PDUFA Waivers, Reductions, and Refunds for Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals under PEPFAR

Guidance for Industry

DRAFT GUIDANCE

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

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

August 2023
User Fees

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

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 certain new drug applications (NDAs) for single-entity (SE) antiretroviral (ARV) and fixed-combination (FC)[3] ARV drug products for the treatment or prevention of human immunodeficiency virus-1 (HIV-1 or HIV). FDA expects that most of the application fees for SE and FC ARV drug products proposed for use in the President's Emergency Plan for AIDS Relief (PEPFAR) will qualify for a waiver under the barrier-to-innovation waiver provision.[4]

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 in the Center for Drug Evaluation and Research (CDER) in cooperation with the Division of Antivirals, CDER, and the Office of Global Policy and Strategy, 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 antiretroviral drug product* is one in which two or more antiretroviral drugs are combined in a single dosage form and the contribution of the individual drugs has been demonstrated to contribute to the effect(s) of the fixed-combination consistent with the requirements of 21 CFR 300.50. For the purposes of this guidance, the term *drug product* will be used to refer to human prescription drugs, under section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act.

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

II. BACKGROUND

PEPFAR is a U.S. Government initiative to help save the lives of those suffering from HIV/AIDS (acquired immunodeficiency syndrome) around the world. It was originally announced in President George W. Bush's State of the Union address in 2003 and was reauthorized in 2008, 2013, and 2018. To date, this historic commitment is among the largest by any nation to combat a single disease internationally. As of 2012, ARV drug products are also available for HIV prevention, and as of 2015, the World Health Organization recommends the use of these drug products to reduce the risk of HIV-1 acquisition. ARV drug products for treatment and prevention play a major role in this relief plan, and it is important that resources are spent on products that have been demonstrated to be safe and effective. ARV drug products for treatment or prevention of HIV must conform to regulatory standards of safety, efficacy, and quality to maximize the success of treatment or prevention and to reduce the emergence and spread of resistant virus. Of note, FDA-approved or tentatively approved ARV drug products 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). Attachment A of the 2006 Fixed-Combination Guidance described some scenarios for the approval of fixed-combination and co-packaged products for the treatment of HIV that might be eligible for the PEPFAR program at that time, and Attachment B provided examples of drug combinations that FDA expected could be developed without conducting new clinical efficacy and safety studies. In 2023, FDA issued a draft guidance, *Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment or Prevention of HIV-1 Under PEPFAR* (2023 Fixed-Combination Guidance),[5] which, when finalized, will revise and replace the 2006 Fixed-Combination Guidance to reflect updated information regarding the PEPFAR program. To replace Attachment B, previously attached to the 2006 Fixed-Combination Guidance, the Agency published a separate list, *Antiretroviral Drug Products Needed for Use Under PEPFAR*,[6] which includes single-entity ARV and FC ARV drug products supported by clinical data and currently needed for PEPFAR procurement. Applicants should refer to this list when considering submission of applications for ARV drugs intended for use under PEPFAR. The 2023 Fixed-Combination Guidance provides recommendations for applications for SE and FC ARV drug products for the treatment or prevention of HIV infection that are intended for use under PEPFAR.

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[5] FDA updates guidances periodically. To ensure you have the most recent version of a guidance, check the FDA Guidances (Drugs) web page available at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

[6] The separate list of ARV drug products, *Antiretroviral Drug Products Needed for Use Under PEPFAR*, can be found under question 6, *What PEPFAR products can companies submit for FDA review?*, at FDA's PEPFAR Database on the Frequently Asked Questions web page: available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar/pepfar-database-frequently-asked-questions. This list is revised periodically to address current public health needs.

When final, this guidance will supersede 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 ARV drug products for the treatment or prevention of HIV infection that are proposed for use under PEPFAR may be eligible for a user fee waiver under the barrier-to-innovation waiver provision.[7]

III. BASIS FOR ASSESSING PDUFA USER FEES

The Prescription Drug User Fee Act of 1992 (PDUFA I) directed 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. Under the Prescription Drug User Fee Amendments of 2022 (PDUFA VII), which includes the reauthorization of PDUFA through September 2027, FDA generally assesses application fees to an applicant when it submits a human drug application (defined by statute to include certain new drug applications under section 505(b) of the FD&C Act and certain biologics license applications under section 351(a) of the Public Health Service Act (PHS Act) [8]), subject to limited statutory exceptions.[9] 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 351(a) of the PHS Act.[10, 11] The PDUFA user fee authorities are in sections 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[12] (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness are required for approval of the application.[13] Specifically, a human drug application for which such data are not required is assessed one-half the fee of an application that requires such data for approval.[14]

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

[8] Section 735(1) of the FD&C Act.

[9] Section 736(a)(1) of the FD&C Act.

[10] PDUFA user fee waivers, reductions, and refunds are discussed in FDA's guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products* (Oct. 2019). FDA updates guidances periodically. To ensure you have the most recent version of a guidance, check the FDA Guidances (Drugs) web page available at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

[11] In this guidance, the terms *prescription drug program fee* and *program fee* have the same meaning.

[12] 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).

[13] Section 736(a)(1) and (b) of the FD&C Act (21 U.S.C. 379h(a)(1) and (b)).

[14] 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.

IV. PDUFA USER FEE WAIVERS, REDUCTIONS, AND REFUNDS

A. Application Fees

Applicants may qualify for a waiver or refund of their application fee under section 736(d) of the FD&C Act. FDA encourages applicants to request a waiver no later than 45 calendar days in advance of submission of an application so that the request can be evaluated before the fee is due.[15] 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 written request for refund *must* be submitted to FDA not later than 180 calendar days after the fee due date.[16, 17] 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 FDA's guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products*.[18]

Section 736(d) of the FD&C Act contains three waiver or reduction provisions under which an applicant may request a waiver or reduction in user fees based on public health necessity, to remove a barrier to innovation, or if the applicant qualifies as a small business submitting its first application. FDA's guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products* describes FDA's interpretation of each of these waiver provisions.[19]

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*** under section 736(d)(1)(B) of the FD&C Act, 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 ARV drug products for the treatment or prevention of HIV on the *Antiretroviral Drug Products Needed for Use Under*

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[15] 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.

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

[17] See footnote 10.

[18] See footnote 10.

[19] See footnote 10.

PEPFAR list[20] 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 expect to answer the first question in the affirmative. At some point, as alternative options for treatment or prevention become available, FDA may reevaluate whether the listed ARV drug products remain innovative and may find that an application fee waiver is no longer appropriate for a drug to be procured under the PEPFAR program. For example, a user fee waiver may not be appropriate if, after consultation with the agencies that administer the PEPFAR program,[21] FDA determines that there are already sufficient alternatives available to fulfill the needs of the PEPFAR program.

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 be classified as "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 ARV drug product for the treatment or prevention of HIV on the *Antiretroviral Drug Products Needed for Use Under PEPFAR* list;[22]
- The applicant is submitting an application that seeks only a tentative approval[23] in the United States, and at the date of submission the application is not expected to become eligible for a final approval as of the user fee goal date;[24]
- The applicant certifies by letter[25] to The U.S. Agency for International Development (USAID) 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, with a copy of the letter included in the waiver request; ***and***

- Certifications are supported with evidence that the product will be offered for procurement by PEPFAR, ***and*** either: (1) 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*** (2) if such approval has not been obtained, the ARV drug product is listed on an HIV

[20] See footnote 6.

[21] The PEPFAR program is led by the Office of the U.S. Global AIDS Coordinator and Health Diplomacy at the U.S. Department of State with support and collaboration from other United States Government agencies, including principally the Office of HIV/AIDS within the Global Health Bureau at U.S. Agency for International Development.

[22] The separate list on the FDA's PEPFAR Database is not meant to be comprehensive and is expected to evolve as HIV clinical research continues and program needs change. Applicants who have access to data supporting the efficacy and safety of drugs or regimens not included in the list of needed ARV drug products are encouraged to contact the Division of Antivirals (DAV) within CDER's Office of New Drugs to discuss the available support for ARV drug products not on the list. The DAV PEPFAR Project Manager may be contacted about these questions at 301-796-1500.

[23] In the PEPFAR context, applicants who are seeking tentative approval have almost always submitted a Paragraph III [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 submission of the application.

[24] See, *e.g.*, 21 CFR 314.107(b) and (d).

[25] Applicants should contact USAID at SCH.HIV.Pharma@usaid.gov with the following subject line: "Request for barrier-to-innovation waiver under PDUFA NDA# (product name)".

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 requires the collection of annual prescription drug program fees for certain FDA-approved prescription drug products. Annual prescription drug program fees are not assessed for drug products that are:

1. Listed on the "Discontinued Drug Product List" in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book"),[26] 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.[27]

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 be assessed unless the product qualifies for a waiver, exception, or exemption. Waiver requests are evaluated on a case-by-case basis. FDA does not anticipate that program fees would generally constitute a barrier to innovation under the "other circumstances" criterion because their Orange Book listing indicates that the drug product is 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 FD&C Act can be found in FDA's guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products Guidance for Industry*.[28] Among other things, the guidance discusses where to submit requests and what information to include.

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[26] 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 FD&C 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.

[27] If a tentatively approved product receives final approval, it would be added to the "Prescription Drug Product List" of the Orange Book and, therefore, would be subject to the annual prescription drug program fee at the beginning of the fiscal year following final approval.

[28] See footnote 10.

VI. FDA RESPONSES TO REQUESTS FOR WAIVERS, REDUCTIONS, AND REFUNDS

FDA will review waiver, reduction, and refund requests, consulting with relevant Agency officials as appropriate. If needed to support an applicant's 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 request. The Agency will respond to requests for waivers, reductions, and refunds 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. Any such disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.