M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 1, 2015

FROM: Martin Shimer
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Office of Generic Drug Policy

TO: ANDA 078340

SUBJECT: 180-day Exclusivity for Imatinib Mesylate Tablets, 100 mg and 400 mg

I. STATUTORY BACKGROUND

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) describes, among other things, certain events that can result in the forfeiture of a first applicant's[1] 180-day generic drug exclusivity as described in section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act).

The forfeiture provisions of the MMA appear at section 505(j)(5)(D) of the Act. Included among these is section 505(j)(5)(D)(i)(IV), which states the following:

> FAILURE TO OBTAIN TENTATIVE APPROVAL.--The first applicant fails to obtain tentative approval of the application within 30 months[2] after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

The "failure to obtain tentative approval" forfeiture provision establishes a bright-line rule: If within 30 months of submission, an abbreviated new drug application (ANDA) has been determined by the agency to meet the statutory standards for approval and it is only patent and/or exclusivity protection that prevents full approval, then an applicant will be given a tentative

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[1] A "first applicant" is eligible for 180-day exclusivity by virtue of filing a substantially complete ANDA with a paragraph IV certification on the first day on which such an ANDA is received. Section 505(j)(5)(B)(iv)(II)(bb). If only one such ANDA is filed on the first day, there is only one first applicant; if two or more such ANDAs are filed on the first day, first applicant status is shared.

[2] For applications submitted between January 9, 2010, and July 9, 2012, during the period of July 9, 2012 to September 30, 2015, section 1133 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-144) extends this period to 40 months.

approval and will maintain eligibility for 180-day exclusivity. If tentative approval or approval[3] is not obtained within 30 months, eligibility for 180-day exclusivity is generally forfeited unless "the failure [to obtain an approval] is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed." Under this provision, it is not sufficient to show that FDA's review of the ANDA (to determine that the ANDA has met the pre-existing approval requirements), caused a failure to obtain a tentative approval or approval at 30 months. Nor is it sufficient for an applicant to show that FDA changed or reviewed (i.e., considered whether to change) the requirements for approval while the application was under review. The applicant must also show that its failure to obtain a tentative approval at the 30 month date is **caused by** this change in or review of approval requirements. FDA generally will presume that the failure to obtain tentative approval or approval was caused by a change in or review of approval requirements if, at the 30 month date, the evidence demonstrates that the sponsor was actively addressing the change in or review of approval requirements (or FDA was considering such efforts), and these activities precluded tentative approval (or approval) at that time. Where the evidence fails to demonstrate that the sponsor was actively addressing the change in or review of approval requirements, and these activities precluded tentative approval (or approval) at the 30-month date, FDA generally does not presume that the failure was caused by a change in or review of approval requirements. If FDA were to hold otherwise, an applicant that receives one or more deficiencies resulting from a change in approval requirements could simply delay addressing those deficiencies and avoid forfeiture.

In addition, FDA has determined that if one of the causes of failure to get tentative approval or approval by the 30-month forfeiture date was a change in or review of the requirements for approval imposed after the application was filed, an applicant will not forfeit eligibility notwithstanding that there may have been other causes for failure to obtain tentative approval or approval by the 30-month forfeiture date. Thus, to avoid forfeiture, an applicant must show that acceptability of at least one aspect of the ANDA (e.g., chemistry) was delayed, and that this delay was caused at least in part, by a change in or review of the requirements for approval (which the sponsor or FDA is actively addressing), irrespective of what other elements may also have been outstanding at the 30-month date. In other words, "but-for" causation is not required in order to qualify for this exception. FDA has determined that this interpretation best effectuates the policy embodied in the exception. It does not penalize applicants for reviews of or changes in approval requirements imposed on applicants after their ANDAs are filed that are a cause of the failure to obtain approvals or tentative approvals within 30 months (and presumes causation if, at the 30 month date, the sponsor was actively addressing those changes, and these changes precluded approval), and continues to incentivize applicants to challenge patents by preserving in many instances the opportunity to obtain 180-day exclusivity.

Under this provision, the 30-month timeframe is generally measured without regard to the length

[3] As explained below, *supra* note 4, FDA interprets this provision to also encompass the failure to obtain final approval, where applicable, within 30 months of filing.

of time the ANDA was under review by the Agency. However, subsection 505(q)(1)(G) of the Act, enacted as part of the Food and Drug Administration Amendments Act of 2007 (Pub. Law 110-85) provides one exception. This subsection provides that

> If the filing of an application resulted in first-applicant status under subsection (j)(5)(D)(i)(IV) and approval of the application was delayed because of a petition, the 30-month period under such subsection is deemed to be extended by a period of time equal to the period beginning on the date on which the Secretary received the petition and ending on the date of final agency action on the petition (inclusive of such beginning and ending dates), without regard to whether the Secretary grants, in whole or in part, or denies, in whole or in part, the petition.

Thus, pursuant to this provision, if approval was delayed because of a 505(q) petition such that the application was not ready to be approved at 30 months from the date of submission because of the time it took the Agency to respond to the 505(q) petition, the 30-month-period-from-initial-submission deadline for obtaining a tentative (or final) approval will be extended by the amount of time that the 505(q) petition was under review.[4]

II. DISCUSSION

Sun Pharma Global's FZE (Sun's) ANDA 078340 for Imatinib Mesylate Tablets, 100 mg and 400 mg, is considered submitted for receipt and review on March 12, 2007.[5] Sun qualified as a "first applicant" and therefore is eligible for 180-day exclusivity absent forfeiture. Thirty months from the submission of the ANDA was September 12, 2009. As of that date, Sun had not received tentative approval of its ANDA. Sun's ANDA was tentatively approved on November 13, 2009, approximately two months after the 30-month forfeiture date.

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[4] In addition to tolling the 30-month period described in 505(j)(5)(D)(i)(IV) in certain circumstances where a petition is under review, section 505(q)(1)(G) clarified the scope of section 505(j)(5)(D)(i)(IV). If the phrase "tentative approval" in section 505(j)(5)(D)(i)(IV) is viewed in isolation, it might be suggested that this section applies only when an ANDA is eligible for a tentative approval due to a patent, 30-month stay or exclusivity blocking final approval, and that this provision cannot serve as a basis for forfeiture when an ANDA would have otherwise been eligible only for a *final* approval because there is no blocking patent, 30-month stay or exclusivity. Although section 505(j)(5)(D)(i)(IV) refers to "tentative approvals," the terms of section 505(q)(1)(G) clearly describe a broader scope. Section 505(q)(1)(G) expressly states that if "approval" of the first applicant's application was delayed because of a petition, the 30-month period described in section 505(j)(5)(D)(i)(IV) will be extended. Thus, Congress contemplated that section 505(j)(5)(D)(i)(IV) establishes a 30-month period within which an ANDA generally must obtain either tentative approval or final approval. This interpretation squares both with the statutory language and with not permitting the 180-day exclusivity for a first applicant whose ANDA is deficient to delay approval of subsequent applications. Therefore, FDA interprets section 505(j)(5)(D)(i)(IV) as requiring that, unless the period is extended for one of the reasons described in the Act, a first applicant that fails to obtain either tentative approval or approval for its ANDA within 30 months will forfeit eligibility for 180-day exclusivity.

[5] Sun's ANDA was submitted on June 16, 2006 and refused to receive on September 5, 2006. Sun submitted amendments on September 13, September 14, and November 28, 2006 and January 31 and March 12, 2007, after which FDA determined the ANDA was substantially comlete..

This memorandum addresses whether Sun has forfeited its eligibility for 180-day exclusivity due to its failure to obtain tentative approval by September 12, 2009. Sun submitted a letter dated September 10, 2009, regarding its eligibility for 180-day exclusivity, discussed in detail below.[6]

We must base our forfeiture analysis on the record before the agency. The following is a timeline of certain key submissions and actions regarding ANDA 078340:

3/12/2007	ANDA submitted
10/19/2007	Chemistry review #1 (deficient); chemistry deficiencies faxed
10/31/2007	Bioequivalence review (deficient)
11/13/2007	Genotoxic impurity letter
11/19/2007	Bioequivalence deficiencies faxed
11/20/2007	Labeling review (deficient); labeling deficiencies faxed
1/4/2008	Impurity amendment
8/14/2008	Chemistry amendment
10/24/2008	Labeling amendment
11/17/2008	Labeling review (deficient); labeling deficiencies faxed
12/15/2008	Chemistry teleconference
12/31/2008	Labeling amendment
1/6/2009	Bioequivalence amendment (firm stated bioequivalence studies are ongoing)
1/16/2009	Labeling review (acceptable)
1/23/2009	Labeling review (acceptable) (same review as 1/16/2009 review)
2/10/2009	Reference Listed Drug (RLD) labeling changes approved
3/10/2009	Chemistry teleconference amendment
4/2/2009	Bioequivalence amendment
5/27/2009	RLD labeling changes approved
6/22/2009	Bioequivalence teleconference (request to submit statement regarding lot # JK80750 and provide chemistry, manufacturing, and controls information for this lot)
6/30/2009	Chemistry teleconference amendment
7/14/2009	Bioequivalence review (deficient)

[6] Letter to Office of Generic Drugs from R. Shrivastava, Sun Pharmaceutical Industries Ltd. (Sep. 10, 2009). We note that ANDA applicants frequently submit correspondence related to forfeiture of 180-day exclusivity. Although FDA does not expect or require such correspondence, the agency will consider any submitted correspondence when making a forfeiture decision. A subsequent applicant, [redacted] (b) (4)), submitted a letter dated [redacted] (b) (4)

7/16/2009	Bioequivalence deficiencies faxed
7/29/2009	Chemistry amendment (dissolution); bioequivalence amendment
8/27/2009	Bioequivalence review (acceptable)
9/8/2009	Chemistry teleconference
9/9/2009	Chemistry amendment
9/11/2009	Patent amendment (also requested expeditious tentative approval to preserve eligibility for 180-day exclusivity)
9/12/2009	**3/12/2007 plus 30 months**
9/28/2009	Letter regarding 180-day exclusivity
9/28/2009	Chemistry email deficiencies
10/5/2009	Chemistry amendment
10/9/2009	Chemistry review #2 (acceptable)
10/27/2009	Labeling amendment
11/4/2009	Labeling review (acceptable)
11/13/2009	Tentative approval

The tentative approval of Sun's ANDA was not delayed because of a citizen petition, such that the 30-month period would be extended past September 12, 2009, under section 505(q)(1)(G).

FDA Review of ANDA 078340

Bioequivalence was determined to be acceptable on August 27, 2009. At the forfeiture date of September 12, 2009, chemistry and labeling were deficient.

Chemistry Review

FDA reviewed the chemistry section of Sun's ANDA and sent a deficiency letter on October 19, 2007. Sun responded to FDA's October 19, 2007 chemistry deficiency letter on August 14, 2008.[7] In addition to responding to FDA's deficiencies, Sun provided, (b) (4) (b) (4) (b) (4)[8] FDA reviewed Sun's amendment and in a December 15, 2008 teleconference, asked the firm to provide (b) (4) (b) (4) Sun submitted an amendment on March 10, 2009 with the requested

[7] Letter to Office of Generic Drugs fr. A. Muthal, General Manager, Regulatory Affairs, Sun Pharmaceutical Industries Ltd. (Aug. 6, 2008).
[8] Id. at 5. (b) (4) (b) (4)

information, noting that a [redacted] (b) (4) Following this amendment, FDA and Sun had a chemistry teleconference that was unrelated to [redacted] (b) (4) requirement, and Sun submitted two additional chemistry amendments, neither of which addressed deficiencies related to [redacted] (b) (4) On September 8, 2009, FDA and Sun held another chemistry teleconference, during which FDA asked the firm, among other things, to provide a commitment to provide [redacted] (b) (4) after tentative approval. Sun responded to this request on September 9, 2009, and provided a commitment to provide [redacted] (b) (4) within 15 days of receiving tentative approval.[10] FDA's review of Sun's September 9, 2009 amendment, including the commitment to submit [redacted] (b) (4), extended past the 30-month date, and on September 28, 2009, FDA held another teleconference with Sun. FDA asked the firm to provide, among other things, [redacted] (b) (4) if they were available. Sun responded to FDA's requests on October 5, 2009, and provided the requested [redacted] (b) (4).[11] FDA reviewed Sun's amendment and found chemistry to be acceptable on October 9, 2009, approximately one month after the 30-month forfeiture date.[12] Based on the above facts, we have determined that there was a change in requirements for approval related to [redacted] (b) (4) which FDA was actively addressing at the 30-month forfeiture date, and that this change was a cause of Sun's failure to obtain tentative approval by the 30-month forfeiture date.

Labeling Review

Sun's labeling was initially determined to be acceptable on January 23, 2009.[13] However, two RLD labeling changes were approved after Sun's labeling was determined to be acceptable but prior to the 30-month date. Because we have determined that there was a change in the approval requirements for chemistry, which was a cause of Sun's failure to obtain tentative approval by September 12, 2009, we need not determine whether there is a separate basis for non-forfeiture with respect to labeling.

Sun's September 26, 2009 Letter Regarding 180-day Exclusivity

Sun submitted a letter dated September 26, 2009, asserting that the company has not forfeited eligibility for 180-day exclusivity for failure to receive tentative approval within 30-months due to a change in bioequivalence requirements.[14] Specifically, the firm claims that after submission

[9] Letter to Office of Generic Drugs fr. A. Muthal, General Manager, Regulatory Affairs, Sun Pharmaceutical Industries Ltd. (Mar. 9, 2009).
[10] Letter to Office of Generic Drugs fr. A. Muthal, General Manager, Regulatory Affairs, Sun Pharmaceutical Industries Ltd. (Sept. 9, 2009).
[11] Letter to Office of Generic Drugs fr. A. Muthal, General Manager, Regulatory Affairs, Sun Pharmaceutical Industries Ltd. (Oct. 2, 2009).
[12] ANDA 078340 Chemistry Review #2 (Oct. 9, 2009).
[13] Approval Summary #1, Labeling Review Branch (Jan. 23, 2009).
[14] Letter to Office of Generic Drugs fr. R. Shrivastava, Vice President, Intellectual Property, Sun Pharmaceutical Industries Ltd. (Sept. 26, 2009) (Sun Letter).

of their ANDA, "FDA required for the first time that the [bioequivalence] studies for this particular product be performed on a *patient population*."[15] Sun characterizes FDA's November 19, 2007 bioequivalence deficiencies as a "new requirement."[16]

Sun sent a letter dated January 6, 2009,[17] approximately 14 months after FDA's November 19, 2007 bioequivalence deficiency letter, stating that bioequivalence studies are ongoing and the firm would respond to FDA's bioequivalence deficiencies upon completion of the studies. On April 2, 2009, Sun responded to FDA's November 19, 2007 bioequivalence deficiencies with data from a steady-state bioequivalence study.[18] FDA reviewed Sun's bioequivalence data and on July 16, 2009 issued deficiencies requesting, among other things, drug product information for the biobatches of both test and reference products, dissolution data for the new biobatch, complete analytical raw data for all subjects, and provided a recommended dissolution specification.[19] Sun submitted an amendment responding to FDA's deficiencies on July 29, 2009.[20] FDA reviewed Sun's amendment and found bioequivalence to be acceptable on August 27, 2009, approximately two weeks prior to the 30-month forfeiture date.[21] Sun's bioequivalence data was determined to be acceptable prior to the 30-month forfeiture date; therefore, any changes in bioequivalence requirements could not have caused Sun's failure to obtain tentative approval within 30-months.

III. CONCLUSION

We conclude that there was a change to the requirements for approval with respect to chemistry (b) (4) which became effective after Sun's ANDA was submitted, as outlined above. We also find that the need to comply with the (b) (4) (b) (4) requirement was a cause of Sun's failure to obtain tentative approval by the forfeiture date. (b) (4) (b) (4) At the 30-month date of September 12, 2009, FDA was reviewing Sun's September 9, 2009 chemistry amendment, which submitted the results of the additional testing and addressed, among other things, (b) (4) requirements.

Sun's ANDA 078340 was considered submitted for receipt and review on March 12, 2007, for Imatinib Mesylate Tablets, 100 mg and 400 mg. The 30-month forfeiture date was September

[15] Id. (Emphasis in original.)
[16] Id. at 2.
[17] Letter to S. Mazzella, Office of Generic Drugs fr. A. Celeste, Senior Vice President, Kendle Regulatory Affairs (Jan. 6, 2009).
[18] Letter to S. Mazzella, Office of Generic Drugs fr. A. Celeste, Senior Vice President, Kendle Regulatry Affairs (Apr. 2, 2009).
[19] Bioequivalence Amendment (Jul. 16, 2009).
[20] Letter to N. Chun, Office of Generic Drugs fr. A. Celeste, Senior Vice President, Kendle Regulatory Affairs (Jul. 29, 2009).
[21] Division of Bioequivalence Review of an Amendment (Aug. 27, 2009).

12, 2009. Sun's ANDA was not tentatively approved within this period. The agency finds that Sun's failure to obtain tentative approval was caused by a change in or a review of the requirements for approval. We therefore conclude that Sun has not forfeited its eligibility for the 180-day exclusivity period described in section 505(j)(5)(B)(iv) of the Act for Imatinib Mesylate Tablets, 100 mg and 400 mg.

Iain Margand -S

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