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The Honorable Tommy G. Thompson
Secretary of Health and Human Services
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Mr. Secretary:

I am concerned that the Administration's new initiative to review promising AIDS drugs for international use will significantly and unnecessarily delay their availability.

With as many as three drugs in one pill, combination therapies are considered the "first choice" AIDS treatment in developing countries. In May, the Administration announced a plan for the U.S. Food and Drug Administration (FDA) to review these drugs within "two to six weeks," raising expectations of their imminent purchase through the President's Emergency Plan for AIDS Relief. This plan received widespread accolades in the news media, with the *New York Times* editorializing that "the Bush administration has finally come to its senses and found a way to provide cheap generic drugs and single-pill combinations of drugs to millions of people infected with the AIDS virus in Africa and the Caribbean."

It now appears, however, that the "two to six weeks" timetable promised by the Administration was highly misleading. Based on a close review of FDA documents and discussions with FDA officials, I have learned that the accelerated timetable starts only after companies submit a complete application to FDA. In order to have a complete application, even those companies whose combination drugs have passed a review by the World Health Organization (WHO) may have to repeat clinical studies, a raw materials review, and detailed inspections. This pre-submission process is burdensome and could easily add many months, if not years, to the approval process.

Delay benefits major U.S. pharmaceutical companies, which do not yet manufacture any of the most recommended combination drugs. But it does not serve the millions of people infected with HIV around the world. As this week's *Lancet* recognized, new research shows that "there is no question about the safety and efficacy" of a leading WHO-approved combination therapy. This therapy and other similar life-saving combination drugs should be made available to HIV-infected individuals across Africa and the developing world as rapidly as possible.

I urge you to develop a realistic plan for quick approval of essential combination therapies by truly expediting the FDA review process or by participating in the WHO approval process. Either option will substantially speed up U.S. purchase of combination drugs for HIV/AIDS.

Background

Outside of the United States, combination therapies for AIDS are rapidly becoming the standard of care because of their ease of use and advantages in avoiding drug resistance. The World Bank and Global Fund to Fight AIDS, Tuberculosis, and Malaria are already purchasing these products. These organizations have relied upon the review process of the WHO, which includes a detailed review of written submissions from companies, quality testing, and inspections. To date, however, the United States has refused to authorize the purchase of the combination AIDS drugs.

This reluctance to accept combination AIDS drugs that have passed the WHO review process has frustrated infectious disease experts, AIDS advocates, and nonprofit service organizations. These individuals and organizations are concerned that a major opportunity to provide the best possible treatment in developing countries is being lost. For example, Interchurch Medical Assistance, a member of the Catholic Relief Services Consortium, has stated that “it is critical that . . . constraints are removed so that FDC ARVs [fixed-dose combination antiretrovirals] are an option for our facilities and patients, as soon as possible.”¹

Last month, in the face of growing international pressure, the Administration announced a new plan to review combination AIDS drugs. Rather than participate in the WHO review process, the Administration promised that the U.S. Food and Drug Administration (FDA) would conduct its own “rapid review of new combination products” with a goal of approval within two to six weeks.²

Newspapers and public health officials quickly praised the announcement as a sign that effective and low-cost combination therapies would soon be purchased by the United States for the developing world.³ *USA Today* reported that the “Bush Program would rush low-cost drugs to Africa,”⁴ the *Washington Post* praised a “promising shift in policy” that could lead to a “big

¹The Catholic Relief Services Consortium is a grantee under the President’s Emergency Plan for AIDS Relief. Interchurch Medical Assistance, Botswana, *Statement of Jacqueline Patterson* (Mar. 29, 2004).

²HHS, *HHS Proposes Rapid Process for Review of Fixed Dose Combination and Co-Packaged Products* (May 16, 2004).

³*U.S. Speeding up Approval Steps for AIDS Drugs*, New York Times (May 17, 2004).

⁴*Bush Program Would Rush Low-Cost AIDS Drugs to Africa, Caribbean*, USA Today (May 17, 2004).

jump in the number of patients receiving treatment,”⁵ and the *New York Times* editorialized that “the Bush administration has finally come to its senses and found a way to provide cheap generic drugs and single-pill combinations of drugs to millions of people infected with the AIDS virus in Africa and the Caribbean.”⁶

Hidden Delays in the FDA Guidance Document

Unfortunately, it now appears that the Administration misled many observers. A close review of the FDA Guidance Document outlining the process for approval of combination drugs — augmented by discussion with FDA staff — reveals that approval of combination therapies is likely to take much longer than promised. In fact, it is unlikely that the most sought-after combination drugs will be approved and available for purchase by the United States until well into 2005 at the earliest.

The fundamental problem is that the promised two- to six-week review period begins only when the drug manufacturer has submitted an application that FDA deems to be complete. According to information provided by FDA staff, satisfying FDA requirements for an acceptable complete application will be difficult and time-consuming for most manufacturers. Although FDA may review the completed application in a matter of weeks, it may be many months, if not years, before the manufacturers have assembled the information necessary for the application.

The following discussion explains the requirements that unnecessarily slow the process of completing an application and obtaining approval — or that may even dissuade manufacturers of existing combinations from applying at all.

The WHO Dossier Cannot Substitute for the FDA Application

In order to pass the WHO review, companies conduct studies to demonstrate that the combination therapies produce the same drug levels as individual pills (“bioequivalence” studies), submit to plant inspections, provide data on drug ingredients and stability, and satisfy a host of other requirements. This information is compiled into a dossier that is the basis of review. According to FDA staff, however, applicants for FDA approval of combination AIDS drugs will not be able to submit the dossier they created for WHO approval. FDA staff said that they were unfamiliar with the WHO dossier and had not been asked to determine whether any parts of it could be used to satisfy FDA requirements. Instead, manufacturers of combination AIDS drugs will have to file a new application meeting all of FDA’s traditional requirements.

Putting together an FDA application for approval of a new drug is a highly technical process. For those companies not familiar with meeting FDA application requirements,

⁵*Progress on AIDS*, Washington Post (May 21, 2004).

⁶*Progress on Pills*, New York Times (May 18, 2004).

assembling an acceptable application generally requires a prolonged exchange with FDA, which can extend over several months. According to FDA staff, the most important factor in the length of time it will take to obtain FDA approval of a combination AIDS drug will be the degree of experience the manufacturer has in filing FDA applications. Unfortunately, key manufacturers of combination therapies lack this prior experience. For example, the manufacturer of Triomune (stavudine + lamivudine + nevirapine), the combination AIDS drug in widest use in Africa, is Cipla, a company with no approved FDA applications. As a result, FDA's refusal to consider the WHO dossier will inevitably cause extensive delays in the approval process.

Bioequivalence Studies May Have to Be Repeated

It has been widely assumed that under the new policy, companies whose products have passed WHO review will not need to conduct additional studies demonstrating bioequivalence of combination therapies to the individual drugs. After all, these studies were required to pass the WHO process. I have learned, however, that the studies completed to satisfy WHO may not be sufficient to gain FDA approval. If the combination drug were compared to individual drugs approved outside of the United States — as appears to be the case — the manufacturer of the generic combination drug is likely to be required to conduct new bioequivalence studies with the U.S.-approved versions.

FDA staff described three potential scenarios, each of which is likely to entail significant delays. In the first scenario, the makers of the combination drug use individual drugs for comparison that were made in the same FDA-approved plant by the same brand-name manufacturer as the U.S. versions. If there is a clear statement from the brand-name manufacturer that the two versions of the drug are the same, FDA could rely upon the bioequivalence study. However, the brand-name company may not wish to provide such a statement, forcing the maker of the combination drug to conduct new bioequivalence studies.

In the second scenario, the makers of the combination drug use one or more individual drugs for comparison that were made in facilities that do not serve the United States by the same manufacturer as the U.S. version. If so, new bioequivalence studies will be required unless there is proof that the facilities are equivalent to those that do serve the United States and that the two versions of the drug are the same. Participation from the brand-name manufacturer, which would be essential for this proof, again might not be forthcoming.

In the third scenario, the makers of the combination drug used drugs for comparison that were made by a different company than the U.S. version. In this case, new bioequivalence studies would always be required.

The most sought-after generic combination drugs, which have been reviewed and approved by WHO, were compared in their bioequivalence studies to European versions of the three single-ingredient drugs. This means that one of the three FDA scenarios will apply to these

products, most likely triggering new bioequivalence studies and causing extended delays in the approval process.

Raw Materials Reviews May Have to Be Repeated

A complete FDA application for a drug usually contains information from a “drug master file” for each of the raw ingredients used in the finished drug.⁷ A drug master file provides highly detailed, technical information on the chemistry, manufacturing, and controls used in the production of a raw ingredient.⁸ The drug master file must be prepared by the manufacturer of the raw ingredient and then reviewed by the FDA.

For raw ingredients already used in U.S.-approved drugs, drug master files may already be in FDA’s possession. For raw ingredients not used in U.S.-approved drugs, however, a new drug master file will have to be submitted to and reviewed by FDA before the application for the combination drug can be approved. FDA will not consider accepting a review by WHO to satisfy this standard.

As an alternative to the submission of a new drug master file, a company may supply detailed information on the raw ingredients used its products. Under this scenario as well, however, FDA will not consider documents submitted to WHO or WHO’s review of these ingredients.

Inspection of Manufacturing Sites Will Have to Be Repeated

According to FDA staff, companies must pass FDA inspection, even if they have already passed an equivalent inspection by WHO. FDA staff report that no attempt is underway to review the inspections already conducted by WHO to determine whether those inspections could suffice for FDA approval.

Instead, FDA staff anticipate that the FDA will conduct new inspections of each manufacturing site where combination AIDS drugs are made. Foreign inspections of manufacturing sites normally take several months to plan and carry out. FDA staff state that the new inspections will be carried out while the applications are being completed, further suggesting that FDA anticipates that assembling a complete application will be a lengthy process.

⁷FDA, *Draft Guidance for Industry — Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV* (May 2004) (online at <http://www.fda.gov/oc/initiatives/hiv/hivguidance.html>); 21 CFR 314.420.

⁸ FDA, *Draft Guidance for Industry — Drug Substance: Chemistry, Manufacturing, and Controls Information* (Jan. 2004) (online at <http://www.fda.gov/cder/guidance/3969DFT.doc>).

Some Drugs Are Barred from Review under the New Policy

FDA's governing statute prohibits the agency from considering a generic drug application for four years after the approval of a "new molecular entity."⁹ This prohibition, which applies to the new policy, could substantially delay the agency's ability to review some new combination products.

Currently, several drugs for treating HIV/AIDS are considered new molecular entities and are in the four-year window during which no generic drug application may be submitted to FDA. These drugs include tenofovir, a drug that is listed in Attachment B of FDA's guidance as a promising drug for a combination therapy.¹⁰ In a public exchange on the internet, Dr. Mark Dybul, Deputy Chief Medical Officer in the Office of the Global AIDS Coordinator, admitted that combination products containing tenofovir "would actually be excluded from this process."¹¹

In further comments, Dr. Dybul stated, "There are ways to work through the process."¹² The meaning of this statement, however, is not clear. FDA staff stated that the agency cannot consider any application that includes tenofovir until October 2005.

I recognize that it is not yet clear whether this gap in FDA's new policy will actually interfere with the development of combination therapies. There are no available single-pill regimens that include tenofovir and the other new molecular entities at the present time. However, the progress of research may spur demand in the future. It seems a mistake to bar the review of any of these drugs for any significant length of time.

Implications of the U.S. Policy

The new FDA process will significantly delay U.S. purchase of the most promising combination therapies that are already in use around the world. These delays may benefit brand-name pharmaceutical companies, who will now be given extra time to submit new applications for their own combination therapies. In fact, on the day of your announcement of the new FDA

⁹21 U.S.C. § 355(j)(5)(D)(ii). An application for a generic version of a new molecular entity may not be approved for five years after the original approval.

¹⁰ FDA, *supra* note 7.

¹¹Kaiser Family Foundation, *Ask the Experts: Fixed Dose Generic Drugs* (June 16, 2004) (online at http://www.kaisernetwork.org/health_cast/uploaded_files/061604_ask_genericdrugs.pdf).

¹² *Id.*

initiative, several brand-name companies also announced that they would be working together to produce their own combination product jointly.¹³

But the delays could seriously undermine international efforts to fight AIDS in the developing world. Organizations providing treatment with U.S. funds are entering into procurement contracts and supply chain systems with the brand-name companies, using more costly and more complicated single-dose drugs. Once locked into these contracts, it will be difficult for U.S.-funded organizations to switch to easier-to-use, more cost-effective drugs.

The delays also promote confusion and inefficiency. Some front-line organizations, funded by international agencies, are already purchasing and providing first-choice combination therapies. A disjointed system could emerge at the local level in which treatment guidelines and regimens are based on source of funding, not public health strategy.

The urgency of the situation is underscored by the publication this week in the *Lancet* of research showing that a combination AIDS treatment approved by the WHO made HIV levels undetectable in 80% of patients treated in Cameroon.¹⁴ An accompanying editorial concluded that “there is no question about the safety and efficacy” of the treatment.¹⁵ The United States is lagging behind an emerging medical consensus that these combination therapies need to play a central role in combating AIDS in developing nations.

Every month, over 240,000 people die from AIDS. With so much at stake, there is no excuse for unnecessary delays that keep recommended drugs from reaching those who need them.

The Need for a New Plan

It is essential that the United States develop a revised plan that will actually accomplish quick approval of essential combination therapies.

One option is for FDA to expedite its existing plan by proactively seeking out existing data on combination therapies, rather than waiting for generic drug applicants to recreate reams of data. FDA could:

¹³Gilead, BMS, Merck *Considering Combining Three HIV Therapies*, Bioworld Today (May 18, 2004).

¹⁴C. Laurent et al., *Effectiveness and Safety of a Generic Fixed-Dose Combination of Nevirapine, Stavudine, and Lamivudine in HIV-1-Infected Adults in Cameroon: Open-Label Multicentre Trial*, *Lancet*, 29–34 (July 3, 2004).

¹⁵N. Kumarasamy, *Generic Antiretroviral Drugs — Will They Be the Answer to HIV in the Developing World?*, *Lancet*, 3–4 (July 3, 2004).

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- request the WHO dossier for WHO-reviewed combination therapies and quickly determine what additional data or information is needed;
- contact European regulators to determine whether drugs approved in Europe and used in bioequivalence studies are the same as U.S. versions;
- request WHO inspection reports and determine if any additional inspection is necessary;
- request WHO reviews of raw materials and determine if any additional review is necessary;
- create a non-FDA review process for drugs subject to the exclusivity period for new molecular entities so as to permit these drugs to be included in combination therapies in developing countries.

An alternative is for you to reconsider the Administration's refusal to participate in the WHO review process. The recent *Lancet* article affirming the safety and effectiveness of the most widely used WHO-reviewed combination drug lends new support to the credibility of the WHO review process. Joining with the international community would allow the United States to review all of the data already presented to WHO, minimizing the costly delays associated with repeating studies and inspections. It could also provide an opportunity to speed up this process by infusing it with needed resources.

Conclusion

The HIV/AIDS pandemic is devastating developing nations across the globe. While the United States has the right and obligation to ensure the safety and effectiveness of medications provided with U.S. funds, unnecessary delays are inexcusable. I urge you to recognize the delays in the new U.S. process and come up with a better process as rapidly as possible.

Sincerely,



Henry A. Waxman
Ranking Minority Member