Guidance for Industry

Generic Drug User Fee Amendments of 2012: Questions and Answers

DRAFT GUIDANCE

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For questions regarding this draft document contact Division of Drug Information at 1-866-405-5367

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)

August 2012
Generic Drugs

Guidance for Industry

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

I. INTRODUCTION

This guidance provides answers to anticipated questions from generic drug industry participants regarding the implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III), commonly referred to as GDUFA. The questions and answers (Q&A) format is intended to promote transparency and facilitate compliance. The Q&As are grouped below in the following categories:

- Fees
- Self-identification of facilities, sites and organizations
- Review of generic drug submissions
- Inspections and compliance

This guidance is one in a series of GDUFA communications. Other communications, including the following, are available on www.fda.gov/gdufa:

- Guidance for industry *Self-Identification of Generic Drug Facilities, Sites and Organizations* (hyperlink)
- *Federal Register* Notice of Opportunity to Withdraw Abbreviated New Drug Applications to Avoid Backlog Fee Obligations (hyperlink)

Where applicable, references to information in these communications are included in this Q&A guidance.

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

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA or the Agency).

II. BACKGROUND

On July 9, 2012, GDUFA was signed into law by the President. GDUFA is designed to speed the delivery of safe and effective generic drugs to the public and reduce costs to industry.

GDUFA is based on an agreement negotiated by FDA and representatives of the generic drug industry to address a growing number of regulatory challenges. GDUFA reflects input received during an open process that included regular public meetings, posting of meeting minutes, and consideration of comments from a public docket. Agreed upon recommendations were sent to Congress, and Congress held hearings on GDUFA that included testimony from FDA, the generic drug industry, and other interested parties.

For more than a quarter of a century, the generic drug industry has been a public health success delivering lower-cost, bioequivalent versions of brand name drugs to a large and growing share of the public. The industry's success has, however, posed significant regulatory challenges, straining limited public resources. As the volume of new generic drug applications has increased and the industry has expanded globally, the time required for scientific review and inspections has grown, and with it, the backlog of pending generic applications.

GDUFA aims to put FDA's generic drug program on a firm financial footing and ensure timely access to safe, high-quality, affordable generic drugs. GDUFA enables FDA to assess user fees to fund critical and measurable enhancements to the performance of FDA's generic drugs program, bringing greater predictability and timeliness to the review of generic drug applications. GDUFA will also enhance FDA's ability to protect Americans in the complex global supply environment by requiring the identification of facilities involved in the manufacture of generic drugs and associated active pharmaceutical ingredients (API). The new requirements in GDUFA will also ensure that foreign and domestic industry participants in the U.S. generic drug system are held to consistent, high-quality standards and inspected biennially, with comparable rigor and frequency, using a risk-based approach.

The GDUFA program is designed to build on the success of the Prescription Drug User Fee Act (PDUFA) program which over the past 20 years has ensured a more predictable, consistent, and efficient premarket review program for new drug applications (NDAs) and biologic license applications (BLAs) and helped speed access to new, safe and effective prescription drugs to the public. Although modeled on PDUFA, GDUFA reflects the unique needs and challenges of generic drug regulation.

GDUFA requires that FDA and human generic drug manufacturers alike must meet certain requirements and commitments. In a Commitment Letter that accompanies the legislation, FDA committed to review and act on 90 percent of original, unamended abbreviated new drug applications (ANDAs) within 10 months following the date of submission by year five of the program. This will reduce the overall expense of bringing a generic product to market, and deliver safe, effective, and affordable generic drugs to the public sooner.
Under GDUFA, FDA has agreed to other program enhancements and performance goals. These include an immediate commitment to provide timely and complete information to applicants by

issuing complete response letters to all ANDAs. These letters will reflect full division-level reviews of any deficiencies noted by relevant review disciplines. FDA has also agreed to make every reasonable effort to communicate promptly with applicants to facilitate the timely revision of easily correctable deficiencies found in ANDAs and to clarify issues and answer questions during first cycle meetings. Additional efficiency enhancements and goals will be phased in over the life of the program (see details in the Commitment Letter).

GDUFA establishes application fees (for ANDAs, prior approval supplements (PASs) to ANDAs, and drug master files (DMFs)), annual facility fees, and a one-time fee for ANDAs pending on October 1, 2012, referred to as backlog applications. Beginning on October 1, 2012, human generic drug applicants will be required to pay application fees when they submit ANDAs and PASs, or the first time a DMF is referenced by an initial letter of authorization in an ANDA or PAS. FDA plans to publish the fee amounts for ANDAs, PASs, and DMFs in the *Federal Register* before October 31, 2012.

The amount of the annual user fees for generic drug facilities will be determined after the GDUFA program is launched. Under GDUFA, facilities, sites, and organizations must first self-identify.[2] Fees will be determined after the self-identification process has been completed, providing FDA information about the number of facilities that will be required to pay user fees. These include facilities manufacturing, or intending to manufacture, API of human generic drugs and/or finished dosage form (FDF) human generic drugs.

Although most facilities that are required to self-identify will also be required to pay an annual facility user fee, certain types of generic facilities, sites and organizations will not be required to pay the annual facility user fee. These include facilities, sites and organizations that solely manufacture positron emission tomography (PET) drugs; clinical bioequivalence or bioavailability study sites; in vitro bioequivalence testing or bioanalytical testing sites; API/FDF analytical testing sites; packagers; and repackagers.

The following responses have been developed in anticipation of questions that may arise as generic drug manufacturers prepare to meet the requirements of GDUFA.

III. QUESTIONS AND ANSWERS

A. FEES

The following questions and answers provide information on the various fees required by GDUFA. For convenience, these are summarized in Table 1.

Table 1. Summary of GDUFA User Fee Requirements

Fee	Who Incurs the Fee?	Payment Frequency	Year One Statutorily-Directed Revenue Target and Method of Calculating Individual Fee Amount	When will the FY 2013 Fee Amount(s) be Published?	For Further Information

[2] See draft guidance for industry *Self-Identification of Generic Drug Facilities, Sites, and Organizations.*

Backlog Fee	An applicant whose original ANDA is pending on Oct. 1, 2012 without a tentative approval	Once	$50 million divided by the total number of original ANDAs pending on Oct. 1, 2012	By 10/31/12	See questions 1-8
DMF Fee	A Type II active pharmaceutical ingredient (API) DMF holder whose DMF is referenced by an initial letter of authorization[A] in a generic drug submission on or after Oct. 1, 2012	Once for each API DMF, no later than when first letter of authorization is submitted	~$15 million divided by current estimates of annual number of DMF applications.	By 10/31/12	See questions 9-20
Generic Drug Submission Fees ANDA and PAS Fee Fee for API not referenced by a DMF (also referred to as (a)(3)(F) Fee)[B]	An applicant submitting an ANDA or PAS on or after October 1, 2012	Once, at time of submission of ANDA or PAS	~$60 million divided by a weighted average of current estimates of annual ANDA and PAS applications. (a)(3)(F) Fee is expected to generate a small portion of the total above.	By 10/31/12	See questions 21-31
Facility Fees API FDF	The owner of a facility identified, or intended to be identified, in at least one generic drug submission that is pending or approved to produce one or more generic drug finished dosage form (FDF) and/or APIs.	Annually	~$174 million total API: ~$35 million divided by number of API facilities. FDF: ~$139 million divided by number of FDF facilities. Facilities located outside of the United States and its territories and possessions will pay a higher fee reflecting the increased costs of inspections.	By 1/13/13	See questions 32-39

[A] See question 11 for information about a letter of authorization.
[B] See questions 27-29 for information about the (a)(3)(F) fee.

1. BACKLOG FEE

Q1. Who will be required to pay a backlog fee?

Each person that owns an original ANDA that is pending on October 1, 2012 and that has not been tentatively approved on that date will be required to pay a backlog fee for that ANDA.

Q2. How will FDA define *pending* applications for purposes of paying the backlog fee?

Any original ANDA that has not been withdrawn, tentatively approved, or approved by September 28, 2012, is considered pending and is subject to a backlog fee. See *Federal Register* Notice of Opportunity to Withdraw Abbreviated New Drug Applications to Avoid Backlog Fee Obligations (hyperlink) for additional details.

Q3. How much is the backlog fee, how will it be assessed, and when will it be due?

The backlog fee will be determined based on the number of original ANDAs pending at the start of the business day on October 1, 2012. In accordance with GDUFA, FDA will divide $50 million by the number of original ANDAs pending to arrive at the amount of the individual one-time backlog fee, which will be due for each pending original ANDA.

Absent withdrawals, there could be 3,000 pending original ANDAs on October 1, 2012. A number of these applications are old and incomplete and may be withdrawn by applicants prior to October 1, 2012 to avoid incurring the backlog fee. If 2,000 original ANDAs remain, the backlog fee amount will be $25,000. This is an estimate, however, and the final backlog fee will be published in the *Federal Register* prior to October 31, 2012. Payment will be due no later than 30 calendar days after the publication date.

Q4. If an applicant wishes to withdraw an original ANDA, how should it do so?

The ANDA applicant should notify the Office of Generic Drugs (OGD) in writing with the request to withdraw the application. To avoid the backlog fee, written notification must be received by September 28, 2012.

Applicants should submit written notification of the request for withdrawal by standard application submission methods. If an application was submitted by the FDA electronic gateway, a request for withdrawal should be submitted to the application by the gateway. In addition, a copy of the electronic notification of withdrawal should be emailed to OGDGDUFA@fda.hhs.gov. Alternatively, the applicant should send written notification to the ANDA archival file at the following address: Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, Maryland 20855.

FDA encourages applicants to notify OGD on or before September 15, 2012, to ensure timely withdrawal. See *Federal Register* Notice of Opportunity to Withdraw Abbreviated New Drug Applications to Avoid Backlog Fee Obligations (hyperlink) for additional information.

Q5. If an original ANDA has been submitted to FDA before October 1, 2012, but has not been accepted for review, will this ANDA be subject to a backlog fee?

Yes.

Q6. If FDA refuses to receive an application in the backlog, will the backlog fee be refunded?

No.

Q7. What is the penalty for failure to pay the backlog fee?

Any person that owns an original ANDA that fails to pay the backlog fee will be placed on a publicly available arrears list, and FDA will not receive a new ANDA or supplement submitted by that person, or any affiliate (see next question and answer) of that person, within the meaning of 505(j)(5)(A) of the Federal Food, Drug and Cosmetic Act, until the outstanding fee is paid.

Note: The fee is an obligation to the U.S. government, and the failure to pay the fee may result in collection activities by the government pursuant to applicable laws.

Q8. What is an *affiliate* for this purpose?

GDUFA defines the term *affiliate* as a business entity that has a relationship with a second business entity if, directly or indirectly, one business entity controls, or has the power to control, the other business entity; or a third party controls, or has power to control, both of the business entities.

2. DRUG MASTER FILE (DMF) FEE

Q9. What DMFs incur fees?

Only DMFs that cover the manufacture of an API (Type II API DMFs) for use in a generic drug application incur fees. Specifically, each person that owns a Type II API DMF (DMF holder) that is referenced on or after October 1, 2012, in a generic drug submission by any initial letter of authorization shall be subject to a DMF fee.

Q10. What is a generic drug submission?

The phrase *generic drug submission* refers to an ANDA, an amendment to an ANDA, or a PAS to an ANDA.

Q11. When is a DMF fee incurred?

The owner of a DMF incurs the fee the first time that a generic drug submission references that DMF by an initial letter of authorization on or after October 1, 2012.

Q12. What is an "initial letter of authorization" as that term is used in this context?

An initial letter of authorization is one that an ANDA applicant has not previously relied on. This means that the DMF fee would be triggered the first time that a DMF is referenced by an ANDA applicant that has not previously relied on a letter of authorization for that DMF. For example, if ANDA applicant X submitted its ANDA (for Drug A) in September, 2012 and relied on a letter of authorization for DMF 11111, it would not trigger a fee for the DMF. If after October 1, 2012, ANDA applicant X amended or supplemented its application, it would not trigger a fee for the DMF. If, however, after October 1, 2012, ANDA applicant X submitted

a new ANDA (for Drug B) with a letter of authorization to DMF 11111, it would trigger a fee for DMF 11111. Furthermore, if a different ANDA applicant submitted a letter of authorization to DMF 11111 after October 1, 2012, it would trigger a fee for the DMF, if the fee had not already been paid for DMF 11111. Once a fee is paid for DMF 11111, no additional fee for this DMF will be assessed, regardless of how many letters of authorization for that DMF are referenced in one or more ANDAs.

Q13. Do holders of DMFs submitted and reviewed by FDA before October 1, 2012, have to pay a DMF fee?

GDUFA does not make a distinction between DMFs submitted before or after October 1, 2012. Holders of DMFs reviewed prior to GDUFA implementation must pay the one-time DMF fee if their DMF is referenced in a new generic drug submission on or after October 1, 2012.

Q14. Will DMF holders be charged each time their DMF is referenced?

No. The DMF fee is a one-time fee, incurred on first reference of the DMF on or after October 1, 2012. This fee is not incurred every time a DMF is referenced.

Q15. How much is the DMF fee?

The fee for fiscal year (FY) 2013 (October 1, 2012 to September 30, 2013) has not yet been determined. Negotiators estimated that 350 DMFs would be submitted to FDA in FY 2013 based on the latest data available at the time, but it was understood that the determination of the number of DMFs to be used in calculating the fee would be made based on the best available data and experience at the time of calculation. If the projection at the time of negotiation remains unchanged, the DMF fee will be approximately $43,000. This is only an estimate, however, and the final DMF fee for FY 2013 will be published in the *Federal Register* prior to October 31, 2012.

Fees for FYs 2014-2017 will be adjusted for inflation and other factors, including the projected number of DMFs that FDA expects to be referenced for the first time in a given year based on experience. Fees will be published in the *Federal Register* no later than 60 days before the start of each fiscal year.

Q16. When will the DMF fee be due?

In FY 2013, DMF fees *will be incurred* at the time of submission of a generic drug submission for all Type II API DMFs referenced for the first time by an initial letter of authorization on or after October 1, 2012. In general, fees will be due on the date the first generic drug submission is submitted that references the associated DMF.

Note: In FY 2013, however, fees will not be due earlier than 30 days after publication of the final DMF fee in the *Federal Register* or 30 days after enactment of an appropriations Act that provides for the collection and obligation of generic drug user fees, whichever is later. If the FY 2013 appropriations Act is delayed, FDA will publish a notice in the *Federal Register* announcing the FY 2013 fee due dates when the appropriations Act is enacted.

If a DMF is referenced for the first time in an ANDA that is submitted on or after October 1, 2012, but an appropriations Act has not yet been enacted, the DMF holder will be obligated to pay the fee for that DMF, but that payment will not be due until after an appropriations Act providing for the collection and obligation of generic drug user fees is enacted.

Fees for FYs 2014-2017 will be due no later than the date on which the first generic drug submission that references the associated DMF holder's file is submitted.

Q17. Do DMF holders need to wait for a new ANDA applicant to request a letter of authorization before the DMF is assessed to be available for reference?

No. DMF holders can pay the fee before a letter of authorization is requested. The DMF will then undergo an initial completeness assessment, using factors that FDA will articulate in forthcoming guidance. If the DMF passes the completeness assessment, it will be placed on a publicly available list of DMFs available for reference.

Q18. What are the criteria for a DMF completeness assessment?

FDA will publish guidance on this issue.

Q19. Can an ANDA applicant pay the DMF fee for an API referenced in its submission?

Yes.

Q20. What is the penalty for failure to pay the DMF fee?

The DMF will be deemed not available for reference. Once the DMF fee becomes due, no generic drug submission submitted on or after October 1, 2012, referencing the DMF will be received unless the fee is paid and the DMF is deemed available for reference.

Note: The DMF fee does not become due until FDA announces the amount of the fee and appropriations legislation authorizing the fee is enacted. It is possible that appropriations legislation will not be enacted until some time after October 1, 2012. If the FY 2013 appropriations Act is delayed, FDA will publish a notice in the

Federal Register announcing the FY 2013 fee due dates when the appropriations Act is enacted.

ANDA applicants that reference a DMF for which a fee is due but has not been paid will be provided notification of the DMF holder's failure to pay. If the DMF fee is not paid within 20 calendar days after notification, the ANDA referencing the DMF will not be received.

3. ABBREVIATED NEW DRUG APPLICATION (ANDA) AND PRIOR APPROVAL SUPPLEMENT (PAS) FEES

Q21. How much are the ANDA and PAS fees?

The FY 2013 fees have not yet been determined. Negotiators estimated that 750 ANDAs and 750 PASs would be submitted to FDA in FY 2013 based on the latest data available at that time, but it was understood that the determination of the number of ANDAs and PASs to be used in calculating the fee would be made based on the best available data and experience at the time of calculation. If the projections at the time of negotiation remain unchanged, the ANDA fee will be approximately $53,000, and the PAS fee approximately $27,000. However, this is an estimate and the final ANDA and PAS fees for FY 2013 will be published in the *Federal Register* on or before October 31, 2012.

Individual fee amounts will be recalculated each fiscal year. Fees for FYs 2014-2017 will be adjusted for inflation and other factors, including the projected number of ANDAs and PASs based on experience and published in the *Federal Register* no later than 60 days before the start of each fiscal year (i.e., no later than 60 days before October 1 of each year).

Q22. When will ANDA and PAS fees be due?

In FY 2013, fees *will be incurred* at the time of submission for each ANDA and PAS submitted on or after October 1, 2012. However, fees will not be due earlier than 30 days after publication of the ANDA and PAS fees in the *Federal Register* or 30 days after enactment of an appropriations Act that provides for the collection and obligation of generic drug user fees, whichever is later. If the FY 2013 appropriations Act is delayed, FDA will publish a notice in the *Federal Register* announcing the FY 2013 fee due dates when the appropriations Act is enacted.

If an ANDA or a PAS is submitted on or after October 1, 2012, but an appropriations Act has not yet been enacted, the applicant will be obligated to pay the fee for that application, but that payment will not be due until after the appropriations Act providing for the collection and obligation of generic drug user fees is enacted.

Fees for FYs 2014-2017 will be due on the date of submission of the application.

Q23. If an ANDA or PAS is refused, is there any provision for partial refund of the application fee?

In certain circumstances, a partial refund may be possible. If the reason that the application was refused was not related to failure to pay fees, then 75 percent of the fee paid will be refunded to the applicant.

Q24. If such a previously refused application is then resubmitted, will the applicant be required to pay the full fee at the time of resubmission?

Yes.

Q25. What is the penalty for failure to pay the ANDA or PAS fee?

The ANDA or PAS will not be received unless the fee is paid within 20 calendar days of the due date.

Q26. If an ANDA or PAS applicant pays its application fee more than 20 calendar days after the due date, what will FDA consider as the application's date of submission?

If an applicant submits payment after the 20 calendar day grace period, its application will be deemed incomplete on the date of submission. It will be received within the meaning of section 505(j)(5)(A) of the Federal Food, Drug, and Cosmetic Act as of the date its payment in full is received.

Q27. What is a generic drug submission?

The phrase *generic drug submission* refers to an ANDA, an amendment to an ANDA, or a PAS to an ANDA.

Q28. If a generic drug submission includes API information other than by reference to a DMF – e.g., the applicant manufactures an API in its own facility or facilities – is the applicant required to pay an additional fee?

Yes. The applicant is required to pay an API-related fee for each API manufactured in its own facility or facilities for which it has not previously paid an API-related fee. As with a DMF fee, this fee is paid only once.

The amount of the API-related fee is a function of the number of APIs referenced in the application and the number of facilities in which those APIs are manufactured. If the ANDA references more than one facility as manufacturing each API, the applicant must pay the API-related fee for each such facility. See the examples that follow.

GDUFA specifies that the ANDA applicant must pay a fee for each API facility for which an API-related fee has not previously been paid that is described in the generic drug submission by means other than reference to a DMF.

Because the calculation is potentially confusing, we provide the following two examples.

Example One:

An applicant submits an ANDA that describes manufacture of APIs, not by reference to DMFs.

Product	API	Facility for which no API fee has previously been paid for that ingredient
Drug X	Alpha	1, 2, 3
	Beta	1, 2
	Gamma	1

The applicant owes the following API-related fee:

Fee = [APIs (Alpha + Beta + Gamma) + extra facilities (Alpha 2 + Alpha 3 + Beta 2) x DMF fee

= (3 APIs + 3 Extra Facilities) x DMF fee

= 6 x DMF fee

Example Two:

The applicant submits a new application for a second product with the following information about API manufacture other than by reference to a DMF:

Product	API	Facility
Drug Y	Alpha	1, 2, 3
	Beta	1, 2
	Gamma	1, 2
	Delta	3

The one-time fee has already been paid for Alpha, Beta and Gamma, so no additional fee is due for these components. In addition, the applicant has already paid for all of the extra facilities except for Gamma 2, so a fee is only owed for Gamma facility 2.

The applicant owes the following API-related fee:

Fee = [APIs (Delta) + extra facilities (Gamma 2)] x DMF fee

= (1 API + 1 Extra Facility) x DMF fee

= 2 x DMF fee

Q29. Are the references to fees for each API facility in the above question and answer different from the annual fee that each API facility must pay (discussed below)?

Yes. The reference to fees for each API facility in the calculation above is meant to replicate the DMF fee required if the information is submitted in a DMF. Annual API facility fees are discussed below and are required for each facility that makes an API for a generic drug, regardless of whether the API is identified in an ANDA or a DMF.

Q30. Is a PAS fee required for such changes as labeling and microbiology?

Yes. User fees are required for all PASs, including labeling and microbiology that require prior approval under FDA regulations.

Q31. If a manufacturer submits a change being effected (CBE) supplement, will FDA convert the supplement to a PAS?

If FDA determines that the proposed manufacturing change to an approved product was submitted incorrectly as a CBE, FDA will notify the applicant that the proposed change is a major change that requires approval before the product made with the change can be distributed. The applicant must resubmit the change as a PAS along with payment of a PAS fee.

The criteria for submitting information as a CBE or a PAS were not changed by GDUFA. For additional information, please refer to 21 CFR 314.70, as well as related guidances, including, but not limited to, *Scale-Up and Post Approval Changes (SUPAC) and Changes to an Approved New Drug Application (NDA) or ANDA*.

4. FACILITY FEES

Q32. What are the FDF and API facility fees for U.S. and foreign manufacturers?

The amount of the FY 2013 facility fees has not yet been determined. Fees will be determined after the self-identification process (described in the guidance, *Self-Identification of Generic Drug Facilities, Sites, and Organizations (hyperlink)*) has been completed, providing FDA information about the number of facilities that will be required to pay user fees. The facility fees will be published in the *Federal Register*.

Fees for FYs 2014-2017 will be adjusted for inflation and other factors, including the number of facilities that have self-identified each year. The fees will be published in the *Federal Register* no later than 60 days before the start of each fiscal year.

Q33. When will facility fees be due?

In FY 2013, facility fees will be determined after the self-identification process has been completed. Fees will be due within 45 days after publication of the final facility fee amounts in the *Federal Register*, or 30 days after the enactment of an appropriations Act providing for the collection and obligation of generic drug user fees, whichever is later. If enactment of the FY 2013 appropriations Act occurs after publication of the final facility fee amounts, FDA will publish a notice in the *Federal Register* announcing the FY 2013 fee due dates when the appropriations Act is enacted.

Fees for FYs 2014-2017 will be due 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 that provides for the collection and obligation of fees.

Q34. Who is required to pay facility fees?

Any person that owns a facility that is identified or intended to be identified in at least one generic drug submission that is pending or approved to produce one or more generic drug FDFs and/or APIs is required to pay facility fees.

Q35. Does GDUFA make any changes to traditional definitions of API and FDF manufacturers?

For purposes of self-identification and payment of fees, GDUFA defines API and FDF manufacturers somewhat differently from the way these traditional categories of manufacturers have been defined historically. For example, generic drug manufacturers who mix an API when the substance is unstable or cannot be transported on its own are considered API manufacturers and not FDF manufacturers for self-identification and the payment of GDUFA user fees only.

GDUFA defines an FDF as:

(A) a drug product in the form in which it will be administered to a patient, such as a tablet, capsule, solution, or topical application;
(B) a drug product in a form in which reconstitution is necessary prior to administration to a patient, such as oral suspensions or lyophilized powders; or
(C) any combination of an active pharmaceutical ingredient (as defined in the statute) with another component of a drug product for purposes of production of a drug product described in subparagraph (A) or (B).

GDUFA defines an API as:

(A) a substance, or a mixture when the substance is unstable or cannot be transported on its own, intended—
  (i) to be used as a component of a drug; and
  (ii) to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the human body; or

(B) a substance intended for final crystallization, purification, or salt formation, or any combination of those activities, to become a substance or mixture described in subparagraph (A).

Q36. If a facility manufactures both generic FDFs and APIs, will it incur more than one facility fee?

Yes. Under GDUFA, such a facility will incur annual FDF and annual API facility fees.

Q37. Is there a difference in fees between foreign and domestic generic drug facilities?

Yes. GDUFA specifies that the amount of the fee for a facility located outside the United States and its territories and possessions shall not be less than $15,000 and not more than $30,000 higher than the amount of the fee for a domestic facility. The differential amount is designed to reflect the higher costs of inspections funded, in part, through GDUFA.

In FY 2013, the cost differential will be set on the basis of the FDA's estimate of the average direct cost differential between foreign inspections and domestic inspections. The cost differential will be announced with publication of the facility fees in the *Federal Register* and will be adjusted in future years.

Q38. Do two locations of the same company have to pay separate facility fees?

The answer depends on geography. If the same company's two locations manufacture a U.S. generic product and they are in different geographic locations, each has to pay an annual facility fee. However, separate buildings within close proximity are considered to be at one geographic location or address if the activities in them are closely related to the same business enterprise, if they are under the supervision of the same local management,[3] and if they are capable of being inspected by the FDA during a single inspection. These are the same criteria used to evaluate whether separate FDA Facility Establishment Identifiers **(**FEIs**)** are

[3] The statute further states that if a business or other entity would meet the definition of a facility but for being under multiple management, the business or entity is deemed to constitute multiple facilities, one per management entity.

necessary for multiple facilities (see guidance *Self-Identification of Generic Drug Facilities, Sites, and Organizations (hyperlink)*). An annual facility fee will be due for each facility assigned a unique FEI.

Q39. What is the penalty for failure to pay a facility fee?

There are several consequences for failure to pay a facility fee. No new generic drug submission referencing the facility will be received until the fee is paid. In addition, the facility will be placed on a publicly available arrears list if the fee is not fully paid within 20 days of the due date. And, FDA will notify the ANDA applicant of the facility's failure to satisfy its user fee obligations. Furthermore, all FDFs or APIs manufactured in the non-paying facility and all FDFs containing APIs manufactured in such a facility will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to pay facility fees are subject to being denied entry into the United States.

Note: The fee is an obligation to the U.S. government, and the failure to pay the fee may result in collection activities by the government pursuant to applicable laws.

5. OTHER FEE RELATED QUESTIONS

Q40. What is the process for paying GDUFA user fees?

The process is similar to payment procedures for PDUFA and other FDA user fees.

- Those responsible for payment of fees will enter required information online at FDA's website to generate a GDUFA user fee payment cover sheet. The cover sheet is designed to provide the minimum necessary information to determine if a person has satisfied all relevant user fee obligations.

- The cover sheet will be submitted to FDA electronically generating a receipt with a user fee payment identification (ID) number to assist in tracking payment.

- Fee payers may pay online by credit card or Automated Clearing House (ACH) electronic check or send payment by check, bank draft, U.S. postal money order, or wire transfer. Cover sheet(s) should be submitted with generic drug submissions or DMFs.

More information, including a link to the GDUFA user fee cover sheet, will be provided when the user fee amounts are published in the *Federal Register*.

Q41. Will payment be accepted in non-U.S. currency?

No. Payment must be made in U.S. currency drawn on a U.S. bank by electronic payments (such as by credit card or ACH electronic check), check, bank draft, U.S. postal money order, or wire transfer.

Q42. What happens if a person pays less than the full amount of required GDUFA fee(s)?

FDA's expectation is for full and timely payment of all GDUFA fees. Penalties associated with non-payment, including refusal to receive a generic drug submission and failure of a DMF to be placed on a publicly available reference list, will apply until such obligations are satisfied in full.

Those paying fees are responsible for determining all financial institution transaction fees that may be deducted from a company's authorized amount for payment to FDA. These include wire transfer and foreign exchange fees. Please ask your financial institution about fees to make sure FDA receives full payment.

Q43. What happens if a person inadvertently pays too high a fee?

Such person will need to make a written request for return of the overpayment within 180 days of the payment. The person must submit a written request justifying the return of the fee within 180 calendar days of the payment receipt date. Note that if a written request is not made within 180 calendar days, no return of fees is permitted.

Q44. Will companies be invoiced for fees?

No. It is FDA's expectation that firms will self-identify and pay. However, in rare and unusual circumstances, FDA may find it necessary to issue an invoice.

Q45. Are there any exemptions from the fees for categories of drugs?

Positron Emission Tomography (PET) drug manufacturers are the only human generic drug manufacturers excluded from payment of GDUFA fees. They are, however, required to self-identify. FDA also requests that all drug manufacturers, including generic PET manufacturers, submit a user fee cover sheet with any new FDA submissions. PET manufacturers should complete a generic drug user fee cover sheet for $0.

Q46. Are reduced fees available for small businesses or others?

No. The majority of generic companies are small companies that are expected to benefit significantly from reductions in the review time needed to commercialize their products and from the certainty associated with performance review metrics and program efficiencies.

In addition to diminishing the fee-paying base, the cost of a fee waiver or reduction provision would have added to the administrative cost of the GDUFA program. As such, no fee waiver or reduction provision was included. Congress specifically considered this issue and agreed with the decision not to have a fee waiver or reduction mechanism in GDUFA, whose individual fee amounts are expected to be orders of magnitude less than those in PDUFA.

Q47. How will FDA communicate and update the arrears list?

The arrears list will be available to the public on the FDA's website. FDA plans to update the arrears list following each annual facility fee payment deadline. In addition, FDA anticipates more frequent updates to reflect payment activity.

Q48. If a company believes that its appearance on the arrears list is in error, whom should it contact?

Persons should contact the Generic Drug Collections Team at the Office of Management at 301-796-7900 or cder-om-collections@fda.hhs.gov.

Q49. How does FDA determine the date and time of submission when a generic drug submission or Type II DMF is sent electronically?

A generic drug submission or Type II API DMF is deemed to be submitted to FDA on the calendar day when the electronic submission arrives at FDA's electronic gateway, except that a submission made on a weekend, Federal holiday, or a day when the FDA office that will review the submission is not otherwise open for business will be deemed to be submitted on the next day when that Office is open for business. For a generic drug submission or Type II API DMF that is submitted in physical media form, the date of submission will be the day it arrives at the appropriate designated FDA document room.

Q50. What is the start date for GDUFA fees?

The start date is October 1, 2012.

Q51. Do GDUFA fees apply to drugs that are not generic drugs or not human generic drugs?

No. GDUFA fees apply only to generic drugs manufactured for human use.

Q52. Does GDUFA provide any mechanism for disputes concerning fees?

A person may submit a written request to the Secretary requesting the return of a fee claimed to have been paid in error. The request justifying the return of the fee must be submitted within 180 calendar days of the payment receipt date. Note that

if a written request is not made within 180 calendar days, no return of fees is permitted.

B. SELF-IDENTIFICATION OF FACILITIES, SITES, AND ORGANIZATIONS

More information is available in the guidance, *Self-Identification of Generic Drug Facilities, Sites and Organizations* (hyperlink). See also www.fda.gov/gdufa.

Q53. Who will be required to self-identify?

1. Facilities[4] that manufacture, or intend to manufacture, human generic drug APIs or FDFs, or both. See question 35 for additional information including definitions.

2. Sites and organizations that package the FDF of a human generic drug into the primary container/closure system and label the primary container/closure system.[5]

3. Sites that are identified in a generic drug submission and, pursuant to a contract with the applicant, remove the drug from a primary container/closure system and subdivide the contents into a different primary container/closure system.

4. Bioequivalence (BE)/bioavailability (BA) sites that are identified in a generic drug submission and conduct clinical BE/BA testing, bioanalytical testing of samples collected from clinical BE/BA testing, and/or in vitro BE testing.

5. Sites that are identified in a generic drug submission and perform testing of one or more attributes or characteristics of the FDF or the API pursuant to a contract with the applicant to satisfy a current good manufacturing practice (CGMP) testing requirement (excludes sites that are testing for research purposes only).

Q54. Are all facilities, sites, and organizations listed above also required to pay facility fees?

No. Only facilities that manufacture, or intend to manufacture, generic drug APIs or FDFs, or both, are required to pay facility fees. Sites and organizations that only perform testing, repackaging, or relabeling are not required to pay a user fee.

[4] GDUFA defines a facility as a business or other entity under one management, either direct or indirect, at one geographic location or address, engaged in manufacturing or processing an API or an FDF. It does not include a business or other entity whose only manufacturing or processing activities are one or more of the following: repackaging, relabeling, or testing. Separate buildings within close proximity are considered to be at one geographic location or address if the activities in them are closely related to the same business enterprise; are under the supervision of the same local management; and are capable of being inspected by FDA during a single inspection.

[5] Sites and organizations that package the FDF of a human generic drug into the primary container/closure system and label the primary container/closure system are considered to be manufacturers, whether or not that packaging is done pursuant to a contract or by the applicant itself.

Q55. Do two locations of the same company have to identify separately?

The answer depends on geography. If the same company's two locations manufacture a U.S. generic product and they are in different geographic locations, each has to pay an annual facility fee. However, separate buildings within close proximity are considered to be at one geographic location or address if the activities in them are closely related to the same business enterprise, if they are under the supervision of the same local management,[6] and if they are capable of being inspected by the FDA during a single inspection. These are the same criteria used to evaluate whether separate FEIs are necessary for multiple facilities. An annual facility fee will be due for each facility assigned a unique FEI.

Q56. What is the penalty for failure to self-identify?

All FDFs or APIs manufactured in the facility, and all FDFs containing APIs manufactured in the facility will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of the failure of the facility to self-identify are subject to being denied entry into the United States.

C. REVIEW OF GENERIC DRUG SUBMISSIONS

Q57. Will priority be given to certain ANDAs under GDUFA? If so, what applications will be expedited?

FDA's Commitment Letter explains that:

> Products to respond to current and anticipated public health emergencies, products under special review programs, such as the President's Emergency Plan for AIDS Relief (PEPFAR), products for which a nationwide shortage has been identified, and first generic products for which there are no blocking patents or exclusivities on the reference listed drug currently may qualify for expedited review. For ANDAs in the year 1 and 2 cohorts, FDA will expedite review of Paragraph IV[7] applications that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted.

[6] The Act further states that if a business entity would meet the definition of a facility but for being under multiple management, the business or entity is deemed to constitute multiple facilities, one per management entity.

[7] For this purpose, "Paragraph IV applications" are those for which a generic drug company submits an ANDA that challenges the innovator's patent as being invalid, or indicates that the patent will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (see 21 USC 505(j)(2)(A)(vii)(IV)).

Q58. How does GDUFA affect FDA's refuse to receive policy?

GDUFA adds a new requirement to FDA's existing refuse to receive policy with respect to payment of fees and the time of receipt of an ANDA.

- Failure to pay an ANDA fee within 20 calendar days of the applicable due date will result in the ANDA not being received.
- Failure to pay the fee for a DMF referenced in the ANDA within 20 calendar days of the date that FDA provides notification of that failure will result in the ANDA not being received.
- Failure to pay a facility fee for any facility referenced in the ANDA within 20 calendar days of the date that FDA provides notification of that failure will result in the ANDA not being received.
- If an application is substantially complete except for failure to pay the ANDA fee, or the failure to pay the facility fee within 20 days of notification, the application will be deemed received as of the date the fee is paid.

FDA will publish further guidance on any other changes to its refuse to receive policy for public comment in advance of their implementation.

Q59. Will FDA continue to accept applications in paper format?

Yes, for the time being. Applications received in paper format after October 1, 2012, however, will not be included as part of the new performance metrics established in GDUFA.

Additionally, electronic submissions will be required 24 months after issuance of final electronic submission guidance. The process for developing the electronic submission guidance will be consistent with the Good Guidance Practice regulation (21 CFR 110.15), providing public notice and opportunity for comment.

Q60. If an ANDA is submitted electronically, but one or more of its referenced DMFs was submitted in paper format, will the ANDA be included as part of GDUFA performance metrics?

Yes.

Q61. How does FDA determine the date and time of submission when a generic drug submission or Type II API DMF is sent electronically?

A generic drug submission or Type II API DMF is deemed to be submitted to the FDA on the calendar day the electronic submission arrives at FDA's electronic gateway, except that a submission made on a weekend, Federal holiday, or a day when the FDA office that will review the submission is not otherwise open for business will be counted as being submitted on the next day when that Office is open for business. For a generic drug submission or Type II API DMF that is

submitted in physical media form, the date of submission will be the day it arrives at the appropriate designated FDA document room.

Q62. What is the process for placement of a DMF on a publicly available reference list?

If the DMF applicant pays the DMF fee and the file passes an initial completeness assessment, FDA will identify the DMF on a list that will be available on www.fda.gov.

Q63. Will GDUFA change the procedure for DMF filing?

No. The process for DMF filing is shared by different departments at FDA and is not being modified for GDUFA purposes. There are no plans to change the process for filing or assigning a DMF number.

Q64. What is the process for requesting a teleconference to clarify deficiencies and answer questions following FDA's issuance of a complete response letter?

An applicant may request a 30-minute teleconference within ten business days after FDA issues a first-cycle review complete response letter to discuss the deficiencies noted in the letter. The request for a teleconference must be submitted in writing to the ANDA file and appropriately identified on its cover page as a "Post Complete Response Teleconference Meeting Request."

The request should include a list of specific written questions for discussion. The scope of the questions should be limited to the content of FDA's complete response letter. Priority for such teleconferences will be given to expedited and first major amendment applications and other applications as detailed in the Commitment Letter (see question 57).

ABBREVIATIONS AND ACRONYMS LIST

The following is a list of abbreviations and acronyms used in the Generic Drug User Fee Amendments of 2012: Questions and Answers Guidance:

ANDA	abbreviated new drug application
API	active pharmaceutical ingredient
BA	bioavailability
BE	bioequivalence
BLA	biologic license application
CBE	changes being effected
CDER	Center for Drug Evaluation and Research
CGMP	current good manufacturing practice
DMF	drug master file
FDA	Food and Drug Administration
FDF	finished dosage form
FEI	Facility Establishment Identifier
FY	fiscal year
GDUFA	Generic Drug User Fee Amendments of 2012
ID	identification
NDA	new drug application
OGD	Office of Generic Drugs
OPS	Office of Pharmaceutical Science
PAS	prior approval supplement
PDUFA	Prescription Drug User Fee Act
PEPFAR	President’s Emergency Plan for AIDS Relief
PET	positron emission tomography
Q&As	questions and answers