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Food and Drug Administration
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Docket No. 2004D-0228

Guidance for Industry: Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV

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The HIV Medicine Association (HIVMA) is pleased to submit comments on this draft guidance. We have publicly stated our support for the purchase and use of low-cost, bioequivalent fixed dose combinations to provide safe and effective treatment to the two million individuals in the 15 countries targeted by the President's Emergency Plan for AIDS Relief (PEPFAR). We have also endorsed the World Health Organization (WHO) precertification process, as a legitimate process to ensure that fixed dose combination (FDC) antiretrovirals produced by generic manufacturers are safe and effective. We also submitted comments on the April 22 draft document: *Scientific and Technical Principles for Fixed Dose Combination Drug Products*. In our comments, we noted that the principles outlined would appear to impose higher standards of safety, efficacy and quality for fixed dose combination drugs than for innovator drugs reviewed and approved by the Food and Drug Administration (FDA) for use in this country. The standards articulated in that document would seem to pose insurmountable barriers to the approval of generic fixed dose combinations for purchase with PEPFAR funds, including drugs that are already being used successfully in many of the countries targeted by the PEPFAR initiative.

It is in that context that we approach the May 2004 draft guidance. Our comments focus primarily on the review and approval process outlined for an application from a noninnovator company for approval of a two or three-drug fixed dose combination—so called Scenario 2 in the guidance.

We are pleased to see the outline of an expedited process for FDA review of such fixed dose combinations and a stated policy goal "to encourage sponsors to submit applications to the Food and Drug Administration (FDA) for approval of fixed dose combination (FDC) and co-packaged versions of previously approved antiretroviral therapies for the treatment of Human

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immunodeficiency virus (HIV). “ (Lines 19-22). We do have some concerns about the ability of foreign generic companies with no experience with the FDA to navigate the FDA application process. We also are concerned that it may be challenging for the FDA to implement this new process in a fashion that ensures expeditious approval so these drugs become a key component of the armamentarium of medications purchased by PEPFAR as year two of the five-year initiative quickly approaches. Nevertheless, on balance, we view the draft guidance as a good faith effort to both ensure quality and efficacy and to facilitate the availability of lower cost, simpler regimens to countries eligible for PEPFAR funds.

We appreciate that the U.S. government has made a policy decision that a U.S.- driven evaluation and approval process to determine safety and efficacy of FDC drugs is critical. Nevertheless, we hope the FDA will work closely with the WHO, especially in instances where a medication has already undergone WHO review. The use of WHO data to establish bioequivalency and efficacy will significantly streamline the process. Since it is unlikely that innovator companies will share data with generic producers, the use of information in the WHO drug dossier can obviate the need for additional clinical studies and save valuable time in the process. Cooperation with European counterparts to the FDA would also be helpful, given that many of the clinical studies conducted by generic manufacturers compared FDCs to drugs produced and sold in Europe. Requiring generic manufacturers to conduct clinical studies comparing their products to drugs manufactured in the U.S. is clearly unnecessary and would obviously undermine the fundamental goals of this accelerated process.

While anecdotal accounts abound from a wide range of developing nations, there is currently limited peer-reviewed data on the efficacy of these combinations. Nevertheless, studies are emerging, including a study published by C. Laurent et al in the July 3, 2004 issue of *Lancet*. It is our understanding that generic manufacturers will be able to submit a literature review of the many studies documenting the efficacy of the individual drugs used in combination to create the FDC.

We have been heartened to hear about FDA’s outreach to generic companies around the world that currently produce these drugs and the offer of technical assistance described in the draft guidance. This level of support will be crucial from the beginning to the end of the application and approval process if the promise of expedited review and approval is to be realized. While the guidance references a two to six week approval time frame once the application is completed, we also know that a great deal of activity and negotiation with the FDA occurs before a completed application is formally submitted. The willingness of the FDA to conduct certain review activities, such as inspecting manufacturing plants, before the application is completed, will help move the process forward more quickly.

The goals set out in the guidance are challenging, and some components of this process are unprecedented, so that no track record exists. The AIDS pandemic demands new and rapid ways of bringing lifesaving treatment to millions. It is indisputable that the need for HIV treatment is urgent, and millions of lives hang in the balance. Ultimately, the value and success of this process will be measured, in part, in lives saved, and the rapid availability of high quality, low-cost medications, particularly FDCs, will play a critical role in determining that success. We look

forward to hearing the announcements of drug approvals under this new guidance, and hearing them soon.