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**Generic Drug  
User Fee Amendments of  
2012:  
Questions and Answers  
Related to Self-Identification  
of Facilities, Review of  
Generic Drug Submissions,  
and Inspections and  
Compliance  
Guidance for Industry**

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

**July 2017  
Generic Drugs**

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# **Guidance for Industry<sup>1</sup>**

## **Generic Drug User Fee Amendments of 2012**

### **Questions and Answers**

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

#### **I. INTRODUCTION**

This guidance provides answers to questions arising from 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 by the generic drug industry. The first draft of this document was issued pursuant to 21 CFR 10.115 in August 2012 and a revised draft was issued in September 2013.<sup>2</sup>

FDA is issuing the final guidance as two separate guidances. This guidance includes questions and answers related to self-identification, review of generic drug submissions, and inspections and compliance. This final guidance clarifies some of the questions and answers included in the previous versions based on FDA's experience in implementing GDUFA. Questions and answers related to GDUFA's user fee provisions that appeared in draft versions of this guidance appear in updated form in Guidance for Industry: Generic Drug User Fee Amendments of 2012: Questions and Answers Related to User Fee Assessments (Nov. 21, 2016).

The questions and answers are grouped below in the following categories:

- 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 guidances and Federal Register notices are available

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<sup>1</sup> This guidance has been prepared by the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research, and the Office of Regulatory Affairs at the Food and Drug Administration (FDA).

<sup>2</sup> See Federal Register notices at 77 FR 51814 (August 27, 2012) and 78 FR 55261 (September 10, 2013).

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on <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm>. Where applicable, this guidance will reference information in these communications.

The Food and Drug Administration's (FDA's or the Agency's) guidance documents, including this guidance, generally 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. GDUFA is designed to speed the delivery of safe and effective generic drugs to the public and improve the review process for abbreviated new drug applications. 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 also enhances 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 (APIs). Further, the requirements in GDUFA ensure that foreign and domestic industry participants in the U.S. generic drug system are held to consistent, high-quality standards 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 and biologic license applications 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.

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Under GDUFA, FDA agreed to other program enhancements and performance goals. These include a commitment to provide timely and complete information to applicants by issuing complete response letters to all ANDAs. These letters reflect full division-level reviews of any deficiencies noted by relevant review disciplines. FDA 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 expeditiously. Additional efficiency enhancements and goals were phased in over the life of the program (see details in the Generic Drug User Fee Act Program Performance Goals and Procedures (Commitment Letter)).<sup>3</sup>

Under GDUFA, facilities, sites, and organizations must electronically self-identify with FDA and update that information 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.

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 required only to self-identify. 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.<sup>4</sup>

The following responses have been developed for implementation of the GDUFA program to assist generic drug manufacturers in meeting the requirements of GDUFA.

### **III. QUESTIONS AND ANSWERS**

#### **A. SELF-IDENTIFICATION OF FACILITIES, SITES, AND ORGANIZATIONS**

##### **Q1. 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:

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<sup>3</sup> The Commitment Letter may be found at <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf>.

<sup>4</sup> See Guidance for Industry: Self-Identification of Generic Drug Facilities, Sites, and Organizations (Sept. 2016) for further information on the self-identification process.

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- 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.

Please note that only facilities, sites or organizations identified or intended to be identified in a generic drug submission are required to self-identify.

#### **Q2. 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).

#### **Q3. Are all facilities, sites, and organizations listed above also required to pay facility fees?**

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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 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.

### **Q4. Who is required to pay facility fees?**

A facility fee is incurred if a facility is identified in a generic drug submission that is pending or approved to produce an API or FDF and the facility is a business or other entity, under one management, either direct or indirect, and at one geographic location or address engaged in manufacturing or processing an API or FDF

### **Q5. What is the penalty for failure of a facility to pay a facility fee or self-identify?**

All FDFs or APIs manufactured in a facility for which fees have not been paid or self-identifying information had not been submitted 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 or self-identify are subject to being denied entry into the United States.

Additionally, there are several consequences for failure to pay a facility fee:

- (1) no new generic drug submission referencing the facility will be received until the fee is paid.
- (2) 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.
- (3) FDA will notify the ANDA applicant of the facility's failure to satisfy its user fee obligations.

Goal dates also may 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.

### **Q6. 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,



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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:

- (1) the activities in them are closely related to the same business enterprise;
- (2) they are under the supervision of the same local management;<sup>5</sup> and
- (3) they are capable of being inspected by FDA during a single inspection

These are the same criteria used to evaluate whether separate facility establishment identifiers (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/downloads/ICECI/Inspections/IOM/UCM123522.pdf>. Foreign firms should contact [FDAGDUFAFEIRequest@fda.hhs.gov](mailto:FDAGDUFAFEIRequest@fda.hhs.gov). Please note that FDA will apply the geographic and organizational criteria outlined above to address requests to consolidate or separate facilities' FEI numbers. Such requests should not be used solely to avoid fees or address a facility's compliance issues.

#### **Q7. Whom does FDA consider as a packager for purposes of self-identification?**

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.

#### **Q8. 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.

#### **Q9. Are contract sterilizers required to self-identify?**

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<sup>5</sup> The Federal Food, Drug, and Cosmetic 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. 21 USC 379j-41(5)(C).

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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.

**Q10. Are facilities that manufacture atypical APIs required to self-identify?**

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

**Q11. 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.

**Q12. 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

**Q13. 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

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2017	June 2, 2015 – June 1, 2016
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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.

**Q14. 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.

### B. REVIEW OF GENERIC DRUG SUBMISSIONS

**Q15. What is a generic drug submission?**

The phrase *generic drug submission* refers to an ANDA, an amendment to an ANDA, or a prior approval supplement (PAS) to an ANDA.

**Q16. 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*.

**Q17. 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

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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.

**Q18. How will a refuse to receive decision for failure to pay facility fees 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.

**Q19. 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](http://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<sup>6</sup> applications that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted.

Further information on prioritization of ANDAs under GDUFA can be found in CDER's Manual of Policies and Procedures (MAPP 5240.3) Prioritization of the Review of Original ANDAs, Amendments, Supplements. <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf>

**Q20. How does GDUFA affect FDA's refuse to receive policy?**

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<sup>6</sup> 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)).

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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.

#### **Q21. 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 through early communication such as Information Requests (IRs) of the 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.

#### **Q22. 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

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- 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 (a delaying amendment).

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.

**Q23. 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 dates.

**Q24. Will ANDA goal dates be adjusted if a sponsor submits an amendment that requires an inspection or identifies a major application change?**

Yes. As stated in the Commitment Letter, any Tier 1 amendment that requires an inspection will have a goal date of 10 months from the date of its submission. Further, to ensure that the Agency has enough time to review any major application changes, FDA has the discretion to change the classification of an amendment based on the type, quantity, and complexity of data submitted. For example, a complete response (CR) letter will advise the applicant whether the CR amendment (or CR response) will be classified as a major or minor amendment. However, if the applicant submits a CR amendment that contains additional information or data beyond what was identified in the CR letter as necessary to correct the deficiency or deficiencies, FDA may change the classification of the amendment from a Tier 1 solicited major or minor amendment to a Tier 2 unsolicited amendment.

**Q25. Will ANDA goal dates be adjusted if a sponsor submits a Tier 2 unsolicited amendment in the period between FDA's issuance of a 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 CR 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.

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**Q26. 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 may delay review.

**Q27. 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 may not apply to applications listing any manufacturing facility that fails to self-identify.

**Q28. 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](http://www.fda.gov/gdufa).

**Q29. What are the consequences 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.

**Q30. What is the process for requesting a teleconference to clarify deficiencies and answer questions following FDA's issuance of a CR letter?**

An applicant may request a 30-minute teleconference within ten business days after FDA issues a first-cycle review CR 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 CR letter. Priority for such teleconferences will be given to expedited and first major amendment applications and other applications as detailed in the Commitment Letter.

**Q31. Will FDA continue to accept applications in paper format?**

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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 as of May 5, 2017, which is 24 months after issuance of final Guidance for Industry, Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.<sup>7</sup> FDA will refuse-to-accept an ANDA that is not submitted in electronic format as specified in the final guidance submitted on or after May 5, 2017.

**Q32. 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.

### **C. INSPECTIONS AND COMPLIANCE**

**Q33. 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 for inspections of foreign and domestic facilities by 2017. See FDA's Commitment Letter.

**Q34. What does *risk-adjusted parity* mean?**

*Risk-adjusted parity* means FDA will direct its limited resources to surveillance 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 others. *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.

**Q35. Under what circumstances can all review activities including inspections be halted?**

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

**Q36. What is a fatal flaw?**

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<sup>7</sup> See *Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (May 2015, Rev. 3) <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf>.



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A fatal flaw is any deficiency that renders an ANDA as a whole unreviewable, including but not limited to an occurrence that requires an ANDA applicant to manufacture a new demonstration batch of its product; to conduct a new bioequivalence (BE) study, including BE studies with clinical endpoints; or significant flaws in the design of a drug product such that the proposed product will not be able to meet all conditions of use of the reference listed drug.

**Q39. If a fatal flaw has not been identified, can the Agency issue a CR letter without inspections information?**

Yes. However, as a rule, a CR 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 CR 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.

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**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
BE	bioequivalence
CBE	changes being effected
CDER	Center for Drug Evaluation and Research
CR	complete response letter
DMF	drug master file
FDA	Food and Drug Administration
FDF	finished dosage form
FEI	facility establishment identifier
GDUFA	Generic Drug User Fee Amendments of 2012
ID	identification
PAS	prior approval supplement
PDUFA	Prescription Drug User Fee Act
PEPFAR	President's Emergency Plan for AIDS Relief
PET	positron emission tomography
Q&A	questions and answers