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: May 15, 2015

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

TO: ANDA 200222

SUBJECT: 180-day Exclusivity for Linezolid Injection, 2 mg/mL, packaged in 600 mg/300 mL Single-use Flexible Plastic Containers

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

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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.

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 or 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 a 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, 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 activities 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

Teva Pharmaceuticals USA (Teva) submitted ANDA 200222 for Linezolid Injection, 2 mg/mL, packaged in 600 mg/300 mL Single-use Flexible Plastic Containers, on September 1, 2009. Teva qualified as a "first applicant" and therefore is eligible for 180-day exclusivity. Thirty months from the submission of the ANDA was March 1, 2012. As of that date, Teva had not received tentative approval of its ANDA. This ANDA was approved on June 27, 2012. The approval letter noted the failure to receive tentative approval within 30 months, but did not make a formal determination at that time regarding eligibility for 180-day generic drug exclusivity.[5]

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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] Letter to P. Erickson, Vice President, Regulatory Affairs, Teva Pharmaceuticals USA fr. K. Webber, Deputy Director, Office of Pharmaceutical Science (Jun. 27, 2012).

This memorandum addresses whether Teva has forfeited its eligibility for 180-day exclusivity due to its failure to obtain tentative approval by March 1, 2012. Teva 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 200222:

9/1/2009	ANDA submitted
12/8/2009	*Reference listed drug (RLD) labeling changes approved*
3/11/2010	Chemistry review #1 (deficient); chemistry deficiencies faxed
4/23/2010	Bioequivalence review (acceptable)
6/9/2010	Microbiology review (deficient)
6/14/2010	Chemistry amendment
6/15/2010	Microbiology deficiencies faxed
7/16/2010	*RLD labeling changes approved*
8/10/2010	Chemistry review #2 (deficient); chemistry deficiencies faxed
11/14/2011	Microbiology amendment
11/30/2011	Chemistry amendment
1/16/2012	Chemistry review #3 (acceptable)
1/19/2012	Microbiology review #2 (acceptable)
2/13/2012	*RLD labeling changes approved*
2/16/2012	Labeling review (deficient); labeling deficiencies faxed
2/27/2012	Labeling amendment
3/1/2012	**9/1/2009 plus 30 months**

The approval of Teva's ANDA was not delayed because of a citizen petition, such that the 30-month period would be extended past March 1, 2012, under section 505(q)(1)(G).

FDA Review of ANDA 200222

At the forfeiture date of March 1, 2012, chemistry, bioequivalence, and microbiology were acceptable. Labeling was not acceptable until May 31, 2012, approximately three months after the 30-month date. FDA has identified a change in the requirements for approval regarding labeling, as discussed below.

Labeling Review

Changes to the RLD labeling were approved three times after submission of the ANDA and prior to the forfeiture date.

- On December 8, 2009, FDA approved changes to the Clinical Pharmacology (Pharmacokinetics and Drug-Drug Interactions), Precautions (Drug Interactions), and Adverse Reactions (Postmarketing Experience) sections.[6]

- Labeling changes were again approved for the RLD on July 16, 2010.[7] These changes, which were proposed in FDA's supplement request letter dated May 14, 2010, updated the product label to include language in the Clinical Pharmacology (Pharmacodynamics) section regarding a QT study.

- A third labeling change to the RLD was approved on February 13, 2012.[8] This labeling change, which was submitted in response to FDA's supplement request letter dated September 19, 2011, provided for the addition of hypoglycemia to the Warnings section and the Adverse Reactions, Postmarketing Experience sub-section of the package insert.

FDA initially reviewed Teva's labeling on February 16, 2012, approximately two weeks prior to the 30-month forfeiture date, and identified a number of deficiencies.[9] One of the deficiencies asked Teva to revise its labeling to be in accord with the most recently approved labeling for the RLD. Teva submitted an amendment responding to FDA's deficiencies on February 27, 2012, three days before the 30-month forfeiture date of March 1, 2012.[10] FDA's review of the amendment extended past the 30-month forfeiture date, and on March 28, 2012, approximately one month after the 30-month date, FDA determined that Teva adequately addressed the deficiencies related to the updated RLD labeling. However, FDA noted a new deficiency, requesting Teva to add the statements "Linezolid is sensitive to light" and "Use immediately once removed from the overwrap."[11] After another review cycle, Teva's labeling was ultimately determined to be acceptable on May 31, 2012.[12]

III. CONCLUSION

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[6] Letter to N. Kirzecky, Associate Director, Worldwide Regulatory Strategy, Pfizer Global Pharmaceuticals fr. K. Laessig, Deputy Director, Division of Anti-Infective and Ophthalmology Products (Dec. 8, 2009).

[7] Letter to N. Kirzecky, Associate Director, Worldwide Regulatory Strategy, Pfizer Global Pharmaceuticals fr. S. Nambiar, Deputy Director for Safety, Division of Anti-infective and ophthalmology Products (Jul. 16, 2010).

[8] Letter to N. Kirzecky, Director, Worldwide Regulatory Strategy, Pharmacia and Upjohn Company, Inc., a subsidiary of Pfizer, Inc. fr. S. Nambiar, Deputy Director for Safety, Division of Anti-Infective Products (Feb. 13, 2012).

[9] Review of Professional Labeling #1, Division of Labeling and Program Support (Feb. 16, 2012).

[10] Letter to K. Webber, Acting Director, Office of Generic Drugs (OGD) fr. P. Erickson, Vice President, Regulatory Affairs, Teva Pharmaceuticals (Feb. 27, 2012).

[11] Review of Professional Labeling #2 (Mar. 28, 2012).

[12] Approval Summary #1, Review of Professional Labeling (May 31, 2012).

We conclude that there were changes to the requirements for approval with respect to labeling, as outlined above. We also find that these labeling changes were a cause of Teva's failure to obtain tentative approval by the forfeiture date. Teva submitted a labeling amendment prior to 30-month forfeiture date of March 1, 2012 to update its labeling to be in accord with recently approved RLD labeling changes and FDA's review of Teva's amendment extended past the forfeiture date.

Teva's ANDA 200222 was submitted on September 1, 2009, for Linezolid Injection, 2 mg/mL, packaged in 600 mg/300 mL Single-use Flexible Plastic Containers. The 30-month forfeiture date was March 1, 2012. Teva's ANDA was not tentatively approved within this period. The agency finds that Teva's failure to obtain tentative approval was caused by a change in or a review of the requirements for approval. We therefore conclude that Teva did not forfeit its eligibility for the 180-day exclusivity period described in section 505(j)(5)(B)(iv) of the Act for Linezolid Injection, 2 mg/mL, packaged in 600 mg/300 mL Single-use Flexible Plastic Containers.

Martin H. Shimer Ii -S

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