MEMORANDUM

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

DATE: June 2, 2016

FROM: Martin Shimer
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Office of Generic Drug Policy

TO: ANDA 201509

SUBJECT: 180-day Exclusivity for Zolpidem Tartrate Sublingual Tablets, 5 mg and 10 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

[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 containing a Paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and approved or tentatively approved during the period of time beginning on July 9, 2012, and ending on 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. For applications submitted between January 9, 2010, and July 9, 2012 (or amended to first contain a paragraph IV certification during that period of time), and approved or tentatively approved during the period of time beginning on October 1, 2015, and ending on September 30, 2016, section 1133 of FDASIA extends this period to 36 months. In addition, if an application was submitted between January 9, 2010, and July 9, 2012 containing a Paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and FDA has not approved or tentatively approved the application but must consider whether the applicant has forfeited exclusivity because a potentially blocked application is ready for approval, FDA will apply the 36-month period if it makes the forfeiture determination between the period of time beginning on October 1, 2015, and ending on September 30, 2016. For all other applications, the 30-month period set forth in FD&C Act section 505(j)(5)(D)(i)(IV) applies.

> 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 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

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

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 of time the ANDA was under review by the agency. However, subsection 505(q)(1)(G) of the FD&C 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

Par Formulations Private Limited (Par) submitted ANDA 201509 for Zolpidem Tartrate

[4] In addition to tolling the 30-month period described in section 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 FD&C Act or section 1133 of FDASIA, 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.

Sublingual Tablets, 5 mg and 10 mg on April 29, 2010.[5] FDA received ANDA 201509 for review on April 29, 2010. ANDA 201509 references Edluar Sublingual Tablets (new drug application (NDA) 021997) as its reference listed drug (RLD). Par qualified as a "first applicant" on both strengths and, therefore, was eligible for 180-day exclusivity for both strengths of its generic Zolpidem Tartrate Sublingual Tablets. Because Par submitted its ANDA within the time period identified in Section 1133 of FDASIA, the company had 36 months to obtain tentative approval for the purposes of section 505(j)(5)(D)(i)(IV) of the FD&C Act.[6] Thirty-six months from the date of receipt of the ANDA was April 29, 2013. As of that date, Par had not received tentative approval of its ANDA.

This memorandum addresses whether Par has forfeited its eligibility for 180-day exclusivity due to its failure to obtain tentative approval by April 29, 2013.

Par has not submitted any correspondence regarding its eligibility for 180-day exclusivity.[7]

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 201509:

4/29/2010	ANDA receipt date
9/2010	Draft Guidance on Zolpidem Sublingual Tablets (product-specific bioequivalence guidance) issued
9/15/2010	Labeling review (deficient); labeling deficiencies faxed
10/26/2010	Bioequivalence dissolution review (deficient)
11/2/2010	Bioequivalence dissolution deficiencies faxed
11/12/2010	Labeling and risk evaluation and mitigation strategy (REMS) amendments
12/17/2010	RLD REMS modifications approved
12/21/2010	Bioequivalence amendment
1/27/2011	Bioequivalence amendment
2/16/2011	Bioequivalence amendment
2/25/2011	Chemistry review (deficient)
2/28/2011	Chemistry deficiencies faxed

[5] ANDA 201509 was submitted originally by Novel Therapeutics Private Limited (Novel). Novel later changed its name to Edict Pharmaceuticals Pvt. Ltd. (Edict). See Letter to K. Webber, OGD/FDA, fr. V. Ramasamy, Senior Manager – Regulatory Affairs, Edict re: ANDA 201509, Company Name Change (August 20, 2010). On June 11, 2012, Edict informed FDA that Edict had changed its name to Par Formulations Private Limited. See Letter to K. Webber, OGD/FDA, fr. M. Prasad, Senior Manager – Regulatory Affairs, Par, re: ANDA 201509, Company Name Change (June 9, 2012).

[6] See *supra*, note 2. Because FDA has not approved or tentatively approved Par's application, but now must determine whether Par has forfeited exclusivity because a potentially blocked application is ready for approval, FDA will apply the 36-month period described in section 1133 of FDASIA.

[7] 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.

4/4/2011	Bioequivalence dissolution review (deficient)
4/14/2011	Bioequivalence dissolution deficiencies faxed
5/6/2011	Chemistry amendment
5/9/2011	Bioequivalence amendment
7/20/2011	Bioequivalence review (deficient)
7/27/2011	Bioequivalence deficiencies faxed
8/10/2011	Elimination of RLD REMS approved
8/18/2011	Bioequivalence amendment
10/13/2011	Bioequivalence review (deficient)
10/31/2011	Bioequivalence deficiencies faxed
11/8/2011	Bioequivalence amendment
11/30/2011	Bioequivalence review (acceptable)
1/20/2012	Chemistry review (deficient); chemistry deficiencies faxed
2/27/2012	Chemistry amendment
6/28/2012	Labeling review (deficient); labeling deficiencies faxed
7/3/2012	Labeling amendment
7/12/2012	Labeling review (deficient); labeling deficiencies faxed
7/16/2012	Labeling amendment
7/30/2012	Labeling review (acceptable)
9/10/2012	Chemistry review (deficient); chemistry deficiencies faxed
11/28/2012	Complete Response letter mailed (chemistry deficiencies)
12/19/2012	Chemistry amendment
4/19/2013	***RLD labeling changes approved***
4/29/2013	**4/29/2010 plus 36 months**
7/22/2013	Letter from Par re: dismissal of patent litigation and request for final approval of ANDA
10/10/2013	Chemistry review (acceptable)
10/21/2013	Labeling amendment
10/28/2013	Labeling review (acceptable)
1/16/2014	Complete Response letter mailed (cGMP deficiencies)
3/14/2014	Chemistry/facility amendment (changed API manufacturer)
10/29/2014	RLD labeling changes approved
1/6/2015	Labeling amendment
1/20/2015	Labeling review (acceptable)
2/24/2015	Chemistry review (API DMF deficiencies)
2/26/2015	Complete Response letter mailed (Chemistry deficiencies)
4/8/2015	Chemistry/facility amendment
8/24/2015	Chemistry/facility amendment
9/30/2015	Complete Response letter mailed (Chemistry and cGMP deficiencies)

Tentative approval of Par's ANDA was not delayed because of a citizen petition, such that the 36-month period would be extended past April 29, 2013, under section 505(q)(1)(G) of the FD&C Act.

FDA Review of ANDA 201509

As the above timeline indicates, the bioequivalence review for ANDA 201509 was found acceptable on November 30, 2011, and the labeling review for the ANDA was found acceptable on July 30, 2012. The chemistry review was found to be deficient on September 10, 2012, and the relevant chemistry deficiencies were sent to Par that same day. On April 19, 2013, FDA approved certain changes to the labeling for the RLD. At the forfeiture date of April 29, 2013, the chemistry review was still pending.

As discussed below, FDA has identified a change in the requirements for approval regarding labeling but has concluded that this change in the approval requirements was not a cause of Par's failure to obtain tentative approval. FDA has not identified a change in or review of the requirements for approval regarding chemistry.

Labeling Review

As noted above, the labeling review for ANDA 201509 was found acceptable on July 30, 2012. FDA approved changes to the RLD labeling (NDA 021997) on April 19, 2013, ten days before the 36-month forfeiture date. These changes included new safety information relating to zolpidem tartrate, including several changes to the "Dosage and Administration" section of the RLD labeling.[8] Despite these changes to the RLD labeling, Par did not submit a labeling amendment to ANDA 201509 to address these changes until October 21, 2013, six months after the approval of the RLD labeling updates.[9] In fact, Par's July 22, 2013 request for final approval of ANDA 201509 noted that "[t]here has been no change in Labeling...."[10]

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 forfeiture 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

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[8] See Letter to C. Yayac, Meda Pharmaceuticals, Inc. fr. E. Bastings, Division of Neurology Products, FDA, re: Approval of NDA 021997/S-005 (April 19, 2013).

[9] See Letter to K. Uhl, OGD, FDA, fr. M. Prasad, Par, re: Gratuitous Labeling Amendment, ANDA 201509 (October 21, 2013).

[10] Letter to K. Uhl, OGD, FDA, fr. M. Prasad, Par, re: Final Approval Requested, ANDA 201509 (July 22, 2013) at 1 ("There has been no change in Labeling, Chemistry, Manufacturing and Control data. Taking into consideration that litigation has been dismissed, we are requesting final approval for ANDA 201509, Zolpidem Tartrate Sublingual Tablets, 5 mg and 10 mg CIV.").

precluded tentative approval (or approval) at the forfeiture date, FDA generally does not presume that the failure was caused by a change in or review of approval requirements.

We conclude that there were changes to the requirements for approval with respect to labeling, as outlined above. Changes to the RLD labeling required Par to revise its labeling. However, we do not find that these labeling changes caused Par's failure to obtain tentative approval by the forfeiture date. At the 36-month date of April 29, 2013, Par had not yet submitted an amendment to address the RLD labeling updates approved on April 19, 2013, and no evidence indicates that Par was actively addressing the labeling deficiencies that resulted from the change in approval requirements at that time. Par's submission related to the labeling changes was almost 6 months after the forfeiture date. The six-month lag between the change in approval requirements with respect to labeling and Par's labeling amendment supports an inference that Par was not actively addressing the labeling changes at the forfeiture date. Therefore, we conclude that the RLD labeling changes were not a cause of Par's failure to obtain tentative approval.

Chemistry Review

As noted above, FDA reviewed the chemistry section of ANDA 201509 on September 10, 2012 and determined that the chemistry section of the application was inadequate.[11] This chemistry review noted the following deficiencies: (1) request to (b) (4) and (2) request to revise (b) (4) [12]. On December 19, 2012, Par submitted a chemistry amendment to address the chemistry deficiencies identified in FDA's September 10, 2012 review of the ANDA.[13] On October 10, 2013, the chemistry section of ANDA 201509 was determined to be acceptable.[14] Although the chemistry deficiencies discussed above were first identified in FDA's September 10, 2012 review, these deficiencies do not represent a change in or a review of the requirements for approval. Rather, these deficiencies represent preexisting requirements under FDA's regulations that were simply identified later in the review process for ANDA 201509. As a result, in reviewing FDA's chemistry reviews of ANDA 201509, we have not identified a change in or a review of the requirements for approval regarding chemistry.

III. CONCLUSION

Par's ANDA 201509 for Zolpidem Tartrate Sublingual Tablets, 5 mg and 10 mg, was received on April 29, 2010. The 36-month forfeiture date was April 29, 2013. Par's ANDA was not tentatively approved within this period. The agency finds that Par's failure to obtain tentative

[11] Chemistry Review of ANDA 201509 (September 10, 2012).
[12] *Id.* at 43.
[13] See Letter to G. Geba, OGD, FDA, fr. M. Prasad, Par, re: Resubmission/After Action – Complete Response Amendment, ANDA 201509 (December 19, 2012).
[14] Chemistry Review of ANDA 201509 (October 10, 2013).

approval was not caused by a change in or a review of the requirements for approval. We therefore conclude that Par forfeited its eligibility for the 180-day exclusivity period described in section 505(j)(5)(B)(iv) of the FD&C Act for Zolpidem Tartrate Sublingual Tablets, 5 mg and 10 mg.

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