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: March 1, 2016

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

TO: ANDA 065488

SUBJECT: 180-day Exclusivity for Azithromycin for Oral Suspension USP, 100 mg/5 mL and 200 mg/5 mL

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 embodied in the exception. It does not penalize applicants for reviews of

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

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 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

Lupin Limited (Lupin) submitted ANDA 065488 for Azithromycin for Oral Suspension USP, 100 mg/5 mL and 200 mg/5 mL, on April 12, 2007. ANDA 065488 references Zithromax (new

[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.

drug application (NDA) 050710) as its reference listed drug (RLD). Following the enactment of the QI Program Supplemental Funding Act of 2008, Pub. L. No. 110-379, 122 Stat. 4075 (2008) (QI Act), Pfizer submitted patent information for Zithromax on December 3, 2008. In an amendment received on January 30, 2009, Lupin submitted a paragraph IV certification to address the newly listed patent in the Orange Book for Zithromax: U.S. Patent No. 6,268,489 (the '489 patent). Lupin's ANDA was the only pending ANDA that referenced Zithromax (azithromycin) for Oral Suspension at the time the patent was listed;[5] it timely filed a paragraph IV certification and sent notice to the owner of the patent and holder of the approved application on January 29, 2009.

Under the transitional rules in section 4(b) of the QI Act, Lupin qualifies as a "first applicant" for azithromycin for oral suspension, because it certified to the patents listed for Zithromax after passage of the QI Act by February 5, 2009. As a "first applicant," Lupin was eligible for 180-day exclusivity absent forfeiture. Thirty months from the submission of the ANDA was October 12, 2009. As of that date, Lupin had not received tentative approval of its ANDA.

This memorandum addresses whether Lupin has forfeited its eligibility for 180-day exclusivity due to its failure to obtain tentative approval by October 12, 2009. Lupin has not submitted any correspondence regarding its eligibility for 180-day exclusivity.[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 065488:

4/12/2007	ANDA submitted
9/27/2007	Bioequivalence dissolution review (deficient)
10/4/2007	Chemistry review #1 (deficient); chemistry deficiencies faxed
10/25/2007	***RLD labeling changes approved***
10/31/2007	Bioequivalence deficiencies faxed
11/20/2007	Bioequivalence amendment
2/19/2008	Bioequivalence review (acceptable)
5/28/2008	Labeling review (deficient)
	(b) (4)
7/23/2008	FDA letter re: overdue responses to Not Approval letters on various applications
8/4/2008	Chemistry amendment
8/15/2008	Labeling amendment
10/16/2008	Chemistry amendment

[5] Three other ANDAs for azithromycin for oral suspension had been approved prior to the QI Act and were not pending at the time the patent was listed (ANDA 065419, ANDA 065297, and ANDA 065246).

[6] 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.

12/2008	***Draft Guidance on Azithromycin (product-specific bioequivalence guidance) recommended***
1/23/2009	Labeling amendment (appears to be duplicate of 8/15/2008 labeling amendment)
2/23/2009	Labeling review (deficient); labeling deficiencies faxed
2/27/2009	***RLD labeling changes approved***
3/9/2009	Chemistry review #2 (deficient); Complete Response faxed (chemistry deficiencies)
6/19/2009	Chemistry amendment
6/26/2009	Labeling amendment
10/12/2009	**4/12/2007 plus 30 months**
3/12/2010	Chemistry review #3 (deficient); chemistry deficiencies faxed
6/30/2010	Labeling review (deficient); labeling deficiencies faxed
9/8/2010	Labeling amendment
1/27/2011	Labeling review (acceptable)
8/8/2011	FDA letter re: additional bioequivalence data needed (b) (4) (b) (4)
10/6/2011	Bioequivalence review (deficient)
(b) (4)	
10/11/2012	Complete Response mailed (chemistry and bioequivalence deficiencies)
1/2/2013	Chemistry amendment; bioequivalence amendment; labeling amendment
5/31/2013	Labeling review (deficient)
2/7/2014	Bioequivalence review (deficient)
4/21/2014	Chemistry review #4 (deficient)
5/1/2014	Complete Response faxed (chemistry, bioequivalence, and labeling deficiencies)
8/27/2014	Chemistry amendment; bioequivalence amendment; labeling amendment
11/10/2014	Bioequivalence review (acceptable)
11/12/2014	Labeling review (deficient)
11/18/2014	Chemistry review #5 (deficient)
12/5/2014	Complete Response faxed (chemistry and labeling deficiencies)
1/27/2015	Chemistry amendment; labeling amendment
2/26/2015	Labeling review (acceptable)
4/22/2015	Telephone conference re: 1/27/2015 chemistry amendment
5/4/2015	Chemistry amendment
5/5/2015	Chemistry review #5[7] (acceptable)

[7] So noted in the review memo; this is likely a typographical error and should be #6.

5/15/2015	ANDA approved

The tentative approval of Lupin's ANDA was not delayed because of a citizen petition, such that the 30-month period would be extended past October 12, 2009, under section 505(q)(1)(G). Pfizer did submit a citizen petition related to another firm's ANDA for generic azithromycin for oral suspension, but this petition did not delay FDA's review of ANDA 065488.[8]

FDA Review of ANDA 065488

As the above timeline indicates, bioequivalence was found adequate on February 19, 2008. At the forfeiture date of October 12, 2009, chemistry and labeling were deficient.

Chemistry Review

FDA reviewed the chemistry section of ANDA 065488 on October 4, 2007 and communicated 25 deficiencies to Lupin.[9] Lupin submitted a chemistry amendment on August 4, 2008 in response to the October 4, 2007 deficiencies. (b) (4) Lupin submitted another chemistry amendment on October 16, 2008 (b) (4). On March 9, 2009, FDA communicated 7 more chemistry deficiencies to Lupin and also requested that Lupin note and acknowledge that (b) (4) had not yet been provided.[10] In response, Lupin submitted a chemistry amendment on June 19, 2009, which purported to address the March 9, 2009 deficiencies.[13] With respect to the comment

[8] Pfizer submitted a citizen petition (received on October 5, 2006) that asserted Pliva Inc.'s (Pliva's) generic azithromycin for oral suspension was misbranded because its label incorrectly identified a polymorphic form of the active ingredient. The petition requested that FDA initiate a recall and "reexamine" the ANDA to determine if suspension or withdrawal of the application was appropriate. FDA denied this petition on August 25, 2011 stating that requests for enforcement action are outside the scope of citizen petition procedures. See Docket No. FDA-2006-P-0448. The petition concerned Pliva's specific ANDA and did not seek broader FDA action with respect to azithromycin. Furthermore, nothing in the review history for Lupin's ANDA suggests that FDA considered this citizen petition in the context of ANDA 065488.

[9] October 4, 2007 Chemistry Minor Deficiency fax to Lupin.

[10] (b) (4)

[11] Letter to V. Sayeed, OGD fr. L. Sands, Lupin re "ANDA #65-488, AZITHROMYCIN FOR ORAL SUSPENSION USP, 100 mg/5 mL and 200 mg/5 mL" (Oct. 13, 2008).

[12] March 9, 2009 Complete Response -- Minor fax to Lupin.

[13] Letter to V. Sayeed, OGD fr. L. Sands, Lupin re "ANDA #65-488, AZITHROMYCIN FOR ORAL SUSPENSION USP, 100 mg/5 mL and 200 mg/5 mL" (June 16, 2009).

(b) (4) Lupin provided: (b) (4) FDA's review of this amendment extended past the 30-month forfeiture date. FDA did not communicate additional deficiencies to Lupin, (b) (4) (b) (4) [14], until March 12, 2010 (after the 30-month forfeiture date of October 12, 2009). Based on these facts, we have determined that there was a change in requirements for approval related to (b) (4) which Lupin had been actively addressing and FDA was reviewing at the 30-month forfeiture date, and that this change was a cause of Lupin's failure to obtain tentative approval by the 30-month forfeiture date.

Labeling Review

As noted in the above timeline, two supplemental labeling changes were approved for the RLD between the date ANDA 065488 was received and the 30-month forfeiture date: S-023 was approved on October 25, 2007 for changes to the ADVERSE REACTIONS and CONTRAINDICATIONS sections and S-028 was approved on February 27, 2009 for changes to the PRECAUTIONS section. Lupin's last labeling amendment before the 30-month forfeiture date was received on June 26, 2009. FDA's review of this labeling amendment, dated June 30, 2010, extended past the 30-month forfeiture date and ultimately found several labeling deficiencies. Notably, none of the labeling deficiencies related to the three sections that had been the subject of RLD labeling updates during the pendency of the application (*i.e.*, the ADVERSE REACTIONS, CONTRAINDICATIONS, and PRECAUTIONS sections). Nonetheless, because FDA has determined that there was a change in the approval requirements for chemistry, which was a cause of Lupin's failure to obtain tentative approval by October 12, 2009, we need not determine whether there is a separate basis for non-forfeiture with respect to labeling.

III. CONCLUSION

Lupin's ANDA 065488 for Azithromycin for Oral Suspension USP, 100 mg/5 mL and 200 mg/5 mL, was submitted on April 12, 2007. The 30-month forfeiture date was October 12, 2009. Lupin's ANDA was not tentatively approved within this period. FDA concludes that there was a change to the requirements for approval with respect to chemistry (b) (4) (b) (4) which became official after Lupin's ANDA was submitted, as outlined above. FDA also concludes that the need to comply with the (b) (4) was a cause of Lupin's failure to obtain tentative approval by the forfeiture date. At the 30-month date of October 12, 2009, FDA was reviewing Lupin's June 19, 2009 chemistry amendment, which attempted to address, among

[14] *Id.*
[15] ANDA 065488 Chemistry Review #3 (Mar. 12, 2010).

[16] March 12, 2010 Quality Deficiency – Minor fax to Lupin.

other deficiencies, those related to the [redacted] (b) (4). Therefore, Lupin has not forfeited its eligibility for the 180-day exclusivity period described in section 505(j)(5)(B)(iv) of the FD&C Act for Azithromycin for Oral Suspension USP, 100 mg/5 mL and 200 mg/5 mL.

Martin H. Shimer Ii -S

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