MEMORANDUM

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

DATE: June 10, 2014

FROM: Robert L. West, Deputy Director
Office of Generic Drugs (HFD-600)

SUBJECT: 180-day Exclusivity Forfeiture

TO: ANDA 079215 - Risedronate Sodium Tablets USP, 150 mg
Teva Pharmaceuticals USA

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 approval and will maintain eligibility for 180-day exclusivity. If tentative approval is not obtained within 30 months, eligibility for 180-day exclusivity is generally forfeited unless "the

[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, section 1133 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-144) extends this period to 40 months.

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, the issues precluding approval at the 30 month date must be causally connected to an approval requirement that FDA reviewed or changed while the ANDA was pending.

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 filed, 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 that were not caused by a change in or review of the requirements for approval. Thus, to avoid forfeiture, an applicant need only show that acceptability of one aspect of the ANDA (e.g., chemistry) was delayed due, at least in part, to 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 cause the failure to obtain approvals or tentative approvals within 30 months, 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

Teva Pharmaceuticals USA (Teva) filed ANDA 079215 for Risedronate Sodium Tablets USP, (b) (4), on September 7, 2007. An amendment was submitted for the 150 mg strength on August 12, 2008. Teva qualified as a "first applicant" on the 150 mg strength and therefore is eligible for 180-day exclusivity for the 150 mg strength product.[4] Thirty months from the submission of the amendment for the 150 mg strength was February 12, 2011. As of that date, Teva had not received tentative approval of its ANDA. This memorandum addresses whether Teva has forfeited its eligibility for 180-day exclusivity due to its failure to obtain tentative approval by February 12, 2011, for the 150 mg strength. Teva has not submitted any correspondence regarding its eligibility for 180-day exclusivity for this product.

The following is a timeline of certain key submissions and actions regarding ANDA 079215:

9/7/2007	ANDA filed for the (b) (4) strength
1/31/2008	Bioequivalence dissolution review (deficient)
2/1/2008	Bioequivalence dissolution deficiencies faxed
2/25/2008	Chemistry review #1 (deficient); chemistry deficiencies faxed
3/6/2008	Labeling review (deficient); labeling deficiencies faxed
8/12/2008	**Amendment for the 150 mg strength**
2/5/2009	Labeling review (deficient); labeling deficiencies faxed
5/1/2009	Bioequivalence amendment
5/29/2009	Bioequivalence review (acceptable)
6/12/2009	Bioequivalence, labeling, and chemistry amendments

[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] It is noted that Teva also qualified as a first applicant on the (b) (4) trength. However, eligibility for 180-day exclusivity for that strength was forfeited by Teva under section 505(j)(5)(D)(i)(II) when it withdrew the (b) (4) strength from ANDA 079215 on December 3, 2009.

7/7/2009	Bioequivalence review (acceptable)
9/25/2009	Chemistry review #2 (deficient); chemistry deficiencies faxed
12/4/2009	Amendment to withdraw (b)(4) trength
12/24/2009	Chemistry amendment
2/5/2010	Chemistry review #3 (deficient)
2/9/2010	Chemistry deficiencies faxed
4/21/2010	Labeling review (deficient); labeling deficiencies faxed
5/20/2010	Chemistry amendment
9/14/2010	Labeling amendment
11/22/2010	Chemistry review #4 (acceptable)
1/12/2011	Labeling review (deficient); labeling deficiencies faxed
1/18/2011	Labeling amendment
1/20/2011	Labeling review (acceptable)
2/2/2011	Labeling amendment
2/7/2011	Labeling review (deficient); labeling deficiencies faxed
2/8/2011	Labeling amendment
2/11/2011	Labeling review (acceptable)
2/12/2011	***8/12/2008 plus 30 months (150 mg strength)***
8/17/2011	Tentative approval

Bioequivalence was determined to be acceptable on July 7, 2009. Chemistry was acceptable on November 22, 2010. It has been determined from agency records that the firm's inspectional status was acceptable prior to and on the 30-month forfeiture date of February 12, 2011.

Changes to the reference listed drug (RLD) labeling were approved three times prior to the 30-month forfeiture date.

- On July 23, 2009, FDA approved labeling revisions to the RLD in the Use in Specific Populations section, Pediatric Use subsection.[5] Revisions were also approved to the Warning and Precautions section, Use in Specific Populations section, Pregnancy, Renal Impairment, and Hepatic Impairment subsections, and the Nonclinical Toxicology section.

- Labeling changes were again approved for the RLD on December 31, 2009.[6] These changes included class labeling changes to the Contraindications and Warnings and Precautions sections of the Highlights and Full Prescribing Information of Physician Labeling. Patient labeling was also updated to reflect the changes to the Physician Labeling.

[5] Letter to T. Demuth, U.S. Regulatory Affairs, Procter & Gamble Pharmaceuticals, Inc. fr. S. Monroe, Director, Division of Reproductive and Urologic Products (Jul. 23, 2009).

[6] Letter to G. Galletta, U.S. Regulatory Affairs, Procter & Gamble Pharmaceuticals, Inc. fr. S. Monroe, Director, Division of Reproductive and Urologic Products (Dec. 31, 2009).

- A third labeling change to the RLD was approved on January 25, 2011, approximately 2.5 weeks prior to the 30-month forfeiture date.[7] This final labeling change provided for revisions to the Indications and Usage and Warnings and Precautions sections, and a proposed risk evaluation and mitigation strategy (REMS).

FDA reviewed Teva's labeling and initially found Teva's labeling acceptable on January 20, 2011. As noted above, on January 25, 2011, changes to the RLD labeling were approved. Teva submitted a labeling amendment on February 2, 2011, for updated labeling in accord with the recently approved RLD labeling.[8] FDA reviewed Teva's amendment and on February 7, 2011, issued a deficiency letter asking Teva to provide its REMS plan.[9] Teva submitted an amendment on February 8, 2011.[10] FDA reviewed Teva's amendment and determined labeling to be acceptable on February 11, 2011, one day prior to the 30-month forfeiture date.[11] Upon review of the record, FDA has not identified any change in or review of the requirements for approval of Teva's ANDA that caused the applicant's failure to obtain tentative approval by the 30-month forfeiture date.

We note that although no individual disciplines were outstanding at the 30-month forfeiture date, FDA had not completed its final review of the ANDA by that date. The decision to approve (or tentatively approve) an ANDA involves not only the disciplines' evaluations of their respective portions of the ANDA, but final review by Office of Generic Drugs management.[12] That final step did not take place by the 30-month forfeiture date, and was complete on August 17, 2011.[13] We also note that any claim that a company should not forfeit because of the possibility that FDA's delays caused the company's failure to obtain tentative approval by the 30-month forfeiture date is unavailing.[14] Under section 505(j)(D)(i)(IV) of the FD&C Act, exclusivity is forfeited "unless" there is a review of or change in the requirements that has delayed approval or tentative approval of the ANDA. The statute does not permit, let alone require, either FDA or an ANDA applicant to comb through the ANDA review records and decide whether, had the review been conducted more quickly, the application could have received tentative approval before the 30-month forfeiture date. Notably, section 1133 of FDASIA (referenced in note 2 above),

---

[7] Letter to M. Lamb, Senior Director, Regulatory Affairs, Warner Chilcott (US), LLC fr. A. Gassman, Deputy Director for Safety, Division of Reproductive and Urologic Products (Jan. 25, 2011).

[8] Letter to K. Webber, Acting Director, OGD fr. J. Zwicker, Senior Director, Regulatory Affairs, Teva Pharmaceuticals (Feb. 2, 2011).

[9] Labeling Comments to J. Zwicker, Teva Pharmaceuticals USA fr. R. Wu, OGD (Feb. 7, 2011).

[10] Letter to K. Webber, Acting Director, OGD fr. J. Zwicker, Senior Director, Regulatory Affairs, Teva Pharmaceuticals (Feb. 8, 2011).

[11] Tentative Approval Summary, Review of Professional Labeling (Feb. 11, 2011).

[12] See, e.g., CDER Office of Pharmaceutical Science Internal Qulaity Procedure, Document No. 4000-LPS-041 "Creating and Processing of an ANDA Approval or Tentative Approval Package."

[13] *Routing Sheet*, ANDA 079215 (Aug. 17, 2011).

[14] As noted above, Teva has submitted no correspondence regarding its eligibility for 180-day exclusivity.

which, among other things, extended the 30-month forfeiture period to 40 months for certain ANDAs, reflects Congress's understanding both that the length of time that it takes FDA to review an ANDA might contribute to a sponsor's failure to obtain tentative approval by the 30-month forfeiture date, and that in such instances forfeiture nonetheless may occur.[15]

III. CONCLUSION

Teva's ANDA 079215 was received on August 12, 2008 for Risedronate Sodium Tablets, 150 mg. The 30-month forfeiture date was February 12, 2011 for the 150 mg strength but Teva did not receive tentative approval until August 17, 2011; therefore, Teva's ANDA was not tentatively approved within 30 months. The agency finds that Teva's failure to obtain tentative approval was not caused by a change in or a review of the requirements for approval. We therefore conclude that Teva forfeited its eligibility for the 180-day exclusivity period described in section 505(j)(5)(B)(iv) of the Act for Risedronate Sodium Tablets, 150 mg.

[15] See also H. REP. NO. 112-495, at 37 (May 25, 2012) (commenting on the proposed extension of the 30-month period in House version of bill to 45 months, noting that "[e]xcept in certain circumstances, if FDA does not grant tentative approval within 30 months of the filing of the generic drug application, the generic company forfeits the 180-day period. The provision would temporarily increase that tentative approval time to 45 months. (The current average time for FDA to approve a generic drug application is 31 months.) This 45-month period would be gradually phased back down to 30 months as the FDA eliminates the backlog of pending generic application pursuant to the generic drug user fee agreement."); see also *Generic Drug User Fee Act Program Performance Goals and Procedures*, at 4 (Jan. 12, 2012) (agency user-fee commitment letter providing that "FDA will strive to review and act on all ANDAs that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted within 30 months of submission to avoid causing first applicants to inadvertently forfeit 180-day exclusivity eligibility under 21 U.S.C. § 355(j)(5)(D)(i)(IV)."), available at http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm337385.htm.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA L DOWNS
06/10/2014

ROBERT L WEST
06/10/2014
Deputy Director, Office of Generic Drugs