Assessing User Fees Under the Prescription Drug User Fee Amendments of 2022

Guidance for Industry

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

July 2023
User Fees

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Contains Nonbinding Recommendations

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Assessing User Fees Under the Prescription Drug User Fee Amendments of 2022 Guidance for Industry[1]

This guidance represents 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 provides information to stakeholders regarding FDA's implementation of the Prescription Drug User Fee Amendments of 2022 (PDUFA VII) under Title I of The FDA User Fee Reauthorization Act of 2022. Because PDUFA VII created changes to the user fee program, this guidance explains the changes created by the statute which includes changes to certain definitions, changes to certain PDUFA fee exceptions, waivers, exemptions, reductions, and returns[2] and certain changes for PDUFA invoicing procedures.

The guidance describes the types of user fees authorized by PDUFA VII, how FDA determines which products are subject to a fee, and discusses FDA's policies regarding exceptions, exemptions, and waivers. This guidance also describes the process for submitting payments to FDA, the consequences for failing to pay PDUFA fees, and the process for requesting a reconsideration of a user fee assessment. FDA has separate guidance documents about waivers, reductions, exemptions, and returns. This guidance does not address how FDA determines and adjusts fees each fiscal year (FY); nor does it address FDA's implementation of other user fee programs (e.g., Biosimilar User Fee Act, Generic Drug User Fee Amendments).[3] Throughout this guidance, references to *user fees* or the *user-fee program* are to prescription drug user fees collected under section 736 of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Changes to statutory provisions that are described in this guidance are effective with respect to fees assessed beginning on the first day of FY 2023.[4]

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[1] This guidance has been prepared by the Division of User Fee Management, Office of Management, in the Center for Drug Evaluation and Research, in consultation with the Center for Biologics Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2017-D-6821 (available at https://www.regulations.gov/docket?D=FDA-2017-D-6821). See the instructions in that docket for submitting comments on this and other Level 2 guidances.

[2] For the purpose of this guidance, the terms "returns" and "refunds" are used interchangeably.

[3] In general, FDA will publish in the *Federal Register* the fee revenue and fee amounts for each fiscal year not later than 60 days before the start of each fiscal year. Section 736(c)(5) of the FD&C Act.

[4] FDA's fiscal year begins on October 1 and ends on September 30.

In general, FDA's guidance documents 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.

II. BACKGROUND

The Prescription Drug User Fee Act of 1992 (PDUFA I) added sections 735 and 736 to the FD&C Act, authorizing FDA to collect user fees for a 5-year period from persons that submit certain human drug applications for review or that are named in approved applications as the sponsor[5] of certain prescription drug products. Since 1992, Congress has revised and extended PDUFA six times, each time for a 5-year period. Fees authorized by this legislation help fund the process for the review of human drug applications and have played an important role in expediting the drug review and approval process. The most recent reauthorization is Title I of the FDA User Fee Reauthorization Act of 2022, enacted on September 30, 2022.

PDUFA VII extends FDA's authority to collect user fees for FY 2023 through FY 2027. Discussions about the next reauthorization of PDUFA are expected to begin before FY 2027, the final fiscal year of PDUFA VII.

III. DEFINITIONS

For purposes of this guidance:

- The term ***affiliate*** means a business entity that has a relationship with a second business entity if, directly or indirectly, (1) one business entity controls, or has the power to control, the other business entity; or (2) a third party controls, or has the power to control, both of the business entities.[6]

- The term ***applicant*** refers to the person who submits a human drug application or is named as the applicant in a human drug application.

- The term ***drug*** includes drug and biological products.[7]

- The term ***final dosage form*** means, with respect to a prescription drug product, a finished dosage form which is approved for administration to a patient without substantial further manufacturing (such as capsules, tablets, or lyophilized products before reconstitution).[8]

[5] For the purposes of this guidance, the terms *sponsor*, *applicant*, and *person* may be used interchangeably.
[6] Section 735(11) of the FD&C Act.
[7] For the purposes of this guidance, the terms *biologic* and *biological product* have the same meaning.
[8] Section 735(4) of the FD&C Act.

- The term ***human drug application*** means an application for (1) approval of a new drug submitted under section 505(b) of the FD&C Act or (2) licensure of a biological product under subsection (a) of section 351 of the Public Health Service Act (PHS Act).[9]

  Such term does not include:
  - a supplement to such an application;
  - an application with respect to whole blood or a blood component for transfusion;
  - an application with respect to a bovine blood product for topical application licensed before September 1, 1992;
  - an application with respect to an allergenic extract product[10] licensed before October 1, 2022;[11]
  - an application with respect to a standardized allergenic extract product submitted pursuant to a notification to the applicant from the Director, Center for Biologics Evaluation and Research regarding the existence of a potency test that measures the allergenic activity of an allergenic extract product licensed by the applicant before October 1, 2022;[12,13]
  - an application with respect to an in vitro diagnostic biologic product licensed under section 351 of the PHS Act;
  - an application with respect to a large volume parenteral drug product approved before September 1, 1992;
  - an application for a licensure of a biological product for further manufacturing use only; and
  - an application or supplement submitted by a State or Federal Government entity for a drug that is not distributed commercially.

  Such term does include an application for licensure of a large volume biological product intended for single dose injection for intravenous use or infusion.

- The term ***person*** means the person subject to fees and includes any affiliates of that person.[14] The term ***person*** includes an individual, partnership, corporation, or association.[15]

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[9] Section 735(1) of the FD&C Act.
[10] Allergenic extract products are administered for the diagnosis, prevention, or treatment of allergies or allergenic disease. There are a wide variety of allergenic extract products derived from various sources (insects, pollens, animals, molds, foods).
[11] Prior to the FDA User Fee Reauthorization Act of 2022, most allergenic extract products were exempt from PDUFA. Under the enactment of the FDA User Fee Reauthorization Act of 2022, allergenic extract product applications approved before October 1, 2022, will not be subject to program fees, and supplements to these applications will continue to be classified as non-PDUFA for review clock purposes. See section 735 (1) of the FD&C Act.
[12] Applications submitted in accordance with 21 CFR 680.3(e).
[13] For examples of standardized allergenic extract products, please see website https://www.fda.gov/vaccines-blood-biologics/allergenics/injectable-allergen-extracts-standardized.
[14] Section 735(9) of the FD&C Act.
[15] Section 201(e) of the FD&C Act.

- The term ***prescription drug product*** means a specific strength or potency of a drug in final dosage form:
    - for which a human drug application has been approved;
    - which may be dispensed only by prescription under section 503(b) of the FD&C Act; and
    - which is on the list of products described in section 505(j)(7)(A) of the FD&C Act[16] (not including the discontinued section of such list) [17] or is on a list created and maintained by the Secretary of Health and Human Services (Secretary) of products approved under human drug applications under section 351(a) of the PHS Act[18] (not including the discontinued section of such list).[19]

  Such term does not include:
    - whole blood or a blood component for transfusion;
    - a bovine blood product for topical application licensed before September 1, 1992;
    - an allergenic extract product[20] licensed before October 1, 2022;
    - a standardized allergenic extract product submitted pursuant to a notification to the applicant from the Director, Center for Biologics Evaluation and Research regarding the existence of a potency test that measures the allergenic activity of an allergenic extract product licensed by the applicant before October 1, 2022;[21]
    - an in vitro diagnostic biologic product licensed under section 351 of the PHS Act;
    - a biological product that is licensed for further manufacturing use only; and
    - a drug that is not distributed commercially AND is the subject of an application or supplement submitted by a State or Federal Government entity.

  Such term does include a large volume biological product intended for single dose injection for intravenous use or infusion.[22]

- The term ***supplement*** means a request to the Secretary to approve a change in a human drug application which has been approved.[23]

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[16] The list of products described in section 505(j)(7)(A) of the FD&C Act is the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book").
[17] See section VI.A.2 of this guidance for more information about written requests to place a product in the Discontinued Section of the Orange Book.
[18] Biologics regulated by the Center for Drug Evaluation and Research (CDER) are listed on the *CDER Billable Biologic Product List*, and biologics regulated by the Center for Biologics Evaluation and Research (CBER) may be found on the list of *User Fee Billable Biologic Products and Potencies Approved Under Section 351 of the PHS Act* (collectively, the CBER/CDER Billable Biologic Lists).
[19] See section VI.A.2 of this guidance for more information on how to place a product in the discontinued section of the *CBER/CDER Billable Biologic Product Lists.*
[20] See footnote 11.
[21] See footnotes 12-13.
[22] Section 735(3) of the FD&C Act.
[23] Section 735(2) of the FD&C Act.

- The term ***skin-test diagnostic product*** means a product (including positive and negative controls required to interpret the results of such tests)[24]—
    - for prick, scratch, intradermal, or subcutaneous administration;
    - expected to produce a limited, local reaction at the site of administration (if positive), rather than a systemic effect;
    - not intended to be a preventive or therapeutic intervention; and
    - intended to detect an immediate or delayed-type skin hypersensitivity reaction to aid in the diagnosis of:
        - (i) an allergy to an antimicrobial agent;
        - (ii) an allergy that is not to an antimicrobial agent, if the diagnostic product was authorized for marketing prior to October 1, 2022; or
        - (iii) infection with fungal or mycobacterial pathogens.

IV. CHANGES TO THE STRUCTURE OF THE PDUFA USER FEE PROGRAM

Previously, section 736 of the FD&C Act excluded all allergenic extract products from the statutory definition of "human drug application" and "prescription drug product". Historically, these products were simply manufactured preparations with minimal information or data. Newer types of allergenic extract products are being developed that have increased structural complexity, advanced product formulations, more complex manufacturing methods, and more extensive evaluations and testing. PDUFA VII revised the definition of "human drug application" and "prescription drug product" to exclude allergenic extract products (including standardized allergenic extract products) licensed before October 1, 2022.[25] However, allergenic extract products (including standardized allergenic extract products) licensed on or after October 1, 2022, will be included in the assessment of user fees.

PDUFA VII also defines the term "skin-test diagnostic product" and excludes fees for certain skin-test diagnostic products that are necessary for the diagnosis of serious and potentially life-threatening conditions (see Section III of this guidance).

In addition, PDUFA VII clarifies exceptions for certain prescription drug products that are not subject to a prescription drug program fee, such as large volume parenteral products and drug products that are pharmaceutically equivalent to another drug product. [26]

Lastly, PDUFA VII added a provision for previously discontinued drug products. This provision states that if a drug product is approved in a human drug application as of October 1 of a fiscal

[24] Section 735(12) of the FD&C Act.
[25] Section 735(1) and 735(3) of the FD&C Act.
[26] Section 736(a)(2)(B) of the FD&C Act.

year, but the drug product does not meet the definition of a "prescription drug product" as of October 1 of that fiscal year because the drug product is listed in the Discontinued Section of the Orange Book[27] or the CBER/CDER Billable Biologic Lists,[28] it will not receive an annual invoice. However, if on any subsequent day during the relevant fiscal year the drug product does meet the definition of a "prescription drug product" (i.e., the drug product is moved to the active section of the Orange Book or listed on the CBER/CDER Billable Biologic Lists) [29], each person who is named as an applicant in a human drug application is subject to pay the annual prescription drug program fee for such prescription drug product.[30]

V. HUMAN DRUG APPLICATION FEES

Under PDUFA VII, FDA assesses a user fee for certain human drug applications. Each person that submits a human drug application beginning in FY 2023 is assessed an application fee under PDUFA VII as follows:

- A human drug application for which clinical data (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness are required for approval is assessed a full application fee.
- A human drug application for which clinical data (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness are not required for approval is assessed one-half of a full fee.[31]

Human drug application fees are due when the application is submitted.[32] For an application where FDA has determined that rolling review[33] (for a fast track or breakthrough therapy product or regenerative medicine advanced therapy) is appropriate, the application fee is due when the first portion of the application is submitted to the Agency.

A. Exceptions to the Application Fee

There are three exceptions to the PDUFA application fee, described below:

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[27] See footnote 16.
[28] See footnote 18.
[29] Excluding the exceptions stated in section 736(a)(2) subparagraph (B) and (C).
[30] For example, if a drug product is not considered a prescription drug product (i.e., was in the Discontinued Section of the Orange Book or the Discontinued Section of the CBER/CDER Billable Biologic Lists) as of October 1, 2022, it would not be issued an annual invoice for FY 2023. If the drug product then meets the definition of a prescription drug product (i.e., by moving to the Active Section of the Orange Book or CBER/CDER Billable Biologics Lists) on any day after October 1, 2022, and before September 30, 2023, then the applicant shall pay the annual prescription drug program fee established for FY 2023 for the prescription drug product (per section 736(a)(2)). In this example, such fee shall be invoiced after the close of the fiscal year, in December 2023.
[31] Section 736(a)(1)(A) of the FD&C Act.
[32] Section 736(a)(1)(B) of the FD&C Act.
[33] Rolling Review is a process applicable to a submission for an application with a fast track designation or breakthrough therapy designation permitting sponsors to submit completed sections of its application for review rather than waiting until every section of the new drug application (NDA) or biologics license application (BLA) is completed before the entire application can be reviewed. The review clock will not begin until the applicant has submitted the entire application to the FDA. See *Expedited Programs for Serious Conditions- Drugs and Biologics* and *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* for more information.

(1) Previously Filed Applications. If an application

- was submitted by a person that paid the fee for the application;
- was accepted for filing; and
- was not approved or was withdrawn prior to approval (without a waiver);

The submission of a human drug application for the same product by the same person (or the person's licensee, assignee, or successor) does not require an application fee.[34]

(2) Designated Orphan Drug. A human drug application for a prescription drug product that has been designated as a drug for a rare disease or condition pursuant to section 526 of the FD&C Act shall not be subject to an application fee unless the human drug application includes an indication for other than a rare disease or condition.[35] More information is provided in the guidance for industry *User Fee Waivers, Reductions, and Refunds for Drug and Biological Products* (Waivers Guidance).[36]

(3) Skin-Test Diagnostic Products. A human drug application for a skin-test diagnostic product shall not be subject to an application fee.

B. Applications Refused for Filing or Withdrawn

If an application is refused for filing by the FDA or withdrawn by the applicant without a waiver before filing, FDA will refund 75 percent of the paid application fee.[37] If an application is withdrawn after it is filed, FDA may refund the fee or a portion of the fee if no substantial work was performed on the application after the application was filed. FDA has sole discretion to refund a fee or a portion of the fee. FDA's determination concerning a refund on this basis (no substantial work was performed on the application) is not reviewable.[38]

An application that was withdrawn before filing or refused for filing, shall be subject to the full application fee when resubmitted or filed over protest, unless the fee is waived or reduced under one of the provisions identified in section VII of this guidance.[39]

VI. PRESCRIPTION DRUG PROGRAM FEES

In general, each person named as the applicant in a human drug application and that, after September 1, 1992, had pending with the FDA a human drug application or supplement is required to pay the annual prescription drug program fee for each prescription drug product that is identified in such a human drug application approved as of October 1 of such fiscal year or, as described later in this section, is considered a prescription drug product on any subsequent day of

[34] Section 736(a)(1)(C) of the FD&C Act.
[35] Section 736(a)(1)(F) of the FD&C Act.
[36] FDA updates guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[37] Section 736(a)(1)(D) of the FD&C Act.
[38] Section 736(a)(1)(G) of the FD&C Act.
[39] Section 736(a)(1)(E) of the FD&C Act.

the fiscal year after October 1.[40] For example, if the approval of a human drug application occurs on or before October 1, 2022, and the prescription drug products identified in the approved application are not on the discontinued list as of October 1, 2022, then program fees will be assessed for the products for FY 2023. However, if approval of a human drug application occurs after October 1, 2022, then program fees are not assessed for the prescription drug products identified in the application for FY 2023.

An applicant may not be assessed more than five prescription drug program fees for a fiscal year for prescription drug products identified in a single approved application.[41, 42]

A prescription drug product is **not** assessed a prescription drug program fee if:

- the product is a large volume parenteral product (a sterile aqueous drug product packaged in a single-dose container with a volume greater than or equal to 100 mL, not including powders for reconstitution or pharmacy bulk packages) identified on the list compiled under section 505(j)(7);[43] or
- the product is pharmaceutically equivalent[44] to another product on the list of products compiled under section 505(j)(7) (not including the discontinued section of such list); or
- the product is a skin-test diagnostic product.

Prescription drug program fees are due on the later of the first business day on or after October 1 of each fiscal year, or the first business day after the enactment of an appropriations Act providing for the collection and obligation of fees for such fiscal year under this section.[45] Applicants may pay fees before the date on which they are due.[46]

There are instances when a drug product that is identified in a human drug application is not invoiced as of October 1 if the drug product is not considered a prescription drug product because the drug product is in the Discontinued Section of the Orange Book or the Discontinued Section of the CBER/CDER Billable Biologic Lists as of that date. If the drug product becomes a prescription drug product on any day after October 1 during such fiscal year, then the applicant shall pay the annual prescription drug program fee established for such fiscal year for the prescription drug product.[47] Such fees shall be invoiced in December following the end of the fiscal year.[48] Such fee shall be paid only once for each product for a fiscal year in which the fee is payable.

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[40] Section 736(a)(2)(A) of the FD&C Act.
[41] Section 736(a)(2)(C) of the FD&C Act.
[42] For example, an applicant that has 10 drug products identified in a single approved NDA for 10 different strengths of tablet dosage form products is eligible for an assessment for a maximum of 5 program fees. As another example, an applicant that has 6 biologic products identified in an approved BLA for 3 strengths of liquid injectable and 3 strengths of lyophilized products will be assessed a maximum of 5 program fees.
[43] Section 736(a)(2)(B)(i) of the FD&C Act.
[44] 21 CFR 314.3.
[45] Section 736(a)(2)(A) of the FD&C Act.
[46] Section 736(g)(2)(C) of the FD&C Act authorizes FDA to accept payment of PDUFA fees for a fiscal year prior to the due date for such fees, in accordance with authority provided in advance in a prior year appropriations Act.
[47] Section 736(a)(2)(A) of the FD&C Act
[48] See footnote 30.

A. When and Where Prescription Drug Products Are Listed

1. In general

The Orange Book[49] includes products that are the subject of approved human drug applications submitted under section 505(b) and approved under section 505(c) of the FD&C Act. FDA publishes updates to the list each month.[50] Drugs are considered to be added to the Orange Book on the day they are approved rather than on the date FDA publishes its next Orange Book update.[51] For example, if a drug product submitted for approval under section 505(b) of the FD&C Act is approved on June 15, it is considered to be added to the Orange Book on June 15. Unless the drug product is moved from the "Prescription Drug Product List" in the Orange Book (the "active section") to the "Discontinued Drug Product List," it may be assessed a program fee for the next fiscal year even if FDA does not publish an update to the Orange Book before the day fees are due.

FDA also maintains a list of products approved under human drug applications under section 351(a) of the PHS Act and also considers such drugs to be added to the list on the date they are approved. FDA periodically provides the public with information about its list by publication to the Agency website in two locations. Biologics regulated by the Center for Drug Evaluation and Research (CDER) are listed on the *CDER Billable Biologic Product List*, and biologics regulated by the Center for Biologics Evaluation and Research (CBER) may be found on the list of *User Fee Billable Biologic Products and Potencies Approved Under Section 351 of the PHS Act* (collectively, the CBER/CDER Billable Biologic Lists).[52]

Applicants may raise questions about product listings with the FDA as follows:

- For new drug application (NDA) products, an applicant should contact the Division of Orange Book Publication and Regulatory Assessment (DOBPRA)[53] at OrangeBook@fda.hhs.gov.

- For CDER biological products, an applicant should contact CDER User Fee staff at CDERCollections@fda.hhs.gov.

- For CBER biological products, an applicant should contact CBER User Fee staff at CBERUserFeeStaff@fda.hhs.gov

Sponsors should send CDER User Fee staff (CDERCollections@fda.hhs.gov) a courtesy copy of information sent to the DOBPRA or CBER User Fee staff to help ensure accurate billing.

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[49] The Orange Book is available at www.fda.gov/orangebook.
[50] Section 505(j)(7)(A)(ii) of the FD&C Act.
[51] Section 505(j)(7)(B) of the FD&C Act.
[52] The CDER Billable Biologic List is available at https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM164641.pdf. The CBER Billable Biologic List is available at https://www.fda.gov/media/113210/download.
[53] Previously known as the Orange Book staff.

2. Moving a Drug Product to the Discontinued Section of the Orange Book or the CBER/CDER Billable Biologic Lists

A drug product is not assessed a prescription drug program fee for a fiscal year if it is in the Discontinued Section of the Orange Book or the Discontinued Section of the CBER/CDER Billable Biologic Lists on the date fees are assessed.[54] Applicants that have decided to stop marketing a prescription drug product, or that have decided to delay launch of a product until after its approval date, should request to have the product moved to the discontinued section at their earliest opportunity to give FDA sufficient time to process the request before fees are assessed. In most cases, we expect that an applicant intending to discontinue or delay marketing a drug product will notify FDA well in advance.[55] If a drug product remains on the "Prescription Drug Product List" of the Orange Book or the CBER/CDER Billable Biologic Lists on the date fees are assessed, the applicant may be assessed a program fee for the drug even if it is not being marketed.

Requests to move a product to the Discontinued Section of the Orange Book should be submitted either (1) to the applicable NDA file through the electronic submissions gateway, for products approved under section 505 of the FD&C Act (as per 506I Guidance), or (2) to the relevant User Fee staff (CDER or CBER) for products approved under section 351(a) of the PHS Act, at the relevant email address listed in section VI.A.1 of this guidance. All requests should clearly identify the product to be moved, and the date marketing has or will be ended. Additionally, if known, the last date of manufacturing, last date of distribution and lot expiration dates should be included.[56] Upon receiving such a request, FDA may ask the applicant for further information to confirm the not-marketed status of the product. If the applicant submits a request as set forth in this paragraph and FDA does not deny the request, then for purposes of assessing user fees, FDA intends to consider the product to have been moved to the Discontinued Section on the date that the request was received or if the product will be withdrawn from sale[57] on a future date, such future date when the product is withdrawn from sale, whichever is later. A product shall be considered withdrawn from sale once the applicant has ceased its own distribution of the product, whether or not the applicant has ordered recall of all previously distributed lots of the product, except that a routine, temporary interruption in supply shall not render a product withdrawn from sale.

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[54] Sections 735(3) and 736(a)(2)(A) of the FD&C Act.

[55] Under section 506I of the FD&C Act, the holder of an application approved under section 505 of the FD&C Act is required to notify FDA in writing 180 days prior to withdrawing the approved drug from sale or, if that is not practicable, as soon as practicable but not later than the date of withdrawal, and is also required to notify FDA in writing within 180 calendar days of the date of approval of the drug if the drug will not be available for sale within 180 calendar days of such date of approval. See guidance for industry *Marketing Status Notifications Under Section 506I of the Federal Food, Drug, and Cosmetic Act; Content and Format* (August 2020) (506I Guidance) for more information: https://www.fda.gov/media/120095/download.

[56] See 506I Guidance.

[57] Withdrawal from sale (or "not marketed" status) is not limited to permanent withdrawal of a product but can also include "any decision to discontinue marketing of [that] product." See "Abbreviated New Drug Application Regulations," proposed rule, 57 FR 17950 at 17956 (April 28, 1992) and the 506I Guidance for more information.

Applicants seeking to move a prescription drug product to a Discontinued Section should clearly indicate the date on which their product is no longer marketed. Applicants should not rely on communications with a review division, the product listing staff, or FDA components other than DOBPRA or the CDER or CBER User Fee staff, as appropriate. Communication with the incorrect division of FDA, or in a manner that does not make clear when a product is no longer marketed, may mean that a prescription drug product is not moved to the Discontinued Section of the Orange Book or the CBER/CDER Billable Biologic Lists before the date program fees are assessed and may result in the applicant being required to pay a fee for the product.

B. Pharmaceutically Equivalent to Another Product

Section 736(a)(2)(B)(ii) of the FD&C Act states that a prescription drug product will not be assessed a prescription drug program fee if it is pharmaceutically equivalent to another drug product in the Orange Book (not including the Discontinued Section).

In PDUFA VII, a prescription drug product that is "pharmaceutically equivalent," as defined in 21 CFR 314.3[58] (or a successor regulation), to another prescription drug product (approved under an application held by a different applicant) that is not on the "Discontinued Drug Product List"[59] of the Orange Book, may qualify for an exception from a prescription drug program fee. Generally, FDA publishes its conclusions regarding pharmaceutical equivalence in the Orange Book as determined through the process for assigning therapeutic equivalence (TE) codes. However, some prescription drug products may not have conclusions regarding pharmaceutical equivalence published in the Orange Book (i.e., do not have a TE code in the Orange Book) but may be considered pharmaceutically equivalent.

Therefore, applicants who believe that their product qualifies for a fee exception based on pharmaceutical equivalence to another prescription drug product that is not in the Discontinued Drug Product List of the Orange Book can submit a request to the Prescription Drug User Fee staff at CDERCollections@fda.hhs.gov no later than 180 calendar days after such fee is due.[60] For information on how to submit written waiver or refund requests (including the content of the

[58] Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, *i.e.*, the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration time, and/or dissolution rates (21 CFR 314.3(b)). They may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, within certain limits, labeling (Orange Book Preface at vii, 43rd ed.)

[59] Section 736(a)(2)(B)(ii) of the FD&C Act

[60] Under section 736(i) of the FD&C Act, to be eligible for consideration of a refund or exception, you must submit a timely written request no later than 180 calendar days of when the program fee was due. This timeline applies even if you have a citizen petition or other request pending with FDA seeking a therapeutic equivalence rating/evaluation for a prescription drug product for the purpose of obtaining the "pharmaceutically equivalent" exception.

request), please refer to the Waivers Guidance.[61] Questions regarding this matter should be emailed to the Prescription Drug User Fee staff at CDERCollections@fda.hhs.gov.

C. Liquid Parenteral Biological Products Approved under Section 351 of the PHS Act

1. Assessing the Strength or Potency of a Drug in Final Dosage Form

As described above, applicants of approved applications are assessed an annual program fee for each eligible prescription drug product, up to a maximum of five program fees for a fiscal year for each approved application.

When evaluating the specific strength or potency of a drug in final dosage form for purposes of assessing program fees for liquid parenteral biological products, FDA intends to take into consideration both the total amount of drug substance in mass or units of activity in a product and the concentration of drug substance (mass or units of activity per unit volume of product). Products considered to have a different strength or potency in a final dosage form will be given separate entries in the CBER/CDER Billable Biologics Lists and subject to separate program fees. The approach described in this guidance is intended to align our treatment of products approved under section 351 of the PHS Act with the way the Agency generally assesses fees for products approved under section 505 of the FD&C Act, providing consistency in our implementation of the program fee. FDA also notes that products subject to the prescription drug program fee will be capped by the limit of five prescription drug program fees for a fiscal year for each approved application.

2. Auto-Injectors, Prefilled Syringes, and Vials

An auto-injector that has the same strength or potency as a prefilled syringe or vial will generally be assessed a separate prescription drug program fee. This is intended to align the Agency's assessment of fees for products licensed under section 351 of the PHS Act with its assessment of fees for products approved under section 505 of the FD&C Act.[62]

D. Orphan Drug Exemption

A drug designated under section 526 of the FD&C Act for a rare disease or condition and approved under section 505 of the FD&C Act or under section 351 of the PHS Act shall be exempt from prescription drug program fees if the drug meets all of the following conditions:

- the drug meets the public health requirements that are applied to requests for waivers for prescription drug program fees, and

[61] See Waivers Guidance.

[62] The distinction described in this guidance between (1) auto-injectors and (2) prefilled syringes or vials is for the purposes of assessing the prescription drug program fee only and not for any other purpose.

- the drug is owned or licensed and is marketed by a company, including its affiliates, that had less than $50 million in gross worldwide revenue during the calendar year prior to the fiscal year for which the orphan exemption is requested.[63]

An applicant seeking to avail itself of this exemption must ensure that the drug meets both of the conditions listed above.[64, 65] For specific information on financial documentation needed for orphan exemption requests, sponsors may refer to the Waivers Guidance.

VII. WAIVERS OF PDUFA FEES

Section 736(d) of the FD&C Act provides that FDA will grant a waiver of or reduction in one or more user fees assessed under section 736(a) of the FD&C Act where it finds that one or more of the following is true:

- A waiver or reduction is necessary to protect the public health.
- The assessment of the fee would present a significant barrier to innovation because of limited resources available to the person or other circumstances.[66]
- The applicant is a small business submitting its first human drug application to the Secretary for review.

For more information on these waiver and reduction provisions, sponsors may refer to the Waivers Guidance.

VIII. EFFECT OF FAILURE TO PAY FEES

A human drug application or supplement submitted by a person subject to fees under section 736(a) of the FD&C Act is considered incomplete and will not be accepted for consideration for filing until *all* such fees owed by the person have been paid.[67] For example, if a person submits an application without an application fee or if the person is in arrears for nonpayment of any prescription drug program fees, the application will be incomplete and FDA will not accept it for filing. Note that the term *person* as used here includes an affiliate of the person, which means that an affiliate's failure to pay all of the user fees that it owes will affect the applicant's ability to file an application.

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[63] Section 736(k)(1) of the FD&C Act.
[64] Section 736(k)(2) of the FD&C Act.
[65] More information is provided in the Waivers Guidance.
[66] Two special circumstances that may affect eligibility for waivers or reductions under the barrier to innovation waiver provision are addressed in separate waiver guidances. Companies participating in the President's Emergency Plan for AIDS Relief should consult the guidance for industry *User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR*. Companies submitting combination products under 21 CFR 3.2(e) should see the guidance for industry *Application User Fees for Combination Products*. FDA updates guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[67] Section 736(e) of the FD&C Act.

IX. PAYMENT INFORMATION AND PROCEDURES

This section briefly describes the general process for assessing and issuing annual invoices for prescription drug program fees under PDUFA VII. More detailed instructions will be provided in FDA's direct notice to affected applicants.

A. Prescription Drug Program Fee Notifications

FDA will issue a notice to applicants regarding their prescription drug products in preparation for assessing prescription drug program fees. These notices will be sent before the due date for prescription drug program fees. Applicants will have the opportunity to review the notice and notify FDA of any changes in contact information, changes in prescription drug product marketing status, or any other information the Agency needs to issue an accurate annual invoice.

B. Prescription Drug Program Fee Assessments and Payments

FDA expects to issue invoices for prescription drug program fees in mid-August based on information available to the Agency at the time the invoices are prepared. Payments are due either on the first business day on or after October 1 of each fiscal year or the first business day after the enactment of an appropriations Act providing for the collection and obligation of fees for that fiscal year, whichever occurs later.[68]

FDA will issue additional invoices[69] at a later date, as needed, to capture program fees owed that were not previously invoiced. For example, fee-eligible prescription drugs that are approved between the date annual notices are prepared and October 1 may be the subject of an invoice during the fiscal year. In addition, fee-eligible prescription drugs that return to the Active Section of the Orange Book or CBER/CDER Billable Biologics Lists during the fiscal year may also be subject to an invoice. Invoices may also be issued after the close of the fiscal year for other reasons.

X. FEE WAIVER, REDUCTION, EXEMPTION, OR RETURN REQUESTS AND APPEALS PROCESS

A. Waiver, Reduction, Exemption, or Return Request

An applicant may request a waiver, reduction, or exemption of user fees, and may request a return[70] of fees it has paid, if it meets the statutory criteria.[71] Policies for such requests, and the permissible grounds for a waiver, reduction, exemption, or return, are discussed in more detail in the Waivers Guidance. Note that any request for a waiver, reduction, exemption, or the return of

[68] Section 736(a)(2)(A) of the FD&C Act.
[69] Also known as "clean-up" invoices.
[70] Otherwise known as "refund".
[71] The FD&C Act does not provide for deferral of user fees, and FDA does not grant deferrals of user fees, based on pending requests for a refund. FDA therefore expects that all fees assessed will be paid when due without regard to a pending request for a refund. See section 736(d) of the FD&C Act.

any fee must be submitted no later than 180 calendar days after such fee is due even if the fee is claimed to have been paid in error.[72]

B. Reconsideration Request

If FDA fully or partially denies a request for a waiver, reduction, exemption, or return of user fees, the applicant may request reconsideration of that decision. A request for reconsideration should be made within 30 calendar days of the issuance of FDA's full or partial denial of a request.

FDA recommends that requests for reconsideration state the applicant's reasons for believing that FDA's decision is in error and include any additional information, including updated financial information that is relevant to the applicant's position. The Agency will issue a response upon reconsideration, setting forth the basis for the decision.

All requests for reconsideration (for both CDER or CBER regulated products) should be submitted via email to CDERCollections@fda.hhs.gov and should be addressed to the following:

Division of User Fee Management
Attention: Division Director
Center for Drug Evaluation and Research

Alternatively, an applicant can mail the request to FDA via the carrier of its choice. For the most updated mailing address, visit the following FDA website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

C. Appeal Request

If a request is denied upon reconsideration, the applicant may choose to appeal the denial. A request for an appeal should be made within 30 calendar days of the issuance of FDA's decision to affirm its denial of a request for a waiver, exemption, reduction, or return of user fees. The following information should be included in the appeal:

- The original request;
- The denial of the original request;
- The reconsideration request;
- The denial of the reconsideration request; and
- A statement of the applicant's reasons for believing that the prior conclusions were in error.

[72] Section 736(i) of the FD&C Act.

No new information or new analyses should be presented in the appeal request. If new information or analyses are presented in the appeal request, the appeal will not be accepted and the matter will be referred back to the original deciding authority to consider the new information or analyses.

All requests for appeals for either CDER or CBER products should be submitted to the Director of CDER's Office of Management via CDERCollections@fda.hhs.gov. Alternatively, an applicant can mail the request to FDA via the carrier of its choice. For the most updated mailing address, visit the following FDA website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

After FDA reviews the information submitted in the appeal request, for CDER regulated products, the Director of CDER's Office of Management will issue a written decision on the applicant's request; for CBER regulated products, the Director of CBER will issue a written decision on the applicant's request.

CDER Products

If the applicant's appeal is denied at one management level, the applicant can appeal the same matter to the next higher management level in the CDER chain of command. A new request should be submitted for each appeal to the next management level and should follow the process provided in this guidance. If the applicant has exhausted the CDER management levels and remains unsatisfied with the decision, the applicant may request review of the matter by the Commissioner of Food and Drugs (Commissioner) under 21 CFR 10.75(c). Requests for review by the Commissioner should be submitted to the FDA's Ombudsman, with a copy provided to CDER. Review of such matters by the Commissioner is discretionary.[73]

CBER Products

If the applicant's appeal is denied by the Director of CBER, the applicant may request review of the matter by the Commissioner under 21 CFR 10.75(c). Requests for review by the Commissioner should be submitted to the FDA's Ombudsman, with a copy provided to CBER. Review of such matters by the Commissioner is discretionary.

XI. OTHER RESOURCES

The following guidance documents may be helpful:

- Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees[74]
- Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products Guidance for Industry [75]

[73] See 40 FR 40682, 40693 (September 3, 1975).
[74] Available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf.
[75] Available at https://www.fda.gov/media/131797/download.

- Prescription Drug User Fee Act Waivers for Fixed Combination Antiretroviral Drugs for the President's Emergency Plan for AIDS Relief[76]

The following manuals of policies and procedures (MAPPs) may be helpful:

- MAPP 6020.4 Classifying Resubmissions of Original NDAs, BLAs, and Efficacy Supplements in Response to Complete Response Letters[77]
- MAPP 6050.1 Revision 2 Refusal to Accept Applications for Filing From Applicants in Arrears[78]

Additional information is also available on the FDA User Fees web page. For any questions, please email the Prescription Drug User Fee staff at CDERCollections@fda.hhs.gov or call 301-796-7900.

[76] Available at https://www.fda.gov/media/114038/download.
[77] Available at https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM082002.pdf.
[78] Available at https://www.fda.gov/media/72756/download.