Prescription Drug User Fee Act Waivers for Fixed-Combination Antiretroviral Drugs for the President's Emergency Plan for AIDS Relief

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Division of User Fee Management and Budget Formulation 301-796-7900.

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

June 2018
User Fees

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Guidance for Industry[1]

I. INTRODUCTION

This guidance describes circumstances in which an applicant may be eligible for a barrier-to-innovation waiver under the Prescription Drug User Fee Act (PDUFA)[2] for some new drug applications (NDA) for fixed-combination (FC)[3] and single-entity versions of previously approved antiretroviral therapies for the treatment of human immunodeficiency virus (HIV).[4] *FDA expects that most of the applications and post-approval fees for fixed-combination and HIV therapies proposed for use in the President's Emergency Plan for AIDS Relief (PEPFAR) will qualify for a waiver under the barrier-to-innovation user fee waiver.*

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.

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[1]This guidance has been prepared by the Division of User Fee Management and Budget Formulation in the Center for Drug Evaluation and Research (CDER) in cooperation with the Division of Antiviral Products, CDER, and the Office of International Programs, Office of the Commissioner.

[2] Sections 735 and 736 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 379g and 379h). Unless otherwise specified, all references to "user fees" in this guidance mean user fees assessed under these sections of the FD&C Act, and not fees assessed under other provisions in the FD&C Act or the Public Health Service Act (PHS Act).

[3] For the purposes of this guidance, a *fixed-combination* product is one in which two or more separate drug ingredients are combined in a single dosage form.

[4] The Prescription Drug User Fee Act of 1992 (PDUFA I) authorized FDA to assess user fees for 5 years in conjunction with the review of human drug applications. This authorization to assess user fees was for fiscal years (FY) 1993 through 1997. PDUFA has been reauthorized five times. The FDA Reauthorization Act of 2017 reauthorized the user fee provisions for another 5 years, beginning in FY 2018 (PDUFA VI). Among other changes, PDUFA VI amended the annual PDUFA user fee structure by removing annual product and establishment fees and adding annual prescription drug program fees.

II. BACKGROUND

The President's Emergency Plan for AIDS Relief (PEPFAR) is a U.S. Government response to help save the lives of those suffering from HIV/AIDS around the world. It was originally announced in President Bush's State of the Union address in 2003 and was reauthorized in 2008 and 2013. This historic commitment is the largest by any nation to combat a single disease internationally. Drug treatment plays a major role in this relief plan, and it is important that resources are spent on treatments that have been demonstrated to be safe and effective. It is also important for antiretroviral drugs to conform to expected regulatory standards of safety, efficacy, and quality to avoid the risks of treatment failure and the emergence and spread of resistant virus. Of note, only antiretroviral drugs that undergo a stringent review by a regulatory authority such as FDA are eligible for procurement under PEPFAR.

In October 2006, to encourage applicants to submit applications for HIV combination therapies that can be used in PEPFAR, FDA issued a final guidance *Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV* (2006 fixed-combination guidance).[5] Attachments to the 2006 fixed-combination guidance describe some scenarios for approval of fixed-combinations for the treatment of HIV, and provide examples of drug combinations considered acceptable as fixed combinations and examples of those not considered acceptable as fixed combinations. Although the 2006 fixed-combination guidance focuses on fixed-combinations, the scientific principles outlined in the guidance also apply to single ingredient versions of antiretroviral drugs that are components of regimens listed in Attachment B. The guidance also explains that the Federal Food, Drug, and Cosmetic Act (FD&C Act) provides for certain circumstances in which FDA may grant a waiver or reduction in user fees.

This guidance is a revision of the guidance for industry *User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR*, issued February 2007. In this guidance, FDA provides information about circumstances under which certain applications for fixed-combination and single-entity versions of previously approved antiretroviral therapies for the treatment of HIV under PEPFAR may be eligible for a barrier-to-innovation user fee waiver.

III. BASIS FOR ASSESSING PDUFA USER FEES

The Prescription Drug User Fee Act of 1992 (PDUFA I) authorized FDA to assess user fees to certain applicants for a five-year period. Beginning in 1997, PDUFA has been reauthorized by Congress every five years. Most recently, in 2017, Congress enacted the FDA Reauthorization Act of 2017. Under this legislation, FDA generally assesses application fees to an applicant when it submits a human drug application (defined by statute to include new drug applications under section 505(b) of the FD&C Act and biologics license applications under section 351(a) of the Public Health Service Act (PHS Act)), subject to certain statutory exceptions. FDA also assesses prescription drug program fees annually, subject to limited exceptions, to applicants of approved drugs whose applications were submitted under section 505(b) of the FD&C Act or section

[5] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

351(a) of the PHS Act.[6, 7] The PDUFA user fee authorities are codified in section 735 and 736 of the FD&C Act.

The amount of the application fee assessed for a human drug application depends on whether clinical data[8] (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness are required for approval of the application.[9] Specifically, a human drug application for which such data is not required is assessed one-half the fee of an application whose approval requires such data.[10]

IV. FEE WAIVERS AND REFUNDS

A. Application Fees

Applicants may qualify for a waiver or refund of their application fee under the statute. FDA encourages firms to request a waiver 45 calendar days in advance of submission of an application so that the request can be evaluated before the fee is due.[11] If the applicant pays the fee upon submission of the application and seeks a refund (rather than waiting to submit the application until such time as the waiver is granted), under the statute, a request for refund *must* be submitted to FDA not later than 180 calendar days after the day on which the applicant submits the application.[12, 13] Even if an applicant would otherwise be eligible for a refund, no refunds are allowed under the statute if the refund request is received by FDA more than 180 calendar days after the payment.[14] Applicants who pay the fee but believe they will be eligible for a refund are encouraged to request a refund simultaneously with payment of the fee. Instructions for the submission of waiver and refund requests are found in section V of this guidance.

Section 736(d) of the FD&C Act contains three waiver or refund provisions under which an applicant may apply to have user fees waived or refunded: public health, barrier-to-innovation, and small business.[15] FDA's guidance for industry *User Fee Waivers, Reductions, and Refunds*

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[6] More information regarding statutory exemptions for user fees can be found in the guidance for industry *User Fee Waivers, Reductions, and Refunds for Drug and Biologic* Products (Sept. 2011). .

[7] The terms *prescription drug program fee* and *program fee* have the same meaning.

[8] For purposes of assessing user fees, FDA's interpretation of clinical data can be found in the guidance for industry *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (Dec. 2004)..

[9] Section 736(a)(1) and (b) of the FD&C Act (21 U.S.C. 379h(a)(1) and (b)). Bioavailability and bioequivalence studies are applicable only to applications submitted under section 505 of the FD&C Act. They are not addressed in section 351 of the PHS Act.

[10] Section 736(a)(1)(A) of the FD&C Act (21 U.S.C. 379h(a)). Information on application and program fees, including fee rates, PDUFA goals, and other various user fee related issues can be found on FDA's PDUFA website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

[11] Normally, FDA encourages the submission of requests for waivers 3 to 4 months in advance of the submission of an application. To further reduce the burden on applicants interested in making products available under PEPFAR, FDA will expedite the processing of waiver requests and will aim to process such requests within 45 calendar days.

[12] Section 736(a)(1)(B) and Section 736(i) of the FD&C Act (21 U.S.C. 379h(a)(1)(B) and, 379h(i)).

[13] Information on PDUFA user fee waivers, reductions, and refunds can be found in the guidance for industry *User Fee Waivers, Reductions, and Refunds for Drug and Biologic Products* (Sept. 2011).

[14] Section 736(i) of the Act (21 U.S.C. 379h(i)).

[15] Section 736(d)(1) of the FD&C Act.

for Drug and Biological Products describes FDA's interpretation of each of these waiver provisions.[16]

Although the Agency determines whether to grant requests for waivers under the statute on a case-by-case basis, at this time FDA expects that PEPFAR participants will generally be eligible for a ***barrier-to-innovation waiver***, which provides a waiver of an application fee when the assessment of the fee would present a significant barrier to innovation because of the limited resources available to such person or other circumstances. The agency considers the following two questions in deciding whether to grant a barrier to innovation waiver:

1. Is the product or other products or technologies under development by the applicant innovative?
2. Would the fee(s) be a ***significant barrier*** to the applicant's ability to develop, manufacture, or market innovative products or to pursue innovative technology?

As to the first question, at this time FDA generally intends to consider any fixed-combination for the treatment of HIV that is listed in Attachment B of the 2007 fixed-combination guidance to be an innovative product because simplified regimens that will facilitate distribution and patient compliance, particularly in treatment-naïve patients, are needed in developing countries. Accordingly, the agency would answer the first question in the affirmative. At some point, as alternative treatments become available, FDA may reevaluate whether particular fixed-combinations remain innovative and may find that an application fee waiver is no longer appropriate for a drug product combination listed in Attachment B. For example, a user fee waiver may not be appropriate if, in FDA's judgment, there are sufficient treatment alternatives available to the public.

As to the second question, a fee may be a significant barrier because of limited resources available or other circumstances. FDA generally intends to consider the development of drugs for PEPFAR to present "other circumstances" that would justify a waiver of PDUFA user fees under the barrier-to-innovation waiver provision where:

- The applicant is submitting an application for an fixed-combination product for treatment of HIV from among the examples that are listed in Attachment B of the 2006 fixed-combination guidance; [17]
- The applicant is only seeking a tentative approval[18] in the United States for the product as it cannot market the product in the United States because of patents or exclusivity on the innovator product; ***and***

[16] Further information regarding PDUFA waivers can be found in the guidance for industry *User Fee Waivers, Reductions, and Refunds for Drug and Biological Products*.

[17] Fixed-combination antiretroviral drugs used for the treatment of HIV under PEPFAR that are not listed in Attachment B may also be eligible to qualify for user fee waiver under the "other circumstances" provision of the barrier-to-innovation waiver. The list in Attachment B is not meant to be comprehensive and is expected to evolve as HIV clinical research continues and treatment program needs change. Applicants who have access to data supporting the efficacy and safety of drugs or regimens not included in Attachment B are encouraged to contact the Division of Antiviral Products within CDER's Office of New Drug Products to discuss the available support for a fixed-combination or product not on the list.

[18] Applicants who are seeking tentative approval have almost always submitted a Paragraph III Certification [21 CFR 314.94(a)(12)(i)(A)(3)] certification to patents listed in the FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (also known as the Orange Book) at the time of submitting the application.

- The applicant certifies that upon receipt of tentative approval, the applicant will make the product available at competitive prices suitable for procurement under PEPFAR in one or more of the designated PEPFAR countries. FDA will accept certifications that are supported with: (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 fixed-combination 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.

B. Annual Prescription Drug Program Fees

PDUFA provides for annual prescription drug program fees for certain prescription drug products. However, these annual prescription drug program fees are not assessed for drug products that are either of the following:

1. listed as discontinued in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book)[19] , or
2. tentatively approved.

Because a drug product that is either listed as discontinued in the Orange Book or is tentatively approved will not be assessed annual prescription drug program fees, a request for a waiver for program fees is not necessary.

If a drug product is listed in the Orange Book as an approved prescription drug product and is not listed as discontinued, an annual prescription drug program fee would ordinarily be assessed. FDA does not anticipate that such fees would generally constitute a barrier to innovation under the "other circumstances" criterion discussed above because the Orange Book listing indicates that the drug product is being marketed in the United States, making other marketing opportunities available.

V. SUBMITTING REQUESTS FOR WAIVERS, REDUCTIONS, AND REFUNDS

Further guidance for applicants regarding the submission of requests for waivers, refunds, and reductions of fees assessed under sections 735 and 736 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), can be found in the FDA's guidance for industry *User Fee Waivers, Reductions, and Refunds for Drug and Biological Products*, issued in September 2011. Among other things, the guidance discusses where to submit requests and what information to include.

[19] The Orange Book is available at https://www.accessdata.fda.gov/scripts/cder/ob/. Prescription drug program fees are assessed under section 736(a) of the Act for certain "prescription drug products". Section 735(3) of the FD&C Act defines a "prescription drug product" to exclude, among other things, drug products in the discontinued section of the Orange Book

VI. FDA RESPONSES TO REQUESTS FOR WAIVERS AND REDUCTIONS

FDA will review waiver, refund, or reduction request, consulting with relevant Agency officials as appropriate. If needed to support applicants' assertions that the applicant qualifies, FDA may request additional information and documentation from the applicant during its review of a waiver, reduction, or refund request. Failure to provide the requested information or documentation may result in a denial of a waiver, reduction, or refund. The Agency will respond to requests for waivers and reductions in a timely fashion based on available resources and collection time for additional information.

VII. DISCLOSURE OF PUBLIC INFORMATION

FDA may disclose information publicly about its actions granting or denying waivers, refunds and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.