Guidance for Industry

User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR

DRAFT GUIDANCE

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For questions regarding this draft document contact Michael Jones at 301-594-2041.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2005

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance describes the circumstances under which some applications for fixed dose combination (FDC) and co-packaged versions of previously approved antiretroviral therapies for the treatment of human immunodeficiency virus (HIV) will not be assessed user fees under the Prescription Drug User Fee Act (PDUFA). The guidance also describes circumstances under which many of the applications, products, and establishments that will be assessed fees may be eligible for a public health or a barrier to innovation waiver. ***We expect that most of the applications, products, and establishments for FDC and copackaged HIV therapies proposed for use in the President's Emergency Plan for AIDs Relief (PEPFAR) will either not be assessed fees in the first instance or will qualify for a waiver under the special circumstances part of the barrier to innovation user fee waiver.*** See the Attachment at the end of the guidance for a summary of available exemptions and waivers.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of Anti-Viral Drug Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Office of Regulatory Policy, CDER.

All guidances mentioned in this draft are available at http://www.fda.gov/cder/guidance/index.htm.

II. BACKGROUND

As part of the President's Emergency Plan for AIDs Relief, the President committed sizeable resources, including $15 billion over a 5-year period to fund a program to develop programs to address the treatment of HIV. [2]

To encourage applicants to submit applications for HIV combination therapies that can be used in PEPFAR, in May 2004, the FDA issued a draft guidance titled *Fixed Dose Combination and Co-Packaged Drug Products for the Treatment of HIV* (Fixed-Dose Guidance). Attachments to the Fixed Dose Guidance described some scenarios for approval of fixed dose combination (FDC) or co-packaged products for the treatment of HIV and provided examples of drug combinations considered acceptable for FDC/co-packaging and examples of those not considered acceptable for FDC/co-packaging. The guidance also explained that the Federal Food, Drug, and Cosmetic Act (the Act) provides for certain circumstances in which FDA can grant applicants a waiver or reduction in user fees normally assessed for drug applications, drug products, and establishments where drugs are made. The Fixed Dose Guidance stated that FDA was evaluating the circumstances under which it may grant user fee waivers or reductions for applicants developing FDC and co-packaged versions of previously approved antiretroviral therapies for the treatment of HIV.

Several potential applicants have asked that we clarify whether applicants submitting drug applications pursuant to the Fixed Dose Guidance for use in PEPFAR will be required to pay user fees under the Prescription Drug User Fee Act (PDUFA) and if so, whether they would be eligible for a waiver of those fees.

III. SOME APPLICATIONS WILL NOT BE ASSESSED FEES; SOME WILL BE ASSESSED HALF THE FEE

Under PDUFA, the following types of drug applications are ***NOT*** assessed user fees:

- Abbreviated new drug applications (ANDAs) submitted under section 505(j) of the FD&C Act (§ 735(1))

- Applications submitted under 505(b)(2) of the FD&C Act that do not request approval of (1) a new molecular entity (i.e., an active moiety that has not been approved under an application under 505(b)) or (2) an indication for a use that has not been approved under an application under 505(b) (§ 735(1)(b))

Most applications submitted under Scenarios 2 and 3 of Attachment A to the draft Fixed Dose Guidance could qualify for these fee exemptions.

[2] White House Fact Sheet "The President's Emergency Plan for AIDS Relief," available on the internet at www.whitehouse.gov/news/releases/2003/01/20030129-1.html.

Any ANDA submitted under section 505(j) of the Act would be exempt. However, because only certain 505(b)(2) applications are exempt, it is important that potential applicants who do not want to be assessed fees be advised to use active ingredients submitted in applications that have already been approved under section 505(b) (that is, they can use any of the ingredients listed in Attachment B to the Fixed Dose Guidance), and they should ***not*** seek any new indications for a use. It is particularly important that they strictly follow the approved labeling for the individual ingredients. If, for example, they seek a different use of the drug, or a different dosing regimen or route of administration, or use in a new population, or compare their product to others in the labeling, they ***will not qualify*** for the 505(b)(2) exemption from fees.

Finally, any application submitted under 505(b)(1) or 505(b)(2) of the Act that does not require clinical data for approval would only be assessed a half fee (§ 736(a)(1)(A)) under the Act. This half fee would be $336,000 for Fiscal Year 2005.[3] Bioavailability and bioequivalence data are not considered clinical data for purposes of assessing user fees.[4]

IV. WAIVERS OF FEES

A. Application Fees

Applicants of applications that will be assessed either a full or a half fee may qualify for waivers of their application fee under several provisions of PDUFA. Waivers must be requested of FDA not later than 180 days after the fees are due, and FDA encourages firms to request a waiver at least 45 days in advance of submission of an application so that the request can be evaluated before the fee is due.[5]

The waivers most likely to be available to PEPFAR participants are:

- The ***small business waiver***, which provides for a complete waiver of the application fee for any company with less than 500 employees (including affiliated companies) for the first application the company (including its affiliates) submits.[6] Applicants must request this waiver from FDA and provide evidence to the Small Business Administration regarding the size of the company.

[3] October 1, 2004, through September 30, 2005.

[4] See FDA's guidance for industry *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*.

[5] Normally, FDA encourages the submission of requests for waivers 90 days in advance of the submission of an application. But to further reduce the burden on sponsors interested in making products available under PEPFAR, FDA will expedite the processing of waiver requests and try to process such requests within 45 days.

[6] Section 736(d)(3), 21 U.S.C. 379h(d)(3).

- The ***public health waiver*** and the ***barrier to innovation waiver***, which provide for waivers of application fees, and annual product and establishment fees for companies that meet the criteria.[7]

FDA's *Attachment G —Draft Interim Guidance Document for Waivers of and Reductions in User Fees* (waiver guidance), sets out the criteria for each of these waivers.[8] FDA evaluates requests for these waivers on a case-by-case basis.

To reduce financial barriers to the development of these products, FDA has determined that any FDC or co-packaged drug product for the treatment of HIV that is listed in Attachment B of the Fixed Dose Guidance will, for the foreseeable future, be considered to benefit the public health because making these products available in the 15 countries that are the targets of the PEPFAR program will have a significant impact on the global efforts to treat HIV.

Furthermore, for the foreseeable future, FDA will consider any FDC or co-packaged drug product for the treatment of HIV that is listed in Attachment B of the Fixed Dose Guidance to be innovative because simplified regimens that will facilitate distribution and patient compliance, particularly in treatment naïve patients, are needed in developing countries. Therefore, FDA has determined that these products will meet the first parts of the two-part PDUFA test for public health and barrier to innovation waivers. At some point in time, after several alternative treatments have been made available, FDA may reevaluate whether these products remain innovative or whether a waiver for these products is necessary to protect the public health and may find that, because of the existence of treatment alternatives, user fee waivers may no longer be appropriate.

The second part of the test for granting a public health or barrier to innovation waiver is a financial test. That is, (1) a waiver of a user fee must be necessary to protect the public health, or (2) the assessment of the fee must be a barrier to innovation because of limited resources or other circumstances. Therefore, the statute gives FDA more discretion under the barrier to innovation test.[9] Normally, a company with greater than $10 million in total annual revenue would not be found to have limited resources and would not be eligible for either a public health or a barrier to innovation waiver. However, ***FDA intends to consider the development of drugs for the PEPFAR program to be the sort of "other circumstances" that would justify a waiver of PDUFA user fees under the barrier to innovation waiver provision provided the applicant meets all of the following***:

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[7] Section 736(d)(1)(A) and (B), 21 U.S.C. 379h(d)(1)(A) and (B).

[8] PDUFA also provides for a fees-exceed-the-cost waiver, in which the fees associated with all of an applicant's submissions are compared with standard costs associated with FDA's reviews of the submissions and if the fees exceed the costs, the applicant gets a refund. FDA does not believe this provision will provide a basis for waivers for PEPFAR participants but is mentioning it for completeness. For further information on this waiver see the *Fees-Exceed-The-Cost Waivers under the Prescription Drug User Fee Act* guidance.

[9] The statute does not provide FDA the ability to consider "other circumstances" when determining whether to grant a public health waiver. Accordingly, a company requesting a public health waiver will have to establish that it has limited resources to receive a public health waiver.

- The applicant is submitting an application for a FDC or co-packaged drug product for treatment of HIV from among the examples that are listed in Attachment B of the Fixed Dose Guidance.
- The applicant will only obtain a tentative approval in the United States for the product because, for example, it cannot market the product in the United States because of patents or exclusivity on the innovator product.
- The applicant certifies that upon receipt of tentative approval for the product, the applicant will make the product available at competitive prices suitable for procurement under PEPFAR in one or more of the 15 designated PEPFAR countries. FDA will accept certifications that are supported with one of the following: (1) evidence that the product is being offered for procurement by PEPFAR, and (2) evidence that the product for which the application is being submitted has been approved for use by the government of one or more PEPFAR countries; or (3) if such approval has not been obtained, the FDC is listed on an HIV treatment guideline for one or more of the PEPFAR countries and the applicant provides a plan and schedule for the submission of an application for approval in one or more of the countries.

To obtain a barrier to innovation waiver, applicants should submit a request for a waiver 45 days before an application will be submitted. The waiver request should contain the certifications described above.

B. Annual Product and Establishment Fees

PDUFA provides for annual user fees for certain prescription drug products and establishments. However, the following are not assessed annual user fees:

1. Products approved under section 505(b)(2) applications that are not assessed application fees because they are not for a new molecular entity or a new indication for a use
2. Products that are the same as another product approved under an application filed under section 505(b) or 505(j) of the Act
3. Products that are only tentatively approved.

If product fees are not assessed, the establishments in which such products are made are not assessed annual establishment fees, unless other fee paying products are made in the same establishment. Therefore, a waiver would not be necessary for these product and establishment fees. However, ***FDA intends to consider the development of drugs for the PEPFAR program to be the sort of "other circumstances" that would justify a waiver of PDUFA product and establishment user fees under the barrier to innovation waiver provision provided the applicant meets all of the following:***

- The applicant has obtained approval for an application for an FDC or co-packaged drug product for treatment of HIV from among the examples that are listed in Attachment B of the Fixed Dose Guidance.

- The applicant certifies that it is making the product available at competitive prices suitable for procurement in one or more of the 15 designated PEPFAR countries. FDA will accept certifications that are supported with one of the following: (1) evidence that the product is being offered for procurement by PEPFAR and (2) evidence that the product for which the waiver is sought has been approved for use by the government of one or more PEPFAR countries; or (3) if such approval has not been obtained, the FDC for which the waiver is sought is listed on an HIV treatment guideline for one or more of the PEPFAR countries and the applicant provides a plan and schedule for the submission of an application for approval in one or more of the countries.

- For establishment fees, no other user fee eligible products owned by the applicant are being manufactured at the establishment at which the PEPFAR product is being manufactured.

The annual product and establishment fees are invoiced in mid-August with fees due to be paid by October 1 of each fiscal year. We encourage applicants to submit requests for waivers of annual product and establishment fees by August 15 of each year.

For information about how to request a waiver or reduction, please contact the user fee team in the Office of Regulatory Policy at 301-594-2041. More information on user fees is available on the Internet at http://www.fda.gov/cder/pdufa/default.htm.

ATTACHMENT: SUMMARY OF AVAILABLE EXEMPTIONS AND WAIVERS

Table 1: User Fee Exemptions

Applications Not Assessed Fees or Assessed Reduced Fees:

- Generic drug application submitted under 505(j)
- Application submitted under 505(b)(2) if not (1) a new molecular entity or (2) a new indication for a use
- Application that only requires BA/BE data will be assessed only 1/2 application fee

Products Not Assessed Product Fees:

- Tentatively approved product or product otherwise not approved
- Product approved under section 505(b)(2) application that is not assessed application fees
- Products that are the same as another product approved under an application filed under section 505(b) or 505(j) of the Act
- If product isn't assessed a fee, establishment in which it is made also not assessed a fee

Table 2: User Fee Waivers for PEPFAR Products

Application Fees:

- Small business waiver if: <500 employees (with affiliates), and first application submitted to FDA by company (including affiliates)

- Barrier to innovation waiver if:
  1. Application for a FDC or co-packaged drug product for treatment of HIV from examples in the Fixed Dose Guidance,
  2. Only tentative approval in US because, for example, of patents or exclusivity on the innovator product, ***and***
  3. Certification that product will be made available at competitive prices in one or more of the 15 designated PEPFAR countries with supporting evidence.

- Public health waiver if:
  1. Application for a FDC or co-packaged drug product for treatment of HIV from examples in the Fixed Dose Guidance, ***and***
  2. Total gross annual revenue of firm and affiliates <$10 million.

Product and Establishment Fees:

- Approval for FDC or co-packaged drug product for treatment of HIV from examples,
- Certification that product will be made available at competitive prices in one or more of the 15 designated PEPFAR countries with supporting evidence, ***and***
- No other user fee eligible products owned by the applicant are being manufactured at the establishment at which the PEPFAR product is being manufactured.