DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUL 12 2013

2013 JUL 16 A 11:45

Priya Jambhekar
Chrai Associates, Inc.
16 Bodine Drive
Cranbury, NJ 08512

Re: Docket No. FDA-2013-P-0204

Dear Ms. Jambhekar:

This responds to the citizen petition (Petition) submitted on behalf of your client, Square Pharmaceuticals Ltd. (Square), received on February 14, 2013. In the Petition, you request that the Food and Drug Administration (FDA or Agency) issue, amend, or clarify the regulation and requirement for the payment of finished dosage form (FDF) facility fees under the Generic Drug User Fee Amendments of 2012 (GDUFA) for a generic finished product manufacturing facility of a foreign-based generic drug manufacturing company. In addition, you request that Square not be required to pay recurring annual FDF facility fees until a decision is made on the Petition.

We have carefully considered the Petition. For the reasons described in detail below, the Petition is denied.

I. BACKGROUND

A. The Generic Drug User Fee Act (GDUFA)

1. GDUFA Background

On July 9, 2012, GDUFA was signed into law under Title III of the Food and Drug Safety and Innovation Act (FDASIA) (Public Law 112-144).[1] GDUFA, as further amended by the FDA User Fee Correction Act of 2012 (Public Law 112-193),[2] amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act).

Designed to speed access to safe and effective generic drugs to the public and reduce costs to the generic drug industry, GDUFA requires the generic drug industry to pay user fees to cover the costs of increasing resources available for reviewing generic drug applications and inspecting facilities. These fees will enable the Agency to reduce the current backlog of pending generic

[1] On October 5, 2012, the FDA User Fee Corrections Act of 2012 was signed into law. 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.
[2] The term *GDUFA* in this response refers to the Generic Drug User Fee Amendments of 2012, signed into law under Title III of the Food and Drug Safety and Innovation Act (Pub. L. 112-144) and then further amended by the FDA User Fee Correction Act of 2012 (Pub. L. 112-193).

drug applications, cut the average time required to review generic drug applications for safety, and increase risk-based inspections. GDUFA will allow for greater predictability and timeliness to the review of generic drug applications, enhance global supply chain safety by requiring that generic drug facilities and sites around the world self-identify, and ensure that foreign and domestic industry participants in the US generic drug system are held to consistent, high standards.

GDUFA is based on an agreement negotiated by FDA and representatives of the generic drug industry. The law 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, which held hearings on the proposed legislation that included testimony from FDA, the generic drug industry, and other interested parties.

2. GDUFA Fees

GDUFA authorizes FDA to assess and collect user fees for certain applications and supplements for human generic drug products (abbreviated new drugs (ANDAs), prior approval supplements (PASs) to ANDAs, and drug master files (DMFs)), on applications in the backlog as of October 1, 2012, on FDF and active pharmaceutical ingredient (API) facilities, and on type II API DMFs to be made available for reference. GDUFA directs FDA to establish each year the Generic Drug User Fee rates for the upcoming year.

Section 744B(a)(4)(A) of the FD&C Act states:

> *(A) In General. – Facilities identified, or intended to be identified, in at least one generic drug submission that is pending or approved to produce a finished dosage form of a human generic drug or an active pharmaceutical ingredient contained in a human generic drug shall be subject to fees as follows:*
>
> *(i) Generic Drug Facility. – Each person that owns a facility which is identified or intended to be identified in at least one generic drug submission that is pending or approved to produce one or more finished dosage forms of a human generic drug shall be assessed an annual fee for each such facility...*

The due dates for facility fees for fiscal year (FY) 2013 are set by the FDA User Fee Correction Act of 2012 as follows:

> *the fee authorized under section 744B(a)(4) of such Act for fiscal year 2013 shall be due not later than 45 days after the publication of the notice under section 744B(a)(4)(C)(i) of such Act.*

Section 744B(a)(4)(D)(ii) of the FD&C Act provides information on fee due dates for subsequent years and states:

> *(ii) Fiscal years 2014 through 2017. – For each of fiscal years 2014 through 2017, the fees under subparagraph (A) for such fiscal year shall be due on the later of –*
>
> *(I) the first business day on or after October 1 of each such year; or*

> *(II) the first business day after the enactment of an appropriations Act providing for the collection and obligation of fees for such year under this section for such year.*

In a Federal Register notice dated October 25, 2012, FDA announced the rate for ANDA, PAS, and DMF fees under GDUFA for FY 2013 (77 FR 65198). In a Federal Register noticed dated Jan. 17, 2013, FDA announced the rate for generic drug API and FDF facility user fees for FY 2013 (78 FR 3900).[3,4]

3. FDF Facility Fee

Under GDUFA, the annual FDF facility fee is owed by each 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 FDFs of the human generic drug as of the due date for that fiscal year. For FY 2013, these fees were due no later than 45 days after the publication of the Federal Register notice announcing FDF facility user fees for FY 2013 (the notice was published on January 17, 2013 (78 FR 3900)). The FY 2013 FDF facility fees were determined to be $175,389 for domestic FDF facilities and $190,389 for foreign FDF facilities.[5]

Failure to pay a facility fee has several consequences. First, 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 (for FY 2013, that due date was March 4, 2013). Further, FDA will notify the ANDA applicant of the facility's failure to satisfy its user fee obligations. 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.

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[3] Under Sec. 744(A)(2) of the FD&C Act, the term "active pharmaceutical ingredient" means—
(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] Under Sec. 744(A)(6) of the FD&C Act, the term "finished dosage form" means—
(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 with another component of a drug product for purposes of production of a drug product described in subparagraph (A) or (B).

[5] See 78 FR 3901 (Jan. 17, 2013).

B. Prescription Drug User Fee Act (PDUFA)

The Prescription Drug User Fee Act (PDUFA) was enacted in 1992 and renewed in 1997 (PDUFA II), 2002 (PDUFA III), 2007 (PDUFA IV), and 2012 (PDUFA V). It authorizes FDA to collect fees from companies that produce certain human drug and biological products. Since the passage of PDUFA, user fees have played an important role in expediting the drug approval process.

II. DISCUSSION

You list the following requests in Section A of your Petition:

(1) The petition requests the Commissioner to issue, amend, or revoke a regulation, the exact wording of the existing regulation (if any) and the proposed regulation or amendment requested.

(2) The petition requests the Commissioner to issue, amend, or revoke an order, a copy of the exact wording of the citation to the existing order (if any) and the exact wording requested for the proposed order.

(3) The petition requests the Commissioner to take or refrain from taking any other form of administrative action, the specific action or relief requested.

(4) The petition request the Commissioner to issue clarification and revision of the following language included in SEC. 102., Part 8, Section 744G(4)(i) of GDUFA, from

Generic drug facility – Each person that owns a facility which is identified or intended to be identified [in] at least one generic drug submission that is pending or approved to produc[e] one or more finished dosage forms shall be assessed an annual fee under subsection (d) for each such facility

To

Generic drug facility – Each person that owns a facility which is identified or intended to be identified at least one generic drug submission that is pending or approved to product one or more finished dosage forms shall be assessed ONE TIME ~~an annual~~ FDF facility fee until the approval of the first ANDA manufactured at the subject FDF facility under the subsection (d) for each such facility. This fee could be charged upon issuance of the approval letter or as a condition of approval of the ANDA. The facility will not be subjected to any other fees under GDUFA until the product manufactured at that facility is commercialized.

(5) The petition also requests commissioner to make a decision that our client should not be required to pay recurring annual FDF fees until a decision is reached on this petition.

(See Petition at 2-3).

Based on the Petition, we interpret these requests as essentially requesting that FDA (1) change language in the GDUFA section of the enacted FDASIA legislation to require collection of manufacturing facility fees only one time, at the approval of the first ANDA manufactured at the subject facility (and to implement all regulatory and administrative changes necessary to make these changes) and (2) waive FDF facility fees for Square until FDA responds to the Petition. For the reasons described below, we deny these requests.

A. GDUFA FDF Facility Fee Language Amendment Request

The Petition requests that FDA issue clarification and revision of language included in "SEC. 102., Part 8, Section 744G(4)(A)(i) of GDUFA" (Petition at 2). As part of your argument that this section of GDUFA should be amended, you state that unlike PDUFA, GDUFA provides no exemptions for small businesses or first-time sponsors of ANDAs who do not have drug products on the US market (Petition at 4). You state that FDF manufacturing fees should be collected only upon commercialization of the first ANDA drug product from that site, as you interpret fees are applied under PDUFA (Petition at 5). Further, you argue that current GDUFA fees are burdensome for small-size companies and/or foreign manufacturers and for Square in particular (Petition at 5). You contend that any costs FDA may require for "pre-approval inspections etc." could be covered by a separate fee, and that a one-time FDF facility fee would adequately cover any Agency expenses that may be required for regulatory site-related activities to support approval of the product (Petition at 5-6). As part of your request to amend GDUFA, your list of requests in Section A seems to imply a general request that FDA also implement all regulatory and administrative changes necessary to change the GDUFA FDF facility fee requirement.

The GDUFA language you cite as "Section 102., Part 8, Section 744G(4)(A)(i) of GDUFA" (Petition at 2) is now section 744(B)(a)(4)(A)(i) of the FD&C Act (21 U.S.C. 379j-42(a)(4)(A)(i)). Once GDUFA, as part of FDASIA legislation, was enacted, it amended the United States Code and the FD&C Act to add the FDF facility fee language to US federal law. FDA is given certain regulatory authorities to implement GDUFA. However, changes to statutory language can only be made through the federal legislative process. To amend the statutory requirements, Congress must pass new legislation amending the FDF facility fee language, and the President must sign the legislation. FDA does not have the authority to make changes to the statutory language.[6] We therefore deny your requests.

We note, however, that there were opportunities during the development of GDUFA to consider different requirements. As discussed above, GDUFA is based on an agreement negotiated by FDA and representatives of the generic drug industry. GDUFA negotiation sessions began on February 28, 2011, and included a total of 16 negotiation meetings.[7] Information regarding the industry members who participated in these negotiations is available on our website.[8] These negotiations resulted in recommendations in the form of a goals letter and were presented at a

[6] For further information on the legislative process, see the Library of Congress Website How Our Laws Are Made, at http://thomas.loc.gov/home/lawsmade.toc.html.

[7] GDUFA negotiation session minutes can be found at http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm256662.htm.

[8] Id.

public meeting and made available to the public for written comments in the Federal Register.[9] Agreed-upon recommendations were sent to Congress, and Congress also held hearings on GDUFA that included testimony from FDA, the generic drug industry, and other interested parties.

GDUFA also reflects input from regular public meetings and consideration of comments from a public docket. There were a total of five public meetings that were announced to the public in advance that provided opportunity for the public to comment on GDUFA in person or through written comment to the public docket.[10] A list of the attendees at these meetings is available on our website.[11] The GDUFA public docket (Docket No. FDA-2010-N-0381) received 47 comments.[12]

The possibility of financial hardship for small to mid-size generic drug companies incurred by a requirement to pay GDUFA fees was in fact a concern that was discussed by the pharmaceutical industry and FDA during GDUFA negotiations meetings. FDA and the parties involved agreed that fee waivers and exemptions would not be included. This decision was reached after considering the relatively low amount of expected individual fees compared to the benefits to small and mid-size companies that will result from more efficient review times and inspections.

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 (and thus increasing the fees for others), the cost of a fee waiver or reduction provision would have added to the administrative cost of the GDUFA program. Congress, by enacting the statute that it did, agreed with the decision not to have a fee waiver or reduction mechanism in GDUFA.[13]

Annual facility fees under GDUFA are considerably lower than comparable PDUFA fees. GDUFA is designed to build on the success of PDUFA, which over the past 20 years has ensured a more predictable, consistent, and streamlined premarket program for industry and helped speed access to new, safe, and effective prescription drugs for the public. Although modeled on PDUFA, GDUFA reflects the unique needs and challenges of generic drug regulation.

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[9] See docket no. FDA-2010-N-0381, available at http://www.regulations.gov/#!docketDetail;D=FDA-2010-N-0381.

[10] More information on GDUFA public meetings can be found at http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm256661.htm.

[11] September 17, 2010 Generic Drug User Fee Public Meeting Attendee List, http://www.fda.gov/downloads/Drugs/NewsEvents/UCM225753.pdf; May 10, 2011 Generic Drug User Fee Meeting Summary, http://www.fda.gov/downloads/Drugs/NewsEvents/UCM255187.pdf.

[12] See docket no. FDA-2010-N-0381, available at http://www.regulations.gov/#!docketDetail;D=FDA-2010-N-0381.

[13] The impact of GDUFA fees on small businesses was addressed in Congressional hearings on the user fee bills. See, e.g,, the testimony of Janet Woodcock, M.D., at the Senate hearing: "The program [GDUFA] is expected to provide significant value to small companies and first-time entrants to the generic market. In particular, these companies will benefit significantly from the certainty associated with performance review metrics that offer the potential to dramatically reduce the time needed to commercialize a generic drug, when compared to pre-GDUFA review times." Hearing on FDA User Fee Agreements: Strengthening FDA and the Medical Products Industry for the Benefit of Patients before the Senate Committee on Health, Education, Labor, and Pensions (March 29, 2012).

B. FDF Facility Fee Waiver Request

In the Petition, you request that FDA waive FDF facility fees for Square until a decision is reached on the Petition (Petition at 3).

GDUFA does not include a fee waiver or reduction provision for small and/or foreign businesses. GDUFA also does not provide a mechanism for postponing fee payment. In addition, the submission of a citizen petition does not affect the fee obligations under GDUFA. For these reasons, we find that you have not provided any basis for this request and it is therefore denied.

III. CONCLUSION

For the reasons described in this response, your Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research