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Congress of the United States

House of Representatives

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March 26, 2004

The President
The White House
1600 Pennsylvania Avenue
Washington, DC 20500

Dear Mr. President:

Your Administration is circulating a proposal for consideration at an upcoming international conference in Botswana that could impede access to the low-cost drugs needed to save the lives of millions of people living with HIV in developing countries. Adopting this proposal would be a tragic mistake. Instead of erecting hurdles that could block or limit the use of these life-saving therapies, the United States should be cooperating with the World Health Organization and other nations to make the therapies widely available as soon as possible.

In addition to affecting access to key medications, your Administration's actions may be alienating essential U.S. allies. I have learned that the leading drug regulatory authority in the European Union, the European Agency for the Evaluation of Medicinal Products, is not sending any experts to the Botswana conference, after having participated in the preliminary conference in Cape Town, South Africa. It is difficult to imagine how progress can be made without the participation of one of the leading drug approval agencies in the world.

At issue are "fixed dose combination" drugs. These combination therapies are promising medications that combine several essential treatments for HIV/AIDS into one tablet and are considered the "first choice" for use when available. Generic drug manufacturers operating in India offer these pills at a fraction of the price of the individual brand-name drugs. The World Health Organization has certified the quality of several of these products, setting the stage for their use in the global campaign to treat three million people by 2005.

Unfortunately, this promising development is being threatened by U.S. actions. Monday, in Gaborone, Botswana, the United States is co-hosting a meeting to discuss whether stringent safety and efficacy standards should be applied to these low-cost combination therapies. On the agenda for discussion in Botswana is a document circulated by the United States called *Scientific and Technical Principles for Fixed Dose Combination Drug Products*. The inflexible standards in the document could block the use of well-supported and widely accepted generic combination therapies. In fact, the proposed requirements are so unreasonable that they appear to exceed the

standards used by the U.S. Food and Drug Administration to approve therapies for use in the United States.

I am not opposed to the establishment of reasonable safety and efficacy standards for HIV combination therapies. Many observers believe that the WHO already has such standards in place, and in other contexts, the United States relies on WHO standards. If health experts conclude that some revisions are necessary, however, there should be a concerted effort to work within the WHO framework to revise its existing standards as quickly as possible.

But I strongly oppose efforts to block the use of low-cost generic drugs through the imposition of unnecessary and onerous drug approval standards. It is no secret that U.S. pharmaceutical companies, which make brand-name drugs, do not want funds to flow to generic drug companies in India. These pharmaceutical companies are among your strongest political supporters, having contributed over $40 million to your political party in the last five years.[1] They should not be dictating policy on U.S. efforts to fight HIV/AIDS in Africa and elsewhere.

Background

In your 2003 State of the Union speech, you expressed your personal commitment to funding low-cost therapies to counter the global scourge of AIDS. You then proposed an ambitious agenda involving nearly $10 billion in new U.S. funding to combat HIV in Africa.[2] As you said in the 2003 State of the Union speech:

> Because the AIDS diagnosis is considered a death sentence, many do not seek treatment. Almost all who do are turned away. A doctor in rural South Africa describes his frustration. He says, "We have no medicines. Many hospitals tell people, you've got AIDS, we can't help you. Go home and die." In an age of miraculous medicines, no person should have to hear those words.
>
> AIDS can be prevented. 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.[3]

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[1] Center for Responsive Politics, *Pharmaceuticals/Health Products: Long-Term Contribution Trends* (online at http://www.opensecrets.org/industries/indus.asp?Ind=H04).

[2] White House, *Fact Sheet: The President's Emergency Plan for AIDS Relief* (Jan. 29, 2003) (online at http://www.whitehouse.gov/news/releases/2003/01/20030129-1.html).

[3] President George W. Bush, *State of the Union Address* (Jan. 28, 2003) (online at http://www.whitehouse.gov/news/releases/2003/01/20030128-19.html).

To make the available funding go as far as possible, the cost of the drugs purchased with U.S. funds needs to be as low as possible. Today, the lowest-cost and most promising drugs are generic combination therapies, which are now available at a price as low as $140 per patient per year.[4] These are widely considered the "first choice" for treatment when available.[5]

Since your State of the Union speech, however, the Administration has shifted away from supporting the purchase of generic combination therapies with U.S. funds. Instead, the United States is now circulating a proposal for drug approval standards that calls into question the existing WHO certification process and would appear to make it difficult, if not impossible, for the international community to purchase low-cost generic combination therapies. This new proposal will be the subject of an international conference being held from March 29 to March 30 in Gaborone, Botswana.

The Current WHO Approval Process

The international standard for the safety, effectiveness, and quality of HIV drugs is set today by WHO. International donors, including the U.S.-funded Global Fund to Fight AIDS, Tuberculosis, and Malaria, rely upon WHO's expert reports and evaluations to determine which drugs to purchase. Because of the preeminent role of WHO in international health, many observers have assumed that drugs meeting WHO standards would be eligible for purchase using U.S. funds for HIV in Africa. Indeed, in other settings, the United States has relied on WHO assessment and review for purchases with U.S. funds.

There are two key elements of the WHO approach to HIV medications: expert recommendations and quality review.

In 2003, WHO convened an expert panel to make recommendations about appropriate therapy for HIV in resource-limited countries. The panel, led by Dr. Scott Hammer of Columbia University, included 15 recognized experts in HIV treatment throughout the world. In October 2003, more than 200 institutional and organizational partners reviewed the draft document, which was then made available for public comment before final publication in December 2003.[6] These recommendations represent the best practices for HIV treatment in the developing world.

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[4] *South Africa Gears up for AIDS Fight*, New York Times (Nov. 21, 2003).

[5] World Health Organization, *Fixed Dose Combinations for AIDS, Tuberculosis, and Malaria* (Dec. 16–18, 2003)(online at: http://www.who.int/medicines/organization/par/FDC/FDCmain.shtml).

[6] World Health Organization, *Scaling up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach, 2003 Revision* (Dec. 2003) (online at http://www.who.int/3by5/publications/documents/arv_guidelines/en/).

Among the highlighted treatments are regimens combining three drugs that are available for simple administration in the form of single pill combinations.[7]

Complementing the WHO's recommendations for therapy is the organization's pre-qualification process for pharmaceuticals. This process certifies the quality of drugs for purchase by U.N. agencies.

Based on a standard procedure developed by WHO's Expert Committee on Specifications on Pharmaceutical Preparations, the pre-qualification process is rigorous. Manufacturers must provide data on the active ingredients, product formula, manufacturing method, stability, and bioequivalence. A team of WHO experts, including staff of drug regulatory authorities from developed and developing nations, must assure that the products meet scientific specifications. Inspectors must certify that the manufacturing sites adhere to international standards.

There is wide international support for the WHO approach. U.N. agencies, the World Bank, and such nongovernmental organizations as Doctors Without Borders all have used WHO-certified and recommended drugs. National regulatory agencies also factor in the recommendations and certifications of WHO in deciding what drugs may be used in their countries.

Indeed, WHO-certified drugs have been purchased and used by U.S. agencies for years in combating diseases in developing countries. For example, the U.S. Agency for International Development has set standards for procurement of non-FDA-approved drugs. In these standards, grant applicants are advised to find "information to attest to safety, efficacy, and quality" by asking:

> Is the drug recognized as being safe and efficacious and recommended for the proposed application by recognized experts in the field, for example, CDC or WHO? . . . Is the drug product on the WHO essential drugs list for the proposed indication?[8]

U.S. funds also purchase oral polio vaccine through the United Nations Children's Fund (UNICEF).[9] This vaccine is no longer available from an FDA-licensed manufacturer. Instead,

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[7] *Id.*, at 15-16.

[8] U.S. Agency for International Development, *Requesting USAID Approval to Procure HIV Test Kits and Other HIV/AIDS-Related Pharmaceutical Products: Guidance and Sources of Information* (Jan. 2002).

[9] Centers for Disease Control and Prevention, Global Immunization Division (2004) (online at http://www.cdc.gov/nip/webutil/about/divisions/gid.htm) (The United States

UNICEF relies upon a WHO prequalification system for vaccines that is similar to its process for drugs.[10] Similarly, the Global Fund to Fight AIDS, Tuberculosis and Malaria, which receives U.S. funds, has agreed that grantees can purchase WHO-certified drugs.[11]

There are several HIV combination therapies that have been pre-qualified under this WHO review process. These therapies include Triomune and Triviro, generic medications manuctured in India that combine in a single pill the recommended regimen of stavudine, lamivudine, and nevaripine.

The Proposed New Standards

Recently, senior Administration officials have questioned the adequacy of the WHO review process. In testimony earlier this month before the International Relations subcommittee of the Appropriations Committee of the House of Representatives, Global AIDS Coordinator Randall Tobias stated:

> You and I know that a process has developed in this country, where if you or I take a prescription to the local pharmacy and get it filled and it's filled with a generic drug, then we know that what we take home is going to be the exact, precise duplicate of the drug that was originally developed by a research-based pharmaceutical company and that the FDA, through its process, will have insured that the dosage, the safety, the effectiveness, the strength, the active ingredients, the purity and so on and so on, are exactly identically the same.
>
> When people describe generic AIDS drugs, they're talking about something very different. They're talking about drugs that are being made by somebody, some place in the world, that may well comply with all of these standards. They may well be perfectly safe and perfectly effective and totally consistent. And then again, they may not be.

"[p]rovides polio vaccine, through UNICEF, for National Immunization Days and mop-up campaigns to eradicate polio").

[10]World Health Organization, *Procedure for Assessing the Acceptability, in Principle, of Vaccines for Purchase by United Nations Agencies* (2002).

[11]The Global Fund to Fight AIDS, Tuberculosis, and Malaria, *Report of the Third Board Meeting* (Oct. 10–11, 2002) (online at http://www.theglobalfund.org/en/files/boardmeeting4/gf%20b4%2002%20 report%20of%20the%20third%20board%20meeting.doc).

> *The problem is, there is no process, no principles, no standards in place today, from a regulatory point of view, to make that assurance.*[12]

Ambassador Tobias's statement ignored the extensive WHO system of expert review and prequalification, which constitutes a process, includes principles, and sets standards. Nonetheless, the allegation that there is no oversight of generic HIV drugs has driven U.S. policy. At Monday's conference in Gaborone, Botswana, the United States will lead discussion on a document called *Scientific and Technical Principles for Fixed Dose Combination Drug Products*.[13] Approximately two weeks from now, this document is to be finalized.

The new standards proposed in this document appear likely to block the use of the low-cost generic drugs that are currently pre-qualified by WHO. In fact, the proposed requirements are so unreasonable that they appear in some circumstances to exceed those of the U.S. Food and Drug Administration. In some instances, they may even require studies that would be unethical to conduct.

The problems with the document appear principally in the proposed requirements for those HIV combination therapies that fall into two categories referred to as Scenario 2 and Scenario 3.

Scenario 2 includes those fixed-dose medications that are composed of drugs whose combination use is well established, at the exact same dose that they are used in clinical practice. This scenario appears to encompass the HIV combination therapies that are most promising today. For example, it would appear to apply to Triomune and Triviro, two generic HIV therapies have already been reviewed and prequalified by WHO. Each of these two drugs combine three drugs (stavudine, lamivudine, and nevaripine) in a dosing regimen that has been well established as safe and effective. There is tremendous interest in using these combination therapies in developing nations on convenience and cost grounds. In fact, Triomune and Triviro are already being used successfully in several countries.[14]

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[12]Global AIDS Coordinator Randall Tobias, *Testimony before the House Appropriations Committee, Foreign Operations Subcommittee*, FDCH Political Transcripts (Mar. 18, 2004) (emphasis added).

[13]Conference on Fixed-Dose Combination (FDC) Drug Products, *Scientific and Technical Principles for Fixed Dose Combination Drug Products, Draft* (Mar. 9, 2004) (online at http://www.globalhealth.gov/fdc.shtml).

[14]Medecins Sans Frontières, *Factsheet, Two Pills a Day Saving Lives: Fixed-Dose Combinations of Anti-Retroviral Drugs* (Feb. 2004) (online at http://www.accessmed-msf.org/documents/factsheetfdc.pdf).

Under the new standards being circulated by the Administration, however, it appears questionable that Triomune and Triviro would be approvable. The document proposes to require for each drug covered by Scenario 2 "a justification supported by data or literature . . . to support the advantage of the combination over monotherapy with each of the individual entities." In other words, the manufacturers of these drugs would have to produce studies comparing and demonstrating an advantage of the combination against stavudine, lamivudine, and nevaripine individually. This is an unnecessarily onerous standard.

In fact, this standard appears to exceed FDA requirements for approval for sale in the United States. In 2000, FDA approved a brand-name combination therapy, GlaxoSmithKline's Trizivir (containing the drugs zidovudine, lamivudine, and abacavir), on the basis of bioequivalence data. Contrary to the new international standards being circulated by the United States, there were no clinical trials of the combination against the individual components. Trizivir's labeling refers to one adult and one pediatric study comparing the combination to zidovudine and lamivudine together;[15] it mentions no studies comparing the combination to each of the individual drugs as monotherapy. Even if the combination of zidovudine and lamivudine were considered "monotherapy," there were no studies comparing the triple combination with abacavir alone.[16]

In some situations, where monotherapy is not the recognized treatment for a life-threatening disease, a comparative trial would be unethical. This would most certainly be the case if a study were required today to establish that Triomune and Triviro were superior to each of their individual components.[17]

Scenario 3 groups together two dissimilar situations: (1) a single pill combination composed of components that have not been shown to be safe and effective in combination and (2) a single pill combination composed of a proven combination, where only the dosing regimen

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[15] According to Trizivir's label, pediatric patients had a "limited response" to the addition of abacavir.

[16] GlaxoSmithKline, *Trizivir: Prescribing Information* (2002) (online at http://us.gsk.com/products/assets/us_trizivir.pdf). In general, FDA's clinical research requirements are more flexible than those proposed in the document, permitting the agency to accept less evidence of safety and effectiveness in the case of serious and life-threatening diseases where there is no satisfactory alternative therapy. See 21 CFR 312, Subpart E and 21 CFR 314, Subpart H. The proposed standards do not acknowledge the need to weigh risks and benefits in light of the severity of the disease and the lack of satisfactory alternatives.

[17] U.S. Department of Health and Human Services, *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, 23 (Mar. 23, 2004).

has been altered. Standards under Scenario 3 also appear to be unreasonable and to exceed FDA requirements for some products that would fall in this category.

The proposed document would require clinical trials against established treatments to show which one is better. A clinical trial to establish the noninferiority of a combination therapy with a change in dosing regimen compared to the standard combination would, in most cases, be prohibitively large and expensive, effectively eliminating this type of drug. I recognize that in many cases, such drugs should not be marketed without new clinical data data. However, for some drugs with a minimal change in dosing regimen, such a study could exceed FDA requirements.[18]

In addition, where the drug combines for the first time two drugs that have dissimilar but well-established indications, FDA does not necessarily require a clinical study comparing the combination with monotherapy. In such cases, the advantage may be presumed based on existing information about the effectiveness of each component for its indication.[19]

Implementation of the Proposed Standards

Monday's meeting in Botswana will not cover the question of who might implement a new set of approval standards for combination therapies. This question, however, is also critical to assessing whether the U.S. effort to assure the safety and effectiveness of these drugs will become an unnecessary drag on their timely purchase and distribution.

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[18]If a change in dosing regimen increases the frequency of dosing, FDA may, depending on pharmacokinetic and pharmacodynamic (PK/PD) relationships, sometimes consider bioequivalence data a sufficient basis for approval. Even if the change decreases frequency of dosing, FDA sometimes approves such changes without clinical data, depending on PK/PD relationships. For example, sustained release versions of immediate release drugs, like Wellbutrin SR, can sometimes be approved without clinical trials. See also FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, 7 (May 1998). Immediate release drugs can, in the right circumstances, also be approved for less frequent dosing regimens than were used in the clinical trials, e.g., propranolol was approved for twice daily use on the basis of a trial showing that propranolol was safe and effective when used 3 times a day, together with PK/PD data. *See also,* FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, 8 (May 1998).

[19] For example, the FDA recently approved Caduet, which combined amlodipine and atorvastatin in a single pill for the first time. According to the drug's label, the agency did not rely on any clinical studies, other than bioequivalence studies, comparing the combination to its constituents.

Establishing a parallel process to WHO to approve drugs for international purchase would make little sense. Such a process could set up conflicting international standards, confusing countries and donors. It could also open the door to political interference, especially if implementation were left with an organization or agency that could be swayed by manufacturers or others with a commercial interest in the outcome.

If global health experts believe additional standards for HIV drugs are necessary, these standards should be quickly built into the existing WHO process. Such a step will accomplish the goal of assuring the quality of drugs without creating duplicate bureaucracies and unnecessary delay.

Conclusion

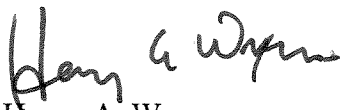
Adopting the proposed standards being circulated by the United States could have major adverse consequences. It is obviously critical to be confident that all drugs for HIV are safe and effective. This goal, however, does not require the imposition of inflexible standards that may block access to essential, life-saving therapies.

To fight the scourge of AIDS on the continent of Africa, a global effort is required. Donors from around the world, including the United States, must commit significant resources as quickly as possible. International expertise in drug review must be brought together to allow for efficient approval and quality manufacturing of essential therapies. Working together, the nations of the world can literally save millions of lives by 2005.

Your approach, however, appears to be dividing the key allies the United States needs. For example, I have just learned that the leading drug approval agency in the European Union, the European Agency for the Evaluation of Medicinal Products is not sending any of its experts to the Botswana conference, after having participated in the preliminary conference in Cape Town, South Africa.

I urge you to cooperate and lead in this global effort. The United States should not break off from the rest of the world, disparage its standards for drug approval, and then squander precious funds on unnecessarily expensive therapies.

Sincerely,



Henry A. Waxman
Ranking Minority Member