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: October 29, 2014

FROM: Martin Shimer
Deputy Director, Division of Legal and Regulatory Support
Office of Generic Drug Policy

TO: ANDA 200828

SUBJECT: 180-day Exclusivity for Lamotrigine Orally Disintegrating Tablets, 25 mg, 50 mg, 100 mg, and 200 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 FD&C Act).

The forfeiture provisions of the MMA appear at section 505(j)(5)(D) of the FD&C 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 approval and will maintain eligibility for 180-day exclusivity. If tentative approval is not

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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) of the FD&C Act. If only one such ANDA is submitted on the first day, there is only one first applicant; if two or more such ANDAs are submitted on the first day, first applicant status is shared.

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

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 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 – that is, at the 30 month date, the sponsor or FDA was actively addressing the change in or review of approval requirements, and these activities precluded tentative approval (or approval) at that time. In circumstances where there is no evidence that the change in or review of approval requirements caused the failure to obtain tentative approval, FDA generally will not presume causation. 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 by the 30-month forfeiture date was a change in or review of the requirements for approval imposed after the application was submitted, an applicant will not forfeit eligibility notwithstanding that there may have been other causes for failure to obtain tentative 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, 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 applicant was actively addressing those changes), 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 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.[3]

II. DISCUSSION

Impax Laboratories Inc. (Impax)[4] submitted ANDA 200828 for Lamotrigine Orally Disintegrating Tablets, 25 mg, 50 mg, 100 mg, and 200 mg, on December 21, 2009. On April 14, 2011, Impax amended its ANDA to include a paragraph IV certification to U.S. Patent Number 7,919,115 (the '115 patent). With this amendment, Impax qualified as a "first applicant" and therefore is eligible for 180-day exclusivity. Because Impax amended its ANDA to first contain a paragraph IV certification within the time period identified in section 1133 of FDASIA, the company had 40 months to obtain tentative approval for purposes of section 505(j)(5)(D)(i)(IV) of the FD&C Act.[5] Forty months from the submission of the ANDA was April 21, 2013.[6] As of that date, Impax had failed to obtain tentative approval of its ANDA. This ANDA was approved on July 15, 2013. The approval letter noted the failure to receive

[3] 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 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 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.

[4] Ownership of ANDA 200828 was transferred from Watson Laboratories, Inc. (Watson) to Impax in July 2014. Although Watson was the holder of ANDA 200828 during the relevant period discussed in this memorandum, Impax will be referred to as the holder.

[5] See note 2, above.

[6] The agency notes that section 1133(b) of FDASIA does not apply to ANDA 200828 because the ANDA was not amended during the applicable time period. Therefore, the 40 month time period is calculated from the ANDA filing date and not the date of the amendment first containing a paragraph IV certification.

tentative approval within 40 months, but did not make a formal determination at that time regarding eligibility for 180-day generic drug exclusivity.[7]

This memorandum addresses whether Impax has forfeited its eligibility for 180-day exclusivity due to its failure to obtain tentative approval by April 21, 2013. Impax has not submitted any correspondence regarding its eligibility for 180-day exclusivity.

The following is a timeline of certain key submissions and actions regarding ANDA 200828:

12/21/2009	ANDA submitted
5/11/2010	Labeling review (deficient); labeling deficiencies faxed
7/13/2010	Labeling amendment
7/30/2010	Bioequivalence dissolution review (deficient)
8/4/2010	Bioequivalence dissolution deficiencies faxed
10/24/2010	*Reference Listed Drug (RLD) labeling changes approved*
11/1/2010	Bioequivalence amendment
2/17/2011	Bioequivalence review (deficient)
2/25/2011	Bioequivalence deficiencies faxed
4/4/2011	Bioequivalence amendment
4/5/2011	Bioequivalence review (deficient)
4/8/2011	Bioequivalence review (acceptable)
5/13/2011	*RLD labeling changes approved*
8/4/2011	*RLD labeling changes approved*
8/31/2011	Chemistry review #1(deficient); chemistry deficiencies faxed
10/23/2011	Labeling review (deficient); labeling deficiencies faxed
11/29/2011	*RLD labeling changes approved*
4/2/2012	Labeling amendment
5/23/2012	Chemistry amendment
8/1/2012	*RLD labeling changes approved*
9/10/2012	Labeling amendment
9/11/2012	Chemistry review #2 (deficient); chemistry deficiencies faxed
12/12/2012	Chemistry amendment
1/14/2013	Chemistry amendment
3/25/2013	EES acceptable
4/16/2013	Chemistry review #3 (acceptable)
4/21/2013	**12/21/2009 plus 40 months**
4/24/2013	Labeling review (deficient); labeling deficiencies faxed
5/7/2013	Labeling amendment

[7] Letter to K. Joshi, Manager, Regulatory Affairs, Watson Laboratories Inc., fr. K. Uhl, Acting Director, OGD (July 15, 2013).

5/30/2013	Labeling review (acceptable)
7/9/2013	Chemistry review #3 addendum (acceptable)
7/15/2013	ANDA approved

FDA Review of ANDA 200828

Bioequivalence was determined to be acceptable on April 8, 2011, current good manufacturing compliance was acceptable on March 25, 2013, and chemistry was acceptable on April 16, 2013. At the forfeiture date of April 21, 2013, labeling was the only deficient discipline.

Changes to the RLD labeling were approved five times prior to the forfeiture date.

- On June 24, 2010, FDA approved a modified risk evaluation and mitigation strategy (REMS) and REMS supporting document.[8] FDA also approved changes in the Warnings and Precautions section and the Medication Guide to incorporate discussion of aseptic meningitis.
- Labeling changes were again approved for the RLD on May 31, 2011.[9] These changes included discontinuing the REMS but maintaining the Medication Guide as part of the approved labeling.
- A third labeling change to the RLD was approved on August 4, 2011.[10] This labeling change provided for consolidation of the discussion of hypersensitivity reactions and multiorgan failure in the Warnings and Precautions section.
- A fourth labeling change was approved on November 29, 2011, for revisions to the Medication Guide.[11]
- A fifth labeling change was approved on August 1, 2012, approximately 8 months before the forfeiture date.[12] This labeling change provided for Agency-requested updates to the Use in Specific Populations/Nursing Mothers (section 8.3) and Patient Counseling Information/Pregnancy and Nursing (section 17.6) section of the labeling, as well as corresponding changes to the Medication Guide.

[8] Letter to E. McConnell, Associate Director, Neurology, US Regulatory Affairs, GlaxoSmithKine fr. R. Katz, Director, Division of Neurology Products (Jun. 24, 2010).

[9] Letter to E. McConnell, Associate Director, Neurology, US Regulatory Affairs, GlaxoSmithKline fr. R. Katz, Director, Division of Neurology Products (May 31, 2011).

[10] Letter to E. McConnell, Associate Director, Neurology, US Regulatory Affairs, GlaxoSmithKline fr. R. Katz, Director, Division of Neurology Products (Aug. 4, 2011).

[11] Letter to E. McConnell, Associate Director, Neurology, US Regulatory Affairs, GlaxoSmithKline fr. R. Katz, Director, Division of Neurology Products (Nov. 29, 2011).

[12] Letter to E. McConnell, Associate Director, Neurology, US Regulatory Affairs fr. R. Katz, Director, Division of Neurology Products (Aug. 1, 2012).

FDA initially reviewed Impax's labeling on May 11, 2010, and identified a number of deficiencies.[13] Impax submitted an amendment responding to FDA's deficiencies on July 13, 2010.[14] FDA reviewed Impax's amendment on October 23, 2011, and identified additional deficiencies. One of the deficiencies asked Impax to update its package insert and medication guide labeling to be in accord with the August 4, 2011 approved labeling changes for the RLD.[15] Impax submitted an amendment responding to FDA's deficiencies on April 2, 2012.[16] Before FDA reviewed Impax's April 2, 2012 amendment, Impax submitted another labeling amendment on September 10, 2012, to update their labeling to be consistent with the RLD labeling changes approved on August 1, 2012.[17] FDA reviewed Impax's April 2, 2012 and September 10, 2012 labeling amendments and on April 24, 2013, three days after the 40-month forfeiture date of April 21, 2013, FDA notified Impax of additional labeling deficiencies.[18] Impax submitted an amendment on May 7, 2013.[19] FDA reviewed Impax's amendment, and ultimately determined Impax's labeling to be acceptable on May 30, 2013.[20]

III. CONCLUSION

We conclude that there were changes to the requirements for approval with respect to labeling, as outlined above. We also find evidence that these labeling changes caused Impax's failure to obtain tentative approval by the forfeiture date. Specifically, changes to the RLD labeling were approved on August 1, 2012, and Impax submitted a labeling amendment on September 10, 2012 to update their labeling. At the 40-month date of April 21, 2013, Impax's labeling amendment had not been reviewed by FDA, and the labeling deficiencies issued by FDA after the 40-month forfeiture date related to the changes to the RLD labeling that occurred after Impax submitted its ANDA.

Impax's ANDA 200828 was received on December 21, 2009, for Lamotrigine Orally Disintegrating Tablets, 25 mg, 50 mg, 100 mg, and 200 mg. The 40-month forfeiture date was April 21, 2013. Impax's ANDA was not tentatively approved within this period. The agency finds that Impax's failure to obtain tentative approval was caused by a change in or a review of the requirements for approval. We therefore conclude that Impax did not forfeit its eligibility for

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[13] Review of Professional Labeling, Division of Labeling and Program Support (May 11, 2010).

[14] Letter to K. Webber, Acting Director, OGD fr. K. Joshi, Manager, Regulatory Affairs, Watson Laboratories, Inc. (Jul. 12, 2010).

[15] Review of Professional Labeling #2 (Oct. 23, 2011).

[16] Letter to K. Webber, Acting Director, OGD fr. K. Joshi, Manager, Regulatory Affairs, Watson Laboratories Inc. (Apr. 2, 2012).

[17] Letter to G. Geba, Director, OGD fr. K. Joshi, Manager, Regulatory Affairs, Watson Laboratories Inc. (Sept. 10, 2012).

[18] Review of Professional Labeling (Apr. 24, 2013).

[19] Letter to K. Uhl, Acting Director, OGD fr. K. Joshi, Manager, Regulatory Affairs, Watson Laboratories Inc. (May 7, 2013).

[20] Approval Summary, Review of Professional Labeling (May 30, 2013).

the 180-day exclusivity period described in section 505(j)(5)(B)(iv) of the FD&C Act for Lamotrigine Orally Disintegrating Tablets, 25 mg, 50 mg, 100 mg, and 200 mg.

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/s/

IAIN MARGAND on behalf of MARTIN H Shimer
10/29/2014