Guidance for Industry

Self-Identification of Generic Drug Facilities, Sites, and Organizations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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

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

August 2012
Generic Drugs

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http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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Guidance for Industry[1] Self-Identification of Generic Drug Facilities, Sites, and Organizations

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 is intended to assist human generic drug facilities, sites, and organizations by describing how the Food and Drug Administration (FDA or Agency) will implement an identification requirement contained in the Generic Drug User Fee Amendments of 2012 (Public Law 112-144, Title III), commonly referred to as GDUFA.

As required by GDUFA, FDA will issue a self-identification requirement notice in the *Federal Register* in the coming weeks explaining that human generic drug facilities, sites, and organizations are required to submit identification information electronically to FDA within 60 days. The notice will also list the self-identification information that must be submitted.

FDA is issuing this guidance to help human generic drug facilities, sites, and organizations prepare to meet the self-identification requirement. Topics discussed in this guidance include:

- which types of generic facilities, sites, and organizations are required to self-identify;
- what information is requested;
- what technical standards are to be used for electronically submitting the requested information; and
- the penalty for failing to self-identify.

The guidance also explains generally which types of generic facilities, sites, and organizations will be required to pay user fees.

FDA'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

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

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 reduce costs to industry. GDUFA enables FDA to assess user fees to support critical and measurable enhancements to FDA's generic drugs program. GDUFA will also significantly improve global supply chain transparency by requiring owners of facilities producing generic drug products, active pharmaceutical ingredients (API), and certain other sites and organizations that support the manufacture or approval of these products to electronically self-identify with FDA and update that information annually.

Self-identification is required for two purposes. First, it is necessary to determine the universe of facilities required to pay user fees. Second, self-identification is a central component of an effort to promote global supply chain transparency. The information provided through self-identification will enable quick, accurate, and reliable surveillance of generic drugs and facilitate inspections and compliance.

Most facilities that self-identify will be required to pay an annual facility user fee. These include facilities manufacturing, or intending to manufacture, API of human generic drugs and/or finished dosage form (FDF) human generic drugs. Other sites and organizations must self-identify, but will not be required to pay the annual facility user fee. These include 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. Once the self-identification process has been completed, FDA will determine facility fees and publish the amounts in the *Federal Register*.

FDA is establishing a new system for the electronic self-identification of generic industry facilities, sites, and organizations. Therefore, entities that are required to register and list (under section 510 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act, and those being required to self-identify under GDUFA, will submit information separately to the respective systems. Each system will populate its own database to meet unique requirements and deadlines. The new GDUFA system will use the same platform and technical standards already familiar to manufacturers required to register and list.

III. GDUFA SELF-IDENTIFICATION REQUIREMENTS

The following discussion explains who is required to self-identify, what information is required for submission, and what the process is for submitting self-identification information.

A. 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[2] that manufacture, or intend to manufacture, human generic drug APIs or FDFs, or both.[3]

2. Sites and organizations that package the FDF of a human generic drug into the primary container/closure system and label the primary container/closure system.[4]

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

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

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

[3] For purposes of self-identification and payment of fees, GDUFA defines API and FDF manufacturers differently from the way these 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 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).

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

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

B. What Information Is Required for Submission?

To meet the self-identification requirement in GDUFA, facilities, sites, and organizations will have to submit self-identification information that may take time to obtain. For this reason, we encourage any facility, site, or organization that does not have the following information readily available to begin as soon as possible the process of obtaining that information. This will help ensure timely submission of self-identification information to FDA.

1. D-U-N-S Numbers

FDA will require Data Universal Numbering System (D-U-N-S) numbers for both the facility or site and the registrant owner of the facility or site if the facility or site is in a different location than the registrant owner location. A D-U-N-S number is required to uniquely identify the registrant (the owner or operator) and each physical location of the business's facility or site (e.g., branches, divisions, and headquarters).

A D-U-N-S number is a unique nine-digit sequence provided by Dun & Bradstreet. The D-U-N-S number is specific for each site. Each distinct physical location of an entity (e.g., branch, division, and headquarter) would be assigned a different D-U-N-S number.

The site-specific D-U-N-S number is a widely recognized business identification tool and serves as a useful resource for FDA in identifying and verifying certain business information submitted by a user.

If no D-U-N-S number has been assigned, a business entity may obtain one at no cost directly from Dun & Bradstreet. A new number may be obtained, or an existing number verified, by phone or online. Existing facilities D-U-N-S numbers may also be verified on FDA's current registration site for drug establishments.

> *Note*: It takes Dun & Bradstreet approximately 30 business days to process a new D-U-N-S number and communicate it via email. A business entity may receive a D-U-N-S number in approximately 10 business days for an expedited service fee. Please note that a business entity may not request or apply for a new D-U-N-S number on behalf of another business entity due to the verification procedures used by Dun & Bradstreet.

More information is available at the Dun & Bradstreet web page. See also the step-by-step instructions for obtaining a D-U-N-S number for businesses based either in the United States or abroad.

2. Facility Establishment Identifier

Facilities must also submit a Facility Establishment Identifier (FEI), a unique identifier designated by FDA to assign, monitor, and track inspections of regulated firms. FDA will assign only one FEI number to separate buildings if they are in close proximity and if the activities conducted in each building are closely related to the same business enterprise, are under the supervision of the same local management,[5] and are capable of being inspected by FDA during a single inspection.

A business entity that has previously obtained an FEI number may verify its FEI number on FDA's registration site for drug establishments.

Business entities that have not previously registered with FDA can obtain an FEI number by sending an email request to FDAGDUFAFEIRequest@fda.hhs.gov. Please type "GDUFA FEI Request" in the subject line and include the following information in the body of the email:

Firm Name
Facility Address including City, Province, Country, and Mail Code
Size of Firm
Type of Operation (Manufacturer, Lab, etc.)
Type of Industry: Drugs

FDA will begin assigning FEI numbers associated with GDUFA self-identification in August. Requests are typically processed within 10 to 15 business days.

3. Additional Information

FDA will request the name and contact information for the registrant owner and facility information, including name, type of business operation, and contact information. Submitters will also be asked to indicate whether they manufacture drugs that are not generic drugs.

C. What Is the Process for Submitting Self-Identification Information?

1. Creating the Self-Identification Submission

The new self-identification process will be familiar to many business entities who have previously submitted information to FDA electronically. Submitters should enter the required information into the eSubmitter tool, a free stand-alone application available on FDA's website at http://www.fda.gov/ForIndustry/FDAeSubmitter/ucm108165.htm, or other commercially available applications. The information entered will automatically populate a self-identification file generated by the software.[6] Submitters can verify the information and check the file for

[5] GDUFA 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.

[6] Self-identification files will be formatted in the same electronic messaging standard used for drug registration and listing information and the content of labeling for abbreviated new drug applications (ANDAs), known as Structured

errors using validation software. Once finalized, the file should be transmitted to FDA through the Electronic Submissions Gateway, FDA's electronic information portal. An electronic receipt will be automatically generated and sent to the submitter following successful submission of the self-identification SPL file.

Step-by-step instructions for electronically creating, validating, and submitting self-identification information will be available at www.fda.gov/gdufa concurrent with publication of the self-identification requirement notice in the *Federal Register*.

2. Establishing an FDA Electronic Submissions Gateway Account

Business entities new to FDA's electronic submission process should prepare for self-identification by creating an FDA Electronic Submissions Gateway (ESG) account to enable them to transmit information securely. The ESG authenticates and validates electronic submissions and signatures (see next section) and routes documents to the appropriate FDA center. Business entities can establish an ESG WebTrader account or an AS2 Gateway-to-Gateway account to transmit self-identification information. The prerequisites for establishing and testing an ESG account are highlighted below. More information on FDA ESG procedures and process is available on the Electronic Submission Gateway website (hyperlink to http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm).

a. Digital Signature Validation

Business entities must enter into a *non-repudiation agreement* with FDA to enable FDA to accept electronically signed submissions as the legally binding equivalent of traditional handwritten signatures (in compliance with 21 Code of Federal Regulations (CFR) Part 11.100). To do this, business entities should submit a *letter of non-repudiation* to FDA before registering as a transaction partner for the ESG.

The letter of non-repudiation must be submitted in paper form (preferably on official letterhead) and signed with a traditional handwritten signature. The letter must be sent to:

Office of Regional Operations, Room 3007
12420 Parklawn Drive
Rockville, MD 20857

Send a copy to:

Center for Biologics Evaluation and Research
Attention: Michael B. Fauntleroy

Product Labeling (SPL). SPL allows information to be exchanged, searched, and combined with other data sources in a manner that supports health information technology initiatives to improve patient care.

Office of the Director, HFM - 99, Room 200N
1401 Rockville Pike
Rockville, MD 20852

Additional information including sample letters is available at http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm113964.htm.

b. Security Encryption Certificate

Once a business entity has obtained a non-repudiation agreement with FDA, as discussed above, it should obtain a *security encryption certificate*. This certificate provides assurance to entities that only FDA will be able to read the message and the file being submitted. The certificate also provides assurance that the message cannot be changed or deleted without the entity's knowledge. Finally, it provides assurance to both the entity and FDA that the message has been sent and received by each party.

Additional information on encryption certificates is available at http://www.accessdata.fda.gov/esg/userguide/webhelp/Digital_Certificates.htm.

D. What Is the Penalty for Failing to Self-Identify?

Under GDUFA, if a facility fails to self-identify, all FDF or API products manufactured at the facility and all FDFs containing APIs manufactured at the facility will be deemed misbranded. It is a violation of federal law to ship misbranded 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 the misbranded products. Products that are deemed misbranded because of failure of the facility to self-identify are subject to being denied entry into the United States.