How to Pay the Piper: FDA Issues New Guidances for PDUFA VI and GDUFA II

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FDA recently issued two draft guidances: *Assessing User Fees Under the Prescription Drug User Fee Amendments of 2017*[1] (PDUFA VI) and *Assessing User Fees Under the Generic Drug User Fee Amendments of 2017*[2] (GDUFA II), which clarify FDA's interpretation of some of the major changes to both user fee programs. PDUFA was reauthorized for the fifth time and GDUFA for the second time by the Food and Drug Administration Reauthorization Act (FDARA), which we outlined in an earlier bulletin.[3] The PDUFA VI and GDUFA II user fee changes took effect on October 1, 2017, which was the beginning of the 2018 fiscal year, and will run through fiscal year 2022, when the programs will again need to be reauthorized. This bulletin highlights some areas in which the guidances have provided needed clarification to certain FDARA provisions.

PDUFA VI Guidance

Elimination of supplement and establishment fees

A significant change in PDUFA VI is the elimination of two types of user fees.[4] The first is the elimination of user fees for supplement applications, which are used when there is a change to a drug with an approved New Drug Application (NDA). The second major fee eliminated by FDARA is the drug establishment registration fee, which had been assessed annually for the owner or operator of an establishment engaged in the manufacture, preparation, propagation, compounding, or processing of drugs, with some limited exceptions. In FY 2017, the annual establishment registration fee was $512,000.[5] Although the establishment fee has been eliminated, the establishment registration and drug listing requirements remain in effect.

The new drug application fee also remains in effect. The FY 2018 PDUFA VI user fee for an NDA with clinical data is $2,410,495, and $1,210,748 for an application not requiring clinical data.[6]

Limitation on Number of Program Fees

PDUFA VI creates a new annual "program fee," and the PDUFA guidance provides needed clarification to two program fee provisions. NDA holders pay an annual program fee, which is $304,162 for FY 2018, for each of their prescription drug products.[7] However, there is a limitation to the number of fees that may be assessed. The statute provides that applicants "shall not be assessed more than 5 prescription drug program fees for a fiscal year for prescription drug products identified in such approved human drug application."[8]

1 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM580099.pdf (last visited Nov. 27, 2017).
2 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM582475.pdf (last visited Nov. 27, 2017).
3 http://www.agg.com/some-may-come-and-some-may-go-fdara-brings-changes-to-user-fees-and-other-fda-programs-09-20-2017/ (last visited Nov. 27, 2017).
4 21 U.S.C. § 379h(a)(1).
5 https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ (last visited Nov. 27, 2017)
6 https://www.federalregister.gov/documents/2017/09/14/2017-19494/prescription-drug-user-fee-rates-for-fiscal-year-2018 (last visited Nov. 27, 2017).
7 21 U.S.C. § 379h(a)(2).
8 21 U.S.C. § 379h(a)(2)(C).

The Guidance clarifies that "prescription drug product" means each specific strength or potency of a drug for which an NDA has been approved. It also explains that an applicant will not be assessed more than five prescription drug program fees for a fiscal year for prescription drug products identified in a single approved application. For example, if a company has one approved NDA that includes 10 different strengths, it will only pay 5 product fees. However, a company that holds 10 separate approved NDAs that each includes one strength, will pay 10 annual program fees.

"Same Product" Program Fee Exception

In addition to the limitation on the total number of fees paid, there are also exceptions for products that are not assessed a program fee. The primary exception applies to a drug that is the "same product as another product."[9] The Guidance notes that this provision is intended to provide an exception to the program fee for drugs that are subject to generic competition. Generic competition, for this purpose, is not limited to therapeutically equivalent drugs approved under ANDAs, but also includes drugs approved through the 505(b)(2) pathway that FDA finds therapeutically equivalent.

It is also important to note that this exception can apply to both products. For example, suppose Drug A is approved through the 505(b)(1) pathway, several years later Drug B is approved under any pathway (ANDA, 505(b)(1) or (b)(2)) and FDA finds Drug B to be therapeutically equivalent to Drug A. Under the "same product" exception, neither Drug A nor Drug B would be assessed an annual program fee. However, because generic drug fees are covered under a different program, if Drug B were approved through the ANDA pathway, although Drug A would no longer be subject to a PDUFA program fee, Drug B may still be subject to program fees under GDUFA.

Moving a Drug to the Discontinued List

Program fees are not assessed for drugs that are in the discontinued section of the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) or the Biologics Lists. NDA holders that no longer market, or never have marketed, a particular product may wish to request the product be moved to the discontinued section so that they do not incur a user fee on the product. Note that moving a product to the discontinued section of the Orange Book or Biologic Lists[10] is different than withdrawing a product from sale. An NDA holder must provide 180-day notice to FDA before withdrawing a drug from sale.[11] NDA holders are also required to give written notice to FDA if the product will not be available for sale within 180 days of the date of approval.[12]

Requests to move a product to the discontinued product section of the Orange Book or Biologics Lists should be sent via email to the relevant FDA contact:

- Products approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA): OrangeBook@fda.hhs.gov.
- Products approved under the Public Health Service Act by the Center for Drug Evaluation and Research: CDERCollections@fda.hhs.gov
- Products approved under the Public Health Service Act by the Center for Biologics Evaluation and Research: CBERPDUFAstaff@fda.hhs.gov

FDA may request additional information from the NDA holder to confirm the product's not-marketed status. If FDA does not deny the request then, for user fee purposes, FDA will consider the product moved to the discontinued section on the date the request was received or on the date the product is no longer marketed, whichever date is later.

9 21 U.S.C. § 379h(a)(2)(B).
10 The Biologics Lists are the *Center for Drug Evaluation and Research Billable Biologic Product List* and the list of *User Fee Billable Biologic Products and Potencies Approved Under Section 351 of the PHS Act.*
11 21 U.S.C. § 356l(a).
12 21 U.S.C. § 356l(b).

GDUFA II Guidance

Program fees

In GDUFA II, FDARA creates a new annual program user fee, which is based on the number of approved ANDAs the applicant holds. There are three tiers of program fees: small, medium, and large. The number of approved ANDAs that define each tier, the annual program fee, and the total number of applicants in each tier as of April 30, 2017 are as follows:[13]

Tier	Number of Approved ANDAs	FY 2018 Program Fee	Total Applicants
Small	1-5	$159,079	339
Medium	6-19	$636,317	74
Large	20+	$1,590,792	65

It should be noted that FDA groups together affiliated companies and counts them as a single entity for the purpose of assessing the GDUFA program fee. FDA defines affiliate as 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 power to control, both of the business entities."[14]

To allow FDA to calculate user fees, each entity that owns an ANDA must submit to FDA, by April 1 of each year, a list that includes,

1. All ANDAs held by the entity and,
2. All ANDAs held by any of the entity's affiliates.[15]

If an ANDA holder wishes to withdraw any ANDAs in order to be assessed a user fee under a lower program fee tier for the next fiscal year, it must do so by April 1 of the previous fiscal year. For example, if a company held 20 ANDAs as of October 1, 2017, they would have been assessed the large tier program fee for FY 2018. However, if the company withdraws one or more ANDAs on or before March 31, 2018, they would pay the medium tier fee for FY 2019. Note that moving a product to the discontinued section of the Orange Book is different than withdrawing a product from sale. An ANDA holder must provide 180-day notice to FDA before withdrawing a drug from sale.[16] ANDA holders are also required to give written notice to FDA if the product will not be available for sale within 180 days of the date of approval.[17]

There are severe consequences for ANDA holders that do not pay their program fees within 20 days of the due date.

1. FDA will refuse to receive any ANDA or supplement from the company or its affiliates until the outstanding fee is paid.
2. The applicant will be placed on a public arrears list if the program fee is not paid within 20 days of the due date.
3. All drugs marketed under an approved ANDA held by the company or any of its affiliates, will be deemed misbranded.

13 https://www.federalregister.gov/documents/2017/08/29/2017-18377/generic-drug-user-fee-rates-for-fiscal-year-2018 (last visited Nov. 27, 2017).
14 21 U.S.C. § 379j-41(4).
15 21 U.S.C. § 379j-42(o).
16 21 U.S.C. § 356l(a).
17 21 U.S.C. § 356l(b).

Note that "receipt" is a term of art. When an ANDA is submitted, FDA makes an initial determination that it is administratively complete; if it is, then the application is "received" and substantive review can begin.[18]

Facility Fees

Under GDUFA II, contract manufacturers are now required to pay an annual facility fee, which is one-third of the fee assessed to noncontract manufacturers.[19] FDA defines a contract manufacturing organization facility as,

> a manufacturing facility of a finished dosage form of a drug approved pursuant to an abbreviated new drug application, where such manufacturing facility is not identified in an approved abbreviated new drug application held by the owner of such facility or an affiliate of such owner or facility.[20]

Foreign contract manufacturers will pay an additional $15,000. The owner of a facility will owe a fee when the facility is referenced in an approved ANDA submission and the facility is engaged in manufacturing or processing of an active pharmaceutical ingredient (API) or finished dosage form (FDF).

Facility fees are assessed every fiscal year for each facility listed in an ANDA on the facility fee due date. A facility may request to withdraw from the ANDA if it no longer manufactures API or FDF for the product. Facility owners and the holders of ANDAs referencing the facility should work together to remove the facility from the ANDA and notify FDA of the withdrawal. There are specific procedures that need to be followed for a facility to properly withdraw, which are outlined in the GDUFA guidance. A facility will not incur additional fees if it is no longer referenced in any generic drug submission or has stopped manufacturing all APIs and FDFs by the fee due date.

The consequences for failure to pay a facility fee are similar, but not identical, to the consequences for failure to pay the GDUFA program fee:

1. FDA will not receive a new ANDA or supplement submitted by the person responsible for paying the facility fee, or its affiliates.
2. FDA will not receive a generic drug submission referencing the facility until the facility fee is paid.
3. The facility will be placed on a public arrears list if the program fee is not paid within 20 days of the due date.
4. FDA will notify the ANDA applicant that references the facility of the facility's failure to pay its user fee.

The GDUFA guidance also covers other types of user fees, such as the drug master file fee and still outstanding backlog fees, as well as the procedures to appeal or request a refund of a fee.

AGG Observations

1. Both NDA and ANDA holders should keep in mind that they can be assessed a program fee for products that they no longer market, or never marketed. Manufacturers may want to review their list of approved products and consider submitting a request to withdraw unmarketed products in order to lower their annual user fees.
2. Note that ANDA program fees are assessed for an applicant and its affiliates as a single entity. Affiliates cannot opt to pay their applicable fees independently.
3. FDA will not send ANDA holders an invoice before the program fees are due on October 1. It is the ANDA holder's responsibility to track how many ANDAs they hold and, thus, what program fee tier they will owe. As noted above, an ANDA holder may request to withdraw an ANDA by April 1 of the previous fiscal year to be assessed a lower fee tier.

18 21 C.F.R. 314.101(b).
19 21 U.S.C. § 379j-42(b)(2)(C).
20 21 U.S.C. § 379j-41(5).

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