Guidance for Industry

Generic Drug User Fee Amendments of 2012: Questions and Answers

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory Affairs (ORA)

September 2013
Generic Drugs
Revision 1

Guidance for Industry

Generic Drug User Fee Amendments of 2012: Questions and Answers

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TABLE OF CONTENTS

Guidance for Industry[1]
Generic Drug User Fee Amendments of 2012
Questions and Answers

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 first version of this document was issued pursuant to 21 CFR 10.115 and was made available on FDA's website on August 22, 2012.

FDA is revising this draft guidance. The revision clarifies some of the questions and answers included in the first version and adds several new questions and answers that have arisen since the launch of the program, including questions FDA received following issuance of the first draft of the guidance.

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 guidances and Federal Register (FR) notices are available on http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Office of Regulatory Affairs (ORA) at the Food and Drug Administration (FDA).

- Guidance for industry *Initial Completeness Assessments for Type II Active Pharmaceutical Ingredient Drug Master Files Under the Generic Drug User Fee Amendments of 2012*
- FR notice, Generic Drug User Fee—Backlog Fee Rate for Fiscal Year 2013
- FR notice, Generic Drug User Fee—Abbreviated New Drug Application, Prior Approval Supplement, and Drug Master File Fee Rates for Fiscal Year 2013
- FR notice, Generic Drug User Fee—Facility Fee Rates for Fiscal Year 2013
- FR notice, Generic Drug User Fee—Abbreviated New Drug Application, Prior Approval Supplement, Drug Master File, Final Dosage Form Facility, and Active Pharmaceutical Ingredient Facility Fee Rates for Fiscal Year 2014
- FR notice, Requirement: Self-Identification of Generic Drug Facilities, Sites and Organizations
- Guidance for industry *Self-Identification of Generic Drug Facilities, Sites and Organizations*
- FR notice, FY 2014 Reporting Period for Self-Identification of Generic Drug Facilities, Sites and Organizations
- FR notice, Opportunity to Withdraw Abbreviated New Drug Applications to Avoid Backlog Fee Obligations

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.

II. BACKGROUND

On July 9, 2012, GDUFA was signed into law by the President.[2] 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.

[2] On October 5, 2012 the President signed into law the FDA User Fee Corrections Act of 2012. This act amends GDUFA so that due dates for GDUFA user fees in fiscal year 2013 are not dependent on enactment of an appropriations act.

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, ANDA applicants and DMF holders are 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. The FY 2013 fee amounts for ANDAs, PASs, and DMFs are cited in the appropriate sections of this guidance.

More information about these fees can also be found in:

- FR notice, Generic Drug User Fee—Backlog Fee Rate for Fiscal Year 2013
- FR notice, Generic Drug User Fee—Abbreviated New Drug Application, Prior Approval Supplement, and Drug Master File Fee Rates for Fiscal Year 2013

The FY 2013 facility fee rates were published in January following the close of the annual facilities self-identification reporting period. Under GDUFA, facilities, sites, and organizations must self-identify annually. FDA calculates annual facility fees for facilities manufacturing, or intending to manufacture, API of human generic drugs and/or finished dosage form (FDF) human generic drugs, based on the number of facilities that have self-identified. More information on these fees can be found in FR notice, Generic Drug User Fee—Facility Fee Rates for Fiscal Year 2013. Additional information on self-identification is available at http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm .

Although most facilities that are required to self-identify are also required to pay an annual facility user fee, certain types of generic facilities, sites and organizations are not 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; and repackagers.

The following responses have been developed for early implementation of the GDUFA program to assist generic drug manufacturers in meeting 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[3]

Fee Type	Who Incurs the Fee?	Payment Frequency	Year 1 and 2 Statutorily-Directed Revenue Target and Method of Calculating Individual Fee Amount	For Further Information	FY 2013 Fee	FY 2014 Fee
Backlog Fee	An applicant whose original ANDA was pending on Oct. 1, 2012 without a tentative approval	Once	$50 million (FY 2013 only) divided by the total number of original ANDAs pending on Oct. 1, 2012	See questions 1-7	$17,434	NA
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	~$18 million in FY 2014 (~$15 million in FY 2013) divided by current estimates of annual number of DMF applications.	See questions 8-19	$21,340	$31,460
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	~$73 million in FY 2014 (~$60 million in FY 2013) 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.	See questions 20-31	ANDA: $51,520 PAS: $25,760	ANDA: $63,860 PAS: $31,930
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	~$214 million in FY 2014 (~$174 million total in FY 2013) API: ~$43 million in FY 2014 (~$35 million in FY 2013) divided by number of API facilities and adjusted for the foreign facility differential. FDF: ~$171 million in 2014 (~$139 million in FY 2013) divided by number of FDF facilities and adjusted for the foreign facility differential. Facilities located outside of the United States and its territories and possessions will pay a higher fee reflecting the increased costs of inspections.	See questions 32-46	Domestic API: $26,458 Foreign API: $41,458 Domestic FDF: $175,389 Foreign FDF: $190,389	Domestic API: $34,515 Foreign API: $49,515 Domestic FDF: $220,152 Foreign FDF: $235,152

[A] See question 11 for information about a letter of authorization.

[B] See questions 26-28 for information about the (a)(3)(F) fee.

[3] Fees will be published in the Federal Register not more than 60 days before the start of each FY (generally in the first week of August each year). Note that the fee totals listed in the fourth column of this chart will rise in each subsequent year because of inflation adjustments.

1. BACKLOG FEE

Q1. Who was required to pay a backlog fee?

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

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

An original ANDA was considered to be pending and subject to the backlog fee, if, as of September 28, 2012, FDA had not *tentatively approved*, *approved*, or *refused to receive* the application. See FR notice, Opportunity to Withdraw Abbreviated New Drug Applications to Avoid Backlog Fee Obligations for additional details.

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

The backlog was 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 divided $50 million by the number of original ANDAs pending to arrive at the amount of the one-time backlog fee, due for each pending original ANDA.

The final backlog fee is $17,434. See FR notice, Generic Drug User Fee – Backlog Fee Rate for Fiscal Year 2013 for additional details. Payment was due no later than November 26, 2012.

Q4. If an original ANDA was submitted to FDA before October 1, 2012, but was not accepted for review, was it subject to a backlog fee?

Yes.

Q5. If FDA refuses to receive an application in the backlog, will the backlog fee be refunded?

No.

Q6. If FDA refuses to receive an application in the backlog, will the sponsor be required to pay an application fee upon resubmission in response to the identified issue(s)?

Yes. An ANDA fee will be due when the application is resubmitted.

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

Any person that owns an original ANDA that failed to pay the backlog fee was placed on a publicly available arrears list available at www.fda.gov/gdufa. 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. Which 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.

Q14. Do DMF holders incur a fee 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 FY 2013 (October 1, 2012-September 30, 2013) fee is $21,340. Additional information is available in FR notice, Generic Drug User Fee —Abbreviated New Drug Application, Prior Approval Supplement, and Drug Master File Fee Rates for Fiscal Year 2013.

The FY 2014 fee is $31,460. Additional information is available in FR notice, Generic Drug User Fee—Abbreviated New Drug Application, Prior Approval Supplement, Drug Master File, Final Dosage Form Facility and Active Pharmaceutical Ingredient Facility Fee Rates for Fiscal Year 2014.

One-time backlog fee revenue generated in FY 2013 only reduced first year fee amounts below subsequent annual fee levels. Annual fees are adjusted for inflation and the projected number of DMFs expected to be referenced for the first time in a given year based on experience. DMF fees are published in the FR not more than 60 days before the start of each FY (generally in the first week of August each year).

Q16. When are DMF fees due?

In FY 2013, DMF fees are *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. FY 2013 DMF fees were due on November 26, 2012 or, if they were incurred after that date, on the date that they were incurred.

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 articulated in the draft guidance *Initial Completeness Assessments for Type II Active Pharmaceutical Ingredient Drug Master Files Under the Generic Drug User Fee Amendments of 2012*. If the DMF passes the initial completeness assessment, FDA will identify the DMF on the Type II Drug Master Files – Available for Reference List.

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

See the draft guidance, *Initial Completeness Assessments for Type II Active Pharmaceutical Ingredient Drug Master Files Under the Generic Drug User Fee Amendments of 2012*.

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 referencing the DMF will be received unless the fee is paid and the DMF is deemed available for reference.

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 satisfy the user fee obligation. If the DMF fee is not paid within 20 calendar days after notification, the ANDA referencing the DMF will not be received.

3. ANDA AND PAS FEES

Q21. How much are the ANDA and PAS fees?

The FY 2013 fees for ANDAs and PASs are $51,520 and $25,760, respectively. These fees were published in FR notice Generic Drug User Fee —Abbreviated New Drug Application, Prior Approval Supplement, and Drug Master File Fee Rates for Fiscal Year 2013.

The FY 2014 fees for ANDAs and PASs are $63,860 and $31,930, respectively. Additional information is available in FR notice, Generic Drug User Fee—Abbreviated New Drug Application, Prior Approval Supplement, Drug Master File, Final Dosage Form Facility and Active Pharmaceutical Ingredient Facility Fee Rates for Fiscal Year 2014.

One-time backlog fee revenue generated in FY 2013 only reduced first year fee amounts below subsequent annual fee levels. Annual fees are adjusted for inflation and the projected number of ANDAs and PASs based on experience. Fees will be published in the FR not more than 60 days before the start of each FY (generally in the first week of August each year).

Q22. When will ANDA and PAS fees be due?

In FY 2013, fees *are incurred* at the time of submission for each ANDA and PAS submitted on or after October 1, 2012. FY 2013 fees were due on November 26, 2012 or, if incurred after that date, on the date that they were incurred. Additional information is available in FR notice, Generic Drug User Fee—Abbreviated New Drug Application, Prior Approval Supplement, and Drug Master File Fee Rates for Fiscal Year 2013.

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 another 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 does not submit payment within 20 calendar days of the due date, its application will be deemed incomplete on the date of submission. So long as FDA finds that none of the disqualifications outlined in 21 CFR 314.101(d) and (e) apply, the application 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.*

Q32. When should the application fee for a serially submitted ANDA be paid?

In some circumstances, ANDA applicants choose to serially submit complete ANDAs in anticipation of a patent being listed for a reference listed drug (RLD) that is protected by new chemical entity (NCE) exclusivity and has no other patents listed. This is done because the ANDA cannot be submitted until the final year of the five-year exclusivity period, and then only if the submitter is challenging the patent. A single payment for multiple submissions of the same ANDA is required. Applicants that choose to serially submit complete ANDAs in anticipation of a patent being listed for an RLD that is protected by NCE exclusivity and has no other patents listed should refrain from remitting their application fee until such time as the applicant is instructed by OGD that it has a valid application. Once a patent has been listed and an application can therefore be received for review by OGD, an applicant will have 20 days in which to pay its user fee.

4. FACILITY FEES

Q33. What are the finished dosage form (FDF) and active pharmaceutical ingredient (API) facility fees for U.S. and foreign manufacturers?

The FY 2013 facility fees are:

Domestic FDF facility:	$175,389
Foreign FDF facility:	$190,389
Domestic API facility:	$26,458
Foreign API facility:	$41,458

Additional information is available in FR notice, Generic Drug User Fee—Facility Fee Rates for Fiscal Year 2013.

The FY 2014 facility fees are:

Domestic FDF facility:	$220,152
Foreign FDF facility:	$235,152
Domestic API facility:	$34,515
Foreign API facility:	$49,515

One-time backlog fee revenue generated in FY 2013 only reduced first year fee amounts below subsequent annual fee levels. Annual fees are adjusted based on the number of facilities that self-identify, inflation, and other relevant factors. Fee amounts will be published in the FR not more than 60 days before the start of each FY (generally in the first week of August each year).

Q34. When will facility fees be due?

Facility fees for FY 2013 were due by March 4, 2013.

Fees for FYs 2014-2017 will be due on the first business day on or after October 1 of each FY.[4]

Q35. 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.

[4] The statute provides as an alternative that the due date might be the first business day after the enactment of an appropriations Act that provides for the collection and obligation of fees, whichever is later. Because a continuing resolution would be considered such an appropriations Act, FDA anticipates that this alternative would not apply in any circumstance in which the government is open at the beginning of the fiscal year.

Q36. If a facility is first identified, or intended to be identified, in a pending or approved generic drug submission after the due date for payment of the facility fee for a fiscal year, is it required to pay the fee for that year?

No. The obligation to pay the fee depends on the status of the facility on the due date (March 4, 2013, for fiscal year 2013, and the first business day on or after October 1 of each subsequent fiscal year). In most cases the critical question will be whether there is a generic drug submission pending or approved on the due date in which the facility is referenced. (Note also that, if there is such a pending submission, and it is intended on the due date that the facility will be added to that submission later, the fee is due.)

If the facility is first identified, or intended to be identified, in a pending or approved generic drug submission after the due date, its owner will be first obligated to pay a facility fee on the next due date. Note, however, that if a facility is identified, or intended to be identified, in a pending or approved generic drug submission on the due date, and that reference to the facility is later withdrawn, or the drug submission is later withdrawn, no refund will be due.

Q37. Does a facility that is not currently manufacturing an API or FDF have to pay the applicable facility fee(s)?

A facility listed in a generic drug submission – pending or approved – incurs annual facility fees as long as it is identified in a generic drug submission, even if the facility has not started commercial-scale production of the API or FDF covered by that submission, or if the facility has stopped, temporarily or permanently, the production of that API or FDF. See question 38 for a description of how a facility can ensure that is no longer identified in an ANDA.

The facility will cease to incur additional fees if it is no longer identified in any generic drug submission on the date that the fee is due. Any outstanding fee obligations will, however, remain due.

Q38. How can a facility be sure that it is no longer identified in an ANDA so that it no longer incurs new user fees?

An ANDA sponsor should remove from the ANDA any reference to a facility as a manufacturing facility when that facility no longer manufactures its API or FDF, and when it no longer seeks to retain the facility as an approved manufacturer of the API or FDF.

An ANDA sponsor can identify a facility that it does not own in its application only if the owner of that facility has provided the ANDA sponsor permission to refer to the facility. If the owner of the facility withdraws that permission, FDA will consider that facility to no longer be identified in the application as of the date when

FDA receives notice of that withdrawal. Note, however, that if the permission is withdrawn the facility will no longer be approved for manufacture of the FDF, or the API, covered by that application. Since a facility continues to incur facility fee(s) until FDA is notified of the facility's withdrawal of permission, the Agency encourages a person who wishes to withdraw permission for its facility to be identified in an ANDA to take the following steps:

1. Notify the ANDA sponsor and/or DMF holder in writing that it is withdrawing its permission to reference the facility in its ANDA and/or DMF.

2. Send copies of this letter to the Office of User Fee Collections and Budget Formulation at CDERCollections@fda.hhs.gov in addition to standard application submission methods for ANDAs and DMFs (via FDA electronic gateway or by mail 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 Pl., Rockville, MD 20855).

3. If you are a DMF holder, be sure to also update your DMF with this change.

Q39. 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).

Q40. If a facility manufactures both generic FDFs and APIs, does it incur more than one facility fee?

Yes. Under GDUFA, such a facility incurs annual FDF and annual API facility fees. Any such facility incurs both fees regardless of whether the API is offered for sale as an API or is offered for sale only after it is further processed so as to become an FDF within the meaning of the statute.

Q41. Is a facility that manufactures an API excipient mixture, or a mixture of two or more APIs, used to produce FDFs required to pay an annual FDF facility fee?

Yes, with one exception. Generally, manufacturers of API mixtures are required to pay the annual FDF facility fee. However, GDUFA provides one exception, for fee paying purposes only, to the definition of in-process mixtures as FDF. GDUFA defines an API mixture as an API when it is produced because the API is unstable and cannot be transported on its own. Examples include: an API mixed with an antioxidant for chemical stability when the API is prone to oxidative degradation; an API excipient mixture for physical stability to maintain its amorphous form.

Any facility producing an API and further processing it with an excipient or another API is also required to pay an annual API fee regardless of whether the API is offered for sale as an API or is offered for sale only after it is further processed so as to become an FDF within the meaning of the statute.

Q42. Are facilities that manufacture atypical APIs, such as sodium chloride, required to pay API facility fees?

Facilities that process raw materials used to manufacture human generic drugs are required to pay annual facility fees if they supply any ingredient that is listed in an ANDA and that ingredient appears in the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations as an active ingredient of the drug covered by that ANDA. (Although the ANDA may not yet be approved, the RLD for which the ANDA drug will be a generic copy will appear in the Orange Book.)

Q43. Who does FDA consider as a packager for purposes of GDUFA?

If you receive product prior to the point in the manufacturing process in which the drug is first packaged in a container/closure system specified in the "How Supplied" section of an approved ANDA and you package that product into such a container/closure system for the first time, you are a packager for purposes of GDUFA. Every ANDA specifies the forms in which the approved drug product may be distributed in the "How Supplied" section.

For example, if you receive bulk drugs and package them into the containers in which they are marketed, you are a packager.

You also are a packager if you receive product in a container/closure specified in the "How Supplied" section of an approved ANDA, and apply the FDA-approved prescription package labeling to that product for the first time.

Q44. Are packagers required to pay FDF facility fees?

Packagers are considered to be manufacturers, whether or not that packaging is done pursuant to a contract or by the applicant itself. Such facilities are required to pay annual FDF facility fees. Repackagers are not required to pay facility fees under GDUFA.

Q45. Are quality control (QC) testing sites required to pay annual facility fees?

No. They are only required to self-identify.

Q46. 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 and FY 2014, the cost differential is $15,000.

Q47. 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,[5] and if they are capable of being inspected by FDA during a single inspection. These are the same criteria used to evaluate whether separate FDA Facility Establishment Identifiers **(**FEIs) are necessary for multiple facilities (see draft guidance *Self-Identification of Generic Drug Facilities, Sites, and Organizations*).

If a firm believes that multiple FEIs have been assigned in error, the firm may request consolidation of the FEIs. Domestic firms should submit the request to the appropriate FDA district office. Contact information is available at http://www.fda.gov/ICECI/Inspections/IOM/ucm124008.htm. Foreign firms should contact FDAGDUFAFEIRequest@fda.hhs.gov.

Q48. 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.

Additionally, goal dates will not apply to applications that have already been received but list facilities for which facility fees are owed.

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

Q49. What is the process for paying GDUFA user fees?

The process is similar to payment procedures for PDUFA and other FDA user fees. The FDA website contains instructions for paying the fees.

[5] 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.

- Those responsible for payment of fees enter required information on 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 is 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.

The Generic Drug User Fee Cover Sheet and additional payment information is available on the GDUFA website (www.fda.gov/gdufa).

Q50. Is payment 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.

Q51. 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 assure FDA receives full payment.

Q52. 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.

A written overpayment or refund request should be submitted to the Office of User Fee Collections and Budget Formulation at CDERCollections@fda.hhs.gov.

Q53. 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.

Q54. Where should responses to FDA correspondence regarding user fee payment issues be directed?

Responses to FDA correspondence regarding user fee payment issues should be directed to the Office of User Fee Collections and Budget Formulation at CDERCollections@fda.hhs.gov.

In addition, responses should be submitted via standard application submission methods. These include submission via FDA electronic gateway or by mail to the ANDA archival file. Correspondence sent by mail should be directed to the following addresses, as appropriate:

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, MD 20855

Center for Biologics Evaluation and Research
Document Control Center
HFM-99, Suite 200N
1401 Rockville Pike
Rockville, MD 20852-1448

The Office of User Fee Collections and Budget Formulation provides assistance in resolving outstanding user fee payment questions from industry. Given fixed statutory deadlines, contacting the Office of Generic Drugs directly, without including the Office of User Fee Collections and Budget Formulation, may result in delays that increase the chances of incurring statutory penalties.

If an applicant has a user fee question unrelated to an issued user fee correspondence from FDA, please email askgdufa@fda.hhs.gov.

Q55. May one entity pay GDUFA fees on behalf of another entity?

Yes.

Q56. 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.

Q57. 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.

Q58. How does FDA communicate and update the arrears lists?

Both the backlog arrears list and the facility arrears list are available on the GDUFA website (www.fda.gov/gdufa) and are updated regularly.

Q59. What are the consequences of a sponsor's affiliation with an entity on the arrears list?

FDA cannot receive generic drug submissions from sponsors that are affiliated with an entity on the arrears list. If FDA discovers that a sponsor, or its affiliate, is on the arrears list, FDA will refuse to receive the generic drug submission until the sponsor or affiliate satisfies all of its outstanding user fee obligations. See question 8 for the definition of an affiliate.

Q60. Will FDA notify sponsors that their affiliate is on the arrears list before refusing to receive the submission?

No, FDA will not notify sponsors before refusing to receive a submission. Companies are in the best position to be aware of and monitor their business affiliates for compliance with GDUFA. Moreover, it is an applicant's responsibility to ensure that its user fee obligations, as well as those of its affiliates, are satisfied before submitting a new generic drug submission.

Q61. What should a sponsor do if FDA refuses to receive a submission because the sponsor, or an affiliate of the sponsor, is on the arrears list?

Before FDA can receive the submission, the sponsor must ensure that it and its affiliates are removed from the arrears list by satisfying the outstanding obligations. The sponsor is not required to pay the ANDA or PAS filing fee a second time; instead, the sponsor need only ensure that all *outstanding* user fee obligations are satisfied.

Q62. If a company believes that its appearance on the arrears list is in error, whom should it contact?

It should contact the Office of User Fee Collections and Budget Formulation at CDERCollections@fda.hhs.gov. Please include a concise rationale for why the facility should not be included on the arrears list.

Q63. 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.

Q64. How will a refuse to receive decision affect the submission receipt date?

FDA cannot receive a submission until all applicable requirements, including user fee obligations, are satisfied. If FDA refuses to receive a submission for failure to pay fees or because a sponsor or its affiliate is on the arrears list, FDA will set the new submission receipt date to the date that the final user fee obligation is satisfied, unless FDA finds that refusal to receive is appropriate for reasons not related to fees.

Q65. When did GDUFA fees begin?

On October 1, 2012.

Q66. 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.

Q67. 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 at www.fda.gov/gdufa.

Q68. Who is required to self-identify?

The following types of generic industry facilities, sites, and organizations are required to self-identify with FDA:

1. Facilities identified, or intended to be identified, in at least one generic drug submission that is pending or approved to produce a human generic FDF or API, or both.

2. A site or organization identified in a generic drug submission that is one or more of the following:

    - A site in which a bioanalytical study is conducted
    - A clinical research organization
    - A contract analytical testing site
    - A contract repackager site

See "Step-by-Step Instructions for Electronic Self-Identification of Facilities, Sites, and Organizations" for additional information including definitions.

Q69. Are all facilities, sites, and organizations listed above also required to pay facility fees?

No. Most facilities that are required to self-identify are also required to pay an annual facility user fee, but certain types of generic facilities, sites and organizations are not. 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; and repackagers. Please note that while repackagers are not required to pay user fees, packagers are, in most cases, FDF manufacturers and subject to facility fees.

Q70. 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 FDA during a single inspection. These are the same criteria used to evaluate whether separate FEIs are necessary for multiple facilities.

If a firm believes that multiple FEIs have been assigned in error, the firm may request consolidation of the FEIs. Domestic firms should submit the request to the appropriate FDA district office. Contact information is available at http://www.fda.gov/ICECI/Inspections/IOM/ucm124008.htm. Foreign firms should contact FDAGDUFAFEIRequest@fda.hhs.gov.

Q71. Who should self-identify as a repackager?

Sites that (1) receive labeled products in a container/closure system specified in the "How Supplied" section of the approved ANDA and place the products in another container/closure system and/or re-label them and (2) are identified in a pending or approved generic drug submission should self-identify as repackagers.

Q72. Are contract sterilizers required to self-identify?

Any contractor that performs part of the manufacturing process for a FDF or API is considered a manufacturer of that FDF or API. For example, if the contract sterilizer is working with the FDF, such as sterilizing the FDF, it is considered a manufacturer of the FDF and must self-identify accordingly and pay the applicable fees.

[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.

Q73. Are facilities that manufacture atypical APIs, such as sodium chloride, required to self-identify?

Facilities that process raw materials used to manufacture human generic drugs are required to self-identify if they supply any ingredient that is listed in an ANDA and that ingredient appears in the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations as an active ingredient of the drug covered by that ANDA. (Although the ANDA may not yet be approved, the RLD for which the ANDA drug will be a generic copy will appear in the Orange Book.)

Q74. Are facilities that manufacture intermediates, final intermediates or starting materials required to self-identify?

Provided the facility does not fall under one of the statutory definitions of an entity required to self-identify—e.g., an API manufacturer—a manufacturer of intermediates is not required to self-identify.

Q75. What is the self-identification reporting period for each fiscal year?

Fiscal Year	Self –Identification submissions received during the following dates
2013	Oct. 1, 2012 — Dec. 3, 2012
2014	May 1, 2013 – June 1, 2013
2015	May 1, 2014 – June 1, 2014
2016	May 1, 2015 – June 1, 2015
2017	May 1, 2016 – June 1, 2016

Q76. When must a facility first identified, or intended to be identified, in a pending or approved generic drug submission, first self-identify?

Please see the table below:

First Fiscal Year Required to Self-Identify	Facilities first identified, or intended to be identified, in a pending or approved generic drug submission
2013	Oct. 1, 2012—Dec. 3, 2012
2014	Dec. 19, 2012 – June 1, 2013
2015	June 2, 2013 – June 1, 2014
2016	June 2, 2014 – June 1, 2015
2017	June 2, 2015 – June 1, 2016

Please note that if a manufacturing facility is first identified, or intended to be identified, in a pending or approved generic drug submission on the annual due date for payment of facility fees (March 4, 2013, for fiscal year 2013, and the first

business day on or after October 1 of each subsequent fiscal year), it is required to pay the facility fee for that fiscal year even if it was not required to self-identify for that year.

Q77. What is the penalty for a facility's 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.

Additionally, goal dates will not apply to applications if any manufacturing facility listed on the application has failed to self-identify.

Q78. Will the failure of a site or organization referred to in an ANDA to self-identify result in a delay in review or approval of that ANDA?

Yes, in many cases. The failure of a site or organization to comply with the law and self-identify may raise significant concerns about that site. Such a failure is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because sites fail to comply with the law requiring self-identification.

C. REVIEW OF GENERIC DRUG SUBMISSIONS

Q79. Will priority be given to certain ANDAs under GDUFA? If so, what applications will be expedited?

FDA's Commitment Letter, available at www.fda.gov/gdufa, 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.

[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

Q80. 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 already owed 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.

Q81. Under what circumstances can all review activities including inspections be halted?

Only the discovery of a fatal flaw will stop review and inspections required for product approval.

Q82. What is a fatal flaw?

A fatal flaw is a serious and rare occurrence that requires an ANDA sponsor to manufacture a new demonstration batch of its product or to conduct a new bioequivalence or clinical study. If a fatal flaw is identified, all review activities including compliance inspections will be stopped.

Q83. If a fatal flaw has not been identified, can the Agency issue a complete response letter without inspections information?

Yes. However, a complete response letter issued without inspections information will not be counted towards meeting GDUFA performance goals unless a fatal flaw is identified.

FDA recognizes industry's preference for prompt communication of any deficiencies identified during the review process. The Agency may issue a complete response letter identifying deficiencies from all review divisions, if inspections have not yet been completed, so as not to delay a sponsor's remediation

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manufacture, use, or sale of the new drug for which the application is submitted (see 21 USC 505(j)(2)(A)(vii)(IV)).

of identified issues. In these cases, review of the application will not be counted toward meeting the GDUFA performance goal until inspections information is sent to sponsors.

Q84. When will easily correctable deficiencies be communicated to sponsors?

In accordance with 21 CFR 314.102(b):

FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application or an abbreviated application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The agency will also inform applicants promptly of its need for more data or information or for technical changes in the application or the abbreviated application needed to facilitate the agency's review. This early communication is intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. Such early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application or abbreviated application by agency managers as well as reviewing staff. Instead, major scientific issues will ordinarily be addressed in a complete response letter.

Q85. What is meant by *tier type* in the context of amendments to ANDAs and PASs?

The tier type determines how review goals will apply to amendments. The different tiers are explained in FDA's Commitment Letter on pages 10-11 as follows:

Tier 1 amendments include:

- All solicited first major and the first five minor amendments
- All unsolicited amendments indicated by sponsor and agreed by FDA to be a result of either delaying actions as determined by FDA's Office of Generic Drugs taking into account the facts and information supplied by the ANDA applicant or that otherwise would eventually be solicited.

Tier 2 amendments include:

- All unsolicited amendments not arising from delaying actions as determined by FDA's Office of Generic Drugs taking into account the facts and information supplied by the ANDA applicant excepting those amendments which only remove information for review.

Tier 3 amendments include:

- Any solicited major amendment subsequent to the first major amendment
- Any solicited minor amendment subsequent to the fifth minor amendment

The effect on the goals of the different tiers is explained in the Commitment Letter.

Q86. Is there a limit to the number of unsolicited amendments a firm may submit under GDUFA?

No. However, unsolicited amendments under GDUFA may extend the existing review goal.

Q87. Will ANDA goal dates be adjusted if a sponsor submits an amendment that requires an inspection or identifies a major application change?

Yes. An unsolicited amendment that requires an inspection, or makes a major application change, is considered a Tier 1 amendment that, per the GDUFA Commitment Letter, may extend the application's review by up to 10 months.

Q88. Will ANDA goal dates be adjusted if a sponsor submits a Tier 2 unsolicited amendment in the period between FDA's issuance of a complete response (CR) letter and the sponsor's submission of its CR response?

Yes. Review of any Tier 2 unsolicited amendments received in the period between FDA's issuance of a complete response letter and the sponsor's submission of its CR response will be deferred until the CR response is received. The goal will be adjusted to 12 months from the date of submission of the eligible CR response.

Q89. Will GDUFA goal dates apply if a manufacturing facility identified in an ANDA fails to pay a facility fee accrued during review?

No. Failure to pay any required fees will delay review.

Q90. Will GDUFA goal dates apply if a facility identified in an ANDA fails to self-identify during annual reporting period(s)?

ANDA review goal dates will not apply to applications listing any manufacturing facility that fails to self-identify.

Q91. 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 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.

Q92. What is the process for placement of a Type II API 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 the Type II Drug Master Files – Available for Reference List available at www.fda.gov/gdufa.

Q93. Does 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.

Q94. 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.

Q95. 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 Guidance for Industry, Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

Q96. 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.

D. INSPECTIONS AND COMPLIANCE

Q97. Has FDA committed in GDUFA to inspect foreign facilities as frequently as domestic ones by 2017 after adjustment for risk?

Yes. FDA has agreed to risk-adjusted parity on a biennial basis between foreign and domestic facilities by 2017. See FDA's Commitment Letter.

Q98. What does *risk-adjusted parity* mean?

Risk-adjusted parity means FDA will direct its limited resources to inspections that are most likely to achieve the greatest public health impact. The assessment model will include risk factors relating to the facility (e.g., the compliance history) and to the type of drugs manufactured at the facility. This may mean that some facilities are inspected more often than every two years and others are inspected less often. *Parity* means that a foreign facility will be inspected at an equal frequency as a domestic facility, plus or minus 20 percent, with comparable depth and rigor. See FDA's Commitment Letter.

Q99. Can FDA issue a complete response letter that does not include inspections information if a fatal flaw has not been identified?

Yes. However, a complete response letter issued without inspections information will not be counted towards meeting GDUFA performance goals unless a fatal flaw is identified. See question 82 for the definition of a fatal flaw.

FDA recognizes industry's preference for prompt communication of any deficiencies identified during the review process. The Agency may issue a complete response letter identifying deficiencies from all review divisions, if inspections have not yet been completed, so as not to delay a sponsor's remediation of identified issues. In these cases, review of the application will not be counted toward meeting the GDUFA performance goal until inspections information is sent to sponsors.

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
CR	complete response letter
DMF	drug master file
FDA	Food and Drug Administration
FDF	finished dosage form
FEI	facility establishment identifier
FR	*Federal Register*
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
RLD	reference listed drug