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Congress of the United States

House of Representatives

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May 11, 2004

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The President
The White House
Washington, DC 20500

Dear Mr. President:

Your Administration appears to be needlessly delaying the purchase of the most effective therapies to fight HIV in developing countries at the lowest possible cost.

With as many as three drugs in one pill, combination therapies are a major advance in HIV care that are changing clinical practice across the globe. Yet your Administration has not even begun to review or purchase these important products. Instead, senior Administration officials have repeatedly cast doubt on their safety and effectiveness. Your Administration is also circulating a new draft of principles for the assessment of combination therapies that could lead to their unjustified rejection.

Your Administration's actions have unnecessarily delayed and complicated the delivery of highly recommended, life-saving therapies. They also appear to signal that your Administration will reject these effective combination therapies, which are made by generic drug manufacturers in India, in favor of more expensive and more complicated alternative drug regimens, which are made by the major pharmaceutical companies.

It is wrong to place the short-term financial interests of the drug industry ahead of the needs of millions of HIV-infected individuals in Africa and other developing nations. Rather than erecting irresponsible roadblocks to important therapeutic advances, the United States should cooperate with other nations in pursuit of a vital goal: fighting the HIV epidemic as effectively and efficiently as possible.

Combination Therapies

At issue are "fixed-dose combinations," which are drugs directed against HIV that include an entire regimen of pharmaceuticals in one pill. On December 1, 2003, the World Health Organization (WHO) determined that several of these products, manufactured at low

cost in India, met high standards of safety, efficacy, and quality.¹ Soon afterwards, a panel of international experts concluded that these convenient therapies can increase adherence and reduce drug resistance, making them the “first choice” treatments for HIV and AIDS.²

The international community has responded quickly. Funders such as the World Bank and frontline relief agencies such as the Catholic Relief Services Consortium now support their widespread use.³ WHO has placed these products at the center of a campaign to treat three million people with antiretroviral therapy by 2005.⁴

Not everyone supports the new treatments, however. The most recommended combination therapies are manufactured by Indian generic drug companies. These manufacturers combine three individual drugs (nevirapine, stavudine, and lamivudine) into one tablet. Because the component drugs are under patent, the large multinational drug companies perceive the combination therapies as a threat to their intellectual property rights. Conservative organizations aligned with the pharmaceutical industry, and the industry itself, have fought the use of these products.⁵

Statements from Administration Officials

So far, your Administration has sided with the world’s largest drug companies in opposing the use of highly recommended combination therapies. Nearly 18 months after you announced your \$15 billion AIDS initiative in a speech that cited the benefits of low-cost generic drugs, your Administration has not even reached a decision about how it might review these drugs’ quality.

Rather than work to review and approve combination drugs as quickly as possible, senior Administration officials are offering a series of criticisms that serve to undermine their use.

¹World Health Organization, *WHO Adds New Fixed Dose Combinations to Its List of Quality Products for AIDS Treatment: Key Component of 3 by 5 Strategy* (Dec. 1, 2003).

²World Health Organization, *Fixed Dose Combinations for HIV/AIDS, Tuberculosis, and Malaria* (Dec. 16–18, 2003).

³Statement of Jacqueline Patterson, Catholic Relief Services Consortium, Botswana (Mar. 29, 2004).

⁴World Health Organization, *supra* note 1.

⁵*See, e.g.*, Carol Adelman and Jeremiah Norris, *Fighting AIDS on the Cheap*, American Outlook Today (Mar. 12, 2004) (online at http://www.hudson.org/index.cfm?fuseaction=publication_details&id=3252); *Plan to Battle AIDS Worldwide Is Falling Short*, New York Times (Mar. 28, 2004).

Criticism #1: WHO Is Not a “Regulatory Authority”

As the health organization for the United Nations, the World Health Organization has long played a critical role in promoting access to lifesaving therapies in developing nations. Several years ago, WHO established a rigorous review process, staffed by drug regulators from member nations, to assure the safety and efficacy of drugs. This process includes review of data, inspection of facilities, and laboratory testing of finished products. In December 2003, WHO found that several combination drugs met its high standards.⁶

Rather than participate in the WHO drug review process, however, your Administration has decided to attack it. Global AIDS Coordinator Randall Tobias testified before Congress that “there is no process, no principles, no standards in place” for evaluating combination therapies. In making this claim, Mr. Tobias said he did not count WHO’s efforts because the international agency does not have a “regulatory approval process.”⁷ John Lange, deputy to Mr. Tobias, has also stated that the problem in relying on WHO is that “[n]ormally one looks to [a] stringent regulatory authority.”⁸

This line of attack on WHO does not make sense. Leading experts designed the WHO drug review process to be the equivalent of review by any regulatory agency in the world, including the U.S. Food and Drug Administration.⁹ One sign that this system works is that products approved only by WHO are purchased for use by many nations, including by the United States. For example:

- The Centers for Disease Control and Prevention (CDC) spends millions of dollars each year on polio vaccine procured by the United Nations Children’s Fund

⁶ World Health Organization, *supra* note 1.

⁷Global AIDS Coordinator Randall Tobias, Testimony before the House Appropriations Committee, Foreign Operations Subcommittee, FDCH Political Transcripts (Mar. 18, 2004).

⁸*US Official Defends Controversial AIDS Drug Policy*, Reuters (Mar. 31, 2004).

⁹World Health Organization, *Procedure for Assessing the Acceptability, in Principle, of Pharmaceutical Products for Purchase by United Nations Agencies* (2001).

(UNICEF).¹⁰ The vaccine obtained by UNICEF is not FDA-approved. It is, however, reviewed for safety, efficacy, and quality by WHO.¹¹

- The U.S. Agency for International Development (USAID) purchases a wide selection of drugs for emergency use, while relying on nonregulatory agencies to certify the quality of these drugs. These agencies have included IDA, a private organization based in Europe that procures medications and conducts some tests of drug quality, and UNICEF.¹² UNICEF, in turn, often relies on the WHO to assure the safety and effectiveness of many of the drugs it procures.¹³

The potential consequences of the argument that WHO is not a “regulatory authority” are severe. Patent laws in the United States and in the countries with comparable systems generally preclude the approval of therapies that combine patented drugs. If your Administration decides that a “regulatory authority” must approve the product, but no “regulatory authority” can approve the product, then you will have barred “first choice” therapies from reaching millions of people around the world.

Criticism #2: Combination therapies may increase resistance

In a recent letter to me, Assistant Secretary of State for Legislative Affairs Paul Kelly argued that the United States was concerned that recommended combination drugs could lead to increased HIV resistance.¹⁴ This argument, which has been repeated by other senior officials, only tells half the story, however. It is certainly true that if combination therapies are sub-potent, inadequate drug levels may provide HIV with the opportunity to mutate into a more resistant form. But if these drugs are made correctly, they pose no more of a risk of increased resistance than a similar regimen of individual drugs.

¹⁰Centers for Disease Control and Prevention, *Global Immunization Division* (2004) (online at <http://www.cdc.gov/nip/webutil/about/divisions/gid.htm>) (The United States “[p]rovides polio vaccine, through UNICEF, for National Immunization Days and mop-up campaigns to eradicate polio”).

¹¹World Health Organization, *Procedure for Assessing the Acceptability, in Principle, of Vaccines for Purchase by United Nations Agencies* (2002).

¹²Conference call between minority staff, Government Reform Committee, and USAID (Apr. 28, 2004).

¹³Conference call between minority staff, Government Reform Committee, and UNICEF (Apr. 30, 2004).

¹⁴Letter from Assistant Secretary of State for Legislative Affairs Paul V. Kelly to Rep. Henry A. Waxman (Apr. 27, 2004).

In fact, experts believe that combination therapies pose less risk than noncombination treatment. Drug resistance occurs when the virus is not hit with the full force of a multi-drug regimen. Patients taking multiple pills at the same time may not be able to adhere to a complex regimen. By contrast, patients taking just one pill are guaranteed to adhere to the entire regimen at once.¹⁵ This potential advantage of these drugs was not mentioned by Assistant Secretary Kelly and is seldom acknowledged by other U.S. officials.

Criticism #3: The United States has not been permitted to review safety and efficacy data on combination therapies.

Administration officials emphasize that the United States has not reviewed the safety, efficacy, and quality data shared by Indian drug manufacturers with WHO. I am also aware that some officials are suggesting that the failure of WHO to share this data with the United States indicates a potential problem with the therapies. This allegation is unfair. To maintain integrity in its review process, WHO assures companies of protection of confidential information. This is no different from FDA's process.

I support U.S. access to data on combination therapies. The easiest way for the United States to obtain such access would be for FDA officials to participate in the WHO review process. Had this step been taken two years ago, when such an invitation was made, this access would already have been achieved. Your Administration has, however, refused this opportunity to review the data.

Principles for the Review of Combination Drugs

In addition to undermining confidence in recommended combination therapies in public statements, your Administration is circulating a draft of principles for the review of these products that could lead to unjustified delays in their approval or to outright rejection.

This draft follows a meeting in Botswana at the end of March. In advance of that meeting, I wrote you to express concern that a number of aspects of the document appeared to set standards higher than those required by FDA.¹⁶ While the revised draft of the document includes a number of appropriate changes, it still sets requirements that could be interpreted as exceeding FDA standards. It also contains omissions and phrases that could be used as needless barriers to combination drugs. I have three major concerns about this draft.

First, the draft lacks a sense of urgency. At the conference, Dr. Clive Ondari of WHO reported that combination drugs were the "first choice" for frontline use against HIV in the developing world. Julian Fleet, a senior adviser to UNAIDS, described these products as

¹⁵World Health Organization, *supra* note 2.

¹⁶Letter from Rep. Henry A. Waxman to the President (Mar. 26, 2004).

“crucial” to the success of the effort to treat 3 million people with antiretroviral therapy by 2005. He said that the goal should be the “most rapid possible approval” of these therapies. Yet the preamble to the draft does not include any of these statements. Nor does it otherwise express any sense of urgency. Instead, it describes combination drugs as simply being one part of “an important approach” to addressing infectious diseases.¹⁷

Second, the draft sets an unreasonable standard for justifying the combination of separate treatments into one pill. In the section on safety and efficacy standards for fixed-dose combination drugs that combine an accepted regimen into one pill, the draft states, “Each active component must be shown to contribute an advantage, when incorporated . . . at the relevant doses.”¹⁸ This standard appears to require manufacturers to provide a series of studies comparing the combined regimen and that regimen minus each of the components. Some of these comparisons may not exist. In addition, they may not be necessary.¹⁹

It is instructive to compare the language in the draft with the practice of FDA and European regulators. These bodies do not appear to have required such a series of comparisons for the approval of Trizivir, a brand-name combination therapy. For example, the approved U.S. labeling for Trizivir (lamivudine + zidovudine + abacavir) states that the drug was approved on the basis of bioequivalence studies. The labeling also describes two clinical studies, each of which compares the combination of lamivudine and zidovudine with the triple combination. Thus, only the contribution of abacavir to Trizivir was tested.²⁰

Similarly, a European Public Assessment Report (EPAR) on Trizivir, which was prepared by the European Agency for the Evaluation of Medicinal Products (EMA), cites only studies that appear to test (1) the contribution of abacavir or (2) the effectiveness of all three drugs together. None of tests relied upon by EMA evaluates the contribution of lamivudine or zidovudine to the triple combination.²¹

¹⁷*Scientific and Technical Principles for Fixed Dose Combination Drug Products: Draft*, 2 (Apr. 22, 2004) (online at <http://www.globalhealth.gov/Final%20Draft%204-22.doc>).

¹⁸ *Id.* at 7.

¹⁹At the Botswana meeting, there was consensus that internationally accepted and recommended regimens did not need to be re-justified as part of the review process for a combination therapy. For example, Swiss and Canadian regulators stated that a demonstration that a particular regimen was appropriate for combining into a fixed-dose combination could be based on international guidelines.

²⁰The U.S. label is online at http://us.gsk.com/products/assets/us_trizivir.pdf.

²¹EMA, *EPAR on Trizivir, Revision 2, Sept. 18, 2003* (online at <http://www.emea.eu.int/humandocs/Humans/EPAR/Trizivir/Trizivir.htm>).

Third, the draft contains unnecessary language on postlicensing responsibilities. At the Botswana meeting, debate focused on whether there was a need for companies to conduct extensive postmarketing surveillance for fixed-dose combination products. Because of the near impossibility of any manufacturer working in the developing world conducting such surveillance, the general consensus at the meeting was that the public health system would have to play the key role in monitoring for quality problems and resistance. Participants also pointed out that postmarketing requirements for combination therapies would be quite similar to those for all HIV drugs, including those already provided in developing countries.

The draft, however, fails to recognize the key role of public health systems in postmarketing surveillance. There is no acknowledgement in the text that the drug distribution system, which is conducted by the public health system in developing countries, should bear the primary responsibility for assessing postmarketing safety and effectiveness in resource-poor settings. The draft therefore leaves open the possibility of unrealistically holding companies responsible for extensive surveillance. This interpretation could then become a barrier to the development and use of these products.

The draft also treats fixed-dose combination drugs as requiring substantially more postmarketing surveillance than other drugs. This distinction makes little sense. Each of the “specific postmarketing issues” cited for fixed-dose combination products — including the possibility of adverse events, “additive or synergistic toxicities,” the change in resistance, and lack of efficacy — applies to all pharmaceutical products, not just fixed-dose combinations.²²

Conclusion

There are few issues that approach the magnitude of the global AIDS epidemic. Your efforts to draw attention and commit resources to this crisis have been extremely valuable. This effort, however, is at a crossroads. One path leads to greater international cooperation in the review and approval of combination therapies. The other path leads to confusion at the local level and the assigning of therapies on the basis of funding source, not clinical need.

It appears to me that your Administration is already several steps down the wrong path. I urge you to reverse course immediately.

FDA reviewers and inspectors should join the WHO drug review process. This step will provide U.S. officials with full access to data on current and future combination therapies and will enhance international efforts to achieve consistency. Administration officials should also speak of the promise of these drugs as well as potential risks. Finally, the United States should seek changes to the document on principles for review to assure that it does not

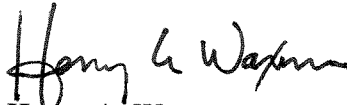
²²*Scientific and Technical Principles for Fixed Dose Combination Drug Products: Draft, supra* note 17, at 10.

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become a needless barrier to the consistent use of "first choice" antiretrovirals in the developing world.

Applications for fiscal year 2005 funding in global AIDS will be due this fall. These issues must be resolved well in advance of these applications.

Sincerely,

A handwritten signature in black ink that reads "Henry A. Waxman". The signature is written in a cursive style with a large initial "H" and a long, sweeping underline.

Henry A. Waxman
Ranking Minority Member