scrambling to continue treatment for their patients. Some mission hospitals and clinics were told by drug companies to stop adding people to their treatment rolls, although the capacity existed to treat many more, because of the shortages. At the time of the reports, generic versions of 2 out of the 3 drugs were listed on the WHO pre-qualified list. Although at a Congressional briefing the Global AIDS ambassador Randall Tobias was asked to use his right to waive regulations and barriers to generic sources of drugs, given the severe drug shortages, he has refused to do so.<sup>vii</sup>

### **Source of Origin restrictions on essential medicines drives up cost and reduces treatment of fatal opportunistic infections**

The Global AIDS Coordinator (OGAC) Randall Tobias told the Senate Subcommittee on Foreign Operations, in May 2004, that antiretrovirals used in the treatment of HIV/AIDS through the President's Emergency Plan for AIDS Relief (PEPFAR) would be waived from so-called "buy American" restrictions.<sup>viii</sup> However no similar blanket waivers have been granted by OGAC for the procurement of non-antiretroviral pharmaceuticals, most notably those used in the treatment of opportunistic infections (OIs), including, most commonly, thrush and cryptococcal meningitis.

The restrictions include limiting procurement to products manufactured or under patent in the U.S. or products manufactured by a U.S. company.<sup>ix</sup> In some countries, these policies have created an alternative procurement chain parallel to ones already in place, which may have relied on local producers. Some facilities facing exorbitant costs of U.S. drugs to treat opportunist infections (e.g. Aciclovir, Fluconazole, Ciproflaxcin) raise private funding in order to shop around for best price. In Kenya, for example, USAID field office has organized an arrangement in which the UK's Department for International Development (DfID) pays for drugs to treat opportunistic infections, allowing a limited number of recipients to purchase more affordable drugs—either locally produced or generics from non-US companies.

In July 2005 Michelle Maloney-Kitts, the Chief of Program Services Division for the Office of the Global AIDS Coordinator, said OGAC was considering issuing a blanket waiver to allow for non-US manufacturers as long as the products are approved by a Stringent Drug Regulatory Authority (SDRA)<sup>x</sup>. However, this seems to exclude WHO pre-qualified drugs and many local producers that do not attempt to enter rich markets and therefore would not be approved by a SDRA.

## Recommendations

1. The **Office of the Global AIDS Coordinator** should cooperate fully with the WHO Pre-qualification Project to expedite approval and prequalification of AIDS medicines.
2. The **Office of the Global AIDS Coordinator** should immediately issue a blanket waiver of “buy American” restrictions with respect to non-ARV AIDS medicines used preventatively and to treat opportunistic infections. The U.S. should also waive FDA and SDRA approval requirements when the relevant medicine meets internationally recognized quality, safety, and efficacy standards including WHO pre-qualification.
3. The **U.S. Congress** should mandate the Office of the Global AIDS Coordinator to use its authority to waive data-exclusivity rules barring tentative FDA approval of generic medicines intended for use abroad in PEPFAR and other Global AIDS Initiative programs and waive restrictions allowing purchase of WHO pre-qualified medicines whenever supply shortages from existing single- or double-source producers create the risk of stock-outs and other supply shortages.
4. The **Office of the Global AIDS Coordinator** should immediately and broadly announce to all relevant embassies and PEPFAR contractees when the FDA has granted tentative approval to generic medicines. In addition, the Office of the Global AIDS Coordinator and its coordinating agencies should be required to immediately authorize procurement of FDA approved AIDS medicines.
5. Procurement of ARVs and other AIDS medicines by the **Office of the Global AIDS Coordinator** should be driven by the principles of encouraging the existence of multiple producers, affordability, and compatibility with national treatment protocols in focus countries. In general, preference should be given to lower cost producers, generic or originator.

### For more information contact:

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<sup>i</sup> U.S. Government Accountability Office, Global HIV/AIDS Epidemic: Selection of Antiretroviral Medications Provided under U.S. Emergency Plan Is Limited (January 2005).

<sup>ii</sup> U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Food and Drug Administration: Guidance for Industry: Fixed Dose Combination and Co-packaged Drug Products for Treatment of HIV (May 2004)

<sup>iii</sup> U.S. Department of Health and Human Services, HHS Proposes Rapid Process for Review of Fixed Dose Combination and Co-Packaged Products (May 16, 2004).

<sup>iv</sup> In Uganda, for example, the import or use of FDA approved generics was barred because of the lack of WHO approval. In response the U.S. said it would begin talks with WHO to harmonize the process so that drugs tentatively approved by FDA would appear on the WHO list of approved medicines.

<sup>v</sup> U.S. Government Accountability Office, Global HIV/AIDS Epidemic: Selection of Antiretroviral Medications Provided under U.S. Emergency Plan Is Limited (January 2005).

<sup>vi</sup> FDA HIV-AIDS section, <http://www.fda.gov/oashi/aids/hiv.html>

<sup>vii</sup> Statement by Congressman Tom Lantos, House International Relations Committee “US Response to Global AIDS Crisis: A Two-Year Review” (April 13, 2005)

<sup>viii</sup> Testimony of Ambassador Randall L. Tobias, U.S. Global AIDS Coordinator before the United States Senate Committee on Appropriations, Subcommittee on Foreign Operations, Washington, DC. (May 18, 2004) and “Under each Foreign Operations Appropriations Bill since fiscal year 2002, the Coordinator has been given the right to pursue the fight against global AIDS notwithstanding any other provisions of law.”—Sen. Edward M. Kennedy and Rep. Henry A. Waxman letter to President Bush (January 26, 2005)

<sup>ix</sup> Foreign Assistance Act of 1961 as amended and the Code of Federal Regulations, Title 22 Foreign Relations, Part 228—Rules on Source, Origin and Nationality for Commodities and Services Financed by USAID

<sup>x</sup> OGAC is likely to consider SDRAs as International Conference on Harmonization (ICH) members (European Union, Japan, U.S.). The GFATM definition includes 26 members of the Pharmaceutical Inspection Cooperation Scheme (PIC/S).