TEVA PARENTERAL MEDICINES

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**BY VIA FEDERAL EXPRESS**

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October 16, 2007

**RE: OGD #07-1254: GENERIC DRUG APPLICATIONS FOR ACARBOSE TABLETS**

Dear Dr. Buehler:

This letter is in reference to your September 26, 2007 request for comments regarding various legal and regulatory issues pertaining to generic drug applications for Acarbose tablets (the "Request"). Teva Parenteral Medicines, Inc. ("Teva") appreciates the opportunity to be heard on these matters, and this letter serves as a statement of our views with respect to the issues raised in your Request.

Based on the facts set forth in the Request, the first applicant for generic Acarbose tablets appears to have forfeited its eligibility for 180-day exclusivity under section 505(j)(5)(D)(i)(IV) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act"), 21 U.S.C. § 355(j)(5)(D)(i)(IV). As a result of that forfeiture, there is no barrier to the Agency's delisting of U.S. Patent No. 4,904,769 (the "'769 patent"). Nonetheless, Teva wishes to make three points clear at the outset of this response.

***First***, we do *not* believe that, under the apparent facts of this case, the first applicant for generic Acarbose tablets has forfeited its exclusivity under section 505(j)(5)(D)(i)(I) of the Act, 21 U.S.C. § 355(j)(5)(D)(i)(I). As set forth in our September 28, 2007 letter regarding 180-day exclusivity for generic granisetron hydrochloride injection (FDA Docket No. 2007N-0389), a first applicant's failure to commence commercial marketing within 30 months of submitting its exclusivity-qualifying paragraph IV certification is *not*, on its own, sufficient to trigger a forfeiture under the Act. Because our position on the issue is explained in our letter regarding generic granisetron hydrochloride injection, we will not reiterate those arguments here, and respectfully refer you to that docket for a complete statement of our views.

***Second***, we do *not* believe that, in circumstances other than those we understand to be presented here, an applicant's failure to obtain tentative approval within thirty months of submitting its exclusivity-qualifying paragraph IV certification is, on its own, sufficient to trigger a forfeiture under the Act. Instead, we believe that a first applicant remains eligible for 180-day exclusivity where (1) the applicant could not possibly have obtained a tentative approval, because it was not sued with the 45-day window set forth in 21 U.S.C. § 355(j)(5)(B)(iii) and there are no other patent barriers or exclusivities that

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would bar an immediate final approval, and (2) that first applicant has diligently pursued final approval and does not bear primary responsibility for its failure to obtain a timely final approval.

***Finally***, we do *not* believe that the reference to the withdrawal of patent information in section 505(j)(5)(D)(i)(I)(bb)(CC) of the Act abrogates the D.C. Circuit's holding that FDA may not "delist a patent upon the request of the NDA holder [where] the effect of delisting is to deprive the applicant of a period of marketing exclusivity." *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120, 125 (D.C. Cir. 2006). Instead, the reference to delisting in section 505(j)(5)(D)(i)(I)(bb)(CC) merely reflects the fact that delisting may result from a court order entered pursuant to section 505(j)(5)(c)(ii)(I) of the Act, which for the first time authorized ANDA applicants who are sued by the NDA holder to "assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted [to the Orange Book]." 21 U.S.C. § 355(j)(5)(c)(ii)(I).

Except where delisting would not deprive a first applicant of its exclusivity period, then, we believe that delisting thus is permissible *only* where a paragraph IV applicant files a counterclaim action seeking to compel the NDA holder or patentee to delist the patent information relating to the reference listed drug; the court overseeing such litigation enters an order requiring the NDA holder to delist each of the exclusivity-qualifying patents; and the NDA holder then requests that FDA withdraw the pertinent patent information from the Orange Book pursuant to the court's order. As FDA is well aware, that is not the case here, and but for the fact that the first applicant for generic Acarbose tablets appears to have forfeited its eligibility for exclusivity under section 505(j)(5)(D)(i)(IV) of the Act, FDA otherwise would be bound to reject Bayer's April 16, 2007 request to delist the '769 patent.

## ARGUMENT

### I. THE FIRST APPLICANT APPEARS TO HAVE FORFEITED ITS ELIGIBILITY FOR EXCLUSIVITY UNDER 21 U.S.C. § 355(J)(5)(D)(IV).

As amended by Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (the "MMA"), Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003), the Act now provides that "180-day exclusivity ... shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant." 21 U.S.C. § 505(j)(5)(D)(ii). The Act then identifies six such "forfeiture events," including:

> (IV) Failure to obtain tentative approval
>
> The first applicant fails to obtain tentative approval of the application within 30 months 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.

21 U.S.C. § 355(j)(5)(D)(i)(IV).

In this case, the Agency received the first applicant's exclusivity-qualifying paragraph IV certification on March 22, 2005. Request at 1. As of September 26, 2007--30 months and 4 days after the applicant's exclusivity-qualifying paragraph IV certification was received--FDA had neither awarded tentative approval to the first applicant's ANDA nor awarded that ANDA a final effective approval. *Id.* Teva is not aware of any post-submission "change in or a review of the requirements for approval," 21 U.S.C. § 355(j)(5)(D)(i)(IV), and the Agency's Request does not disclose that there has been any such change or review. Based on the facts known to Teva, the first applicant thus appears to have forfeited its eligibility for 180-day exclusivity under the plain terms of the statute. *Id.*

The apparent problem here, however, is that the first applicant may not have been eligible to receive a tentative approval in the first place. Consistent with FDA's longstanding regulations, the Act now defines "tentative approval" to mean:

> notification to an applicant ... that [its ANDA] meets the requirements of [21 U.S.C. § 355(j)(2)(A)], but cannot receive effective approval because the application does not meet the requirements of [21 U.S.C. § 355(j)(5)(B)], there is a period of exclusivity for the listed drug under [21 U.S.C. § 355(j)(5)(F) or 21 U.S.C. § 355a], or there is a 7-year period of [orphan drug] exclusivity for the listed drug under [21 U.S.C. § 527].

*Id.* § 505(j)(5)(B)(iv)(II)(dd)(AA).

In this case, there are no unexpired periods of exclusivity under 21 U.S.C. §§ 355(j)(5)(F), 355a, or 527 for the reference listed drug, Precose®, and there is thus no exclusivity-based barrier to the final effective approval of the first paragraph IV applicant's ANDA for generic Acarbose tablets. *See* United States Food and Drug Administration, *Electronic Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, *available at* http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm? Appl_No=020482&Product_No=001&table1=OB_Rx (last visited Oct. 11, 2007) ("There is no unexpired exclusivity for this product."). And because the NDA holder listed only one patent in the Orange Book and does not appear to have initiated a lawsuit against the first paragraph IV applicant with respect to that single patent in time to trigger a thirty-month stay, it appears that nothing in 21 U.S.C. § 355(j)(5)(B) bars the approval of the first applicant's ANDA.

In these circumstances—where the first applicant could not possibly have obtained tentative approval—a literal and unyielding application of this forfeiture trigger would be manifestly unjust and, indeed, irrational. Congress could not possibly have intended to punish first applicants simply for failing to achieve the impossible; that result would represent to the sort of paradigmatic absurdity that courts long have sought to avoid. *See, e.g.*, *Johnson v. United States*, 529 U.S. 694, 706 n.9 (2000) ("'Nothing is better settled, than that statutes should receive a sensible construction, such as will effectuate the legislative intention, and, if possible, so as to avoid an unjust or an absurd conclusion.'") (quoting *In re Chapman*, 166 U.S. 661, 667 (1897) (alteration omitted)).

But the mere fact that a literal application of this trigger would produce absurd results in certain cases hardly means there is no role for the trigger to play in all similar circumstances. When courts confront a statute that on its face would yield absurd results, they do not ignore the statute; they interpret it in a manner that would further Congress's intent. *See, e.g., Burns v. United States*, 501 U.S. 129, 137 (1991) ("[W]hen 'confronted with a statute which, if interpreted literally, produces an absurd, and perhaps unconstitutional result, our task is to give some alternative meaning to the statute that avoids this consequence.'") (quoting *Green v. Bock Laundry Machine Co.*, 490 U.S. 504, 527 (1989) (Scalia, J., concurring in the judgment) (internal alterations omitted)). Administrative agencies are no different. *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1068 (D.C. Cir. 1998) ("When the agency concludes that a literal reading of a statute would thwart the purposes of Congress, it may deviate ... from the statute ... to protect congressional intent.").

In this case, Congress' intent in promulgating the tentative-approval forfeiture trigger is obvious: it was to prevent first applicants from gumming up generic competition by failing diligently to pursue an approvable file. After all, the general impetus for the MMA's forfeiture provisions was to prevent exclusivity-eligible applicants from unduly delaying market entry to the detriment of consumers, *see generally Closing The Gaps In Hatch-Waxman, Assuring Greater Access To Affordable Pharmaceuticals: Hearing Before The Committee On Health, Education, Labor, And Pensions*, 107th Cong. (May 8, 2002), and FDA has always conditioned an award of tentative approval on an applicant's showing "that the drug meets the statutory standards for manufacturing and controls, labeling, and, where applicable, bioequivalence." 21 C.F.R. § 314.105(c), (d). And the terms of the trigger itself make clear that it is directed at dilatory applicants, by making an exception for cases where FDA changes or reviews "the requirements for approval ... after the date on which the application is filed," 21 U.S.C. § 355(j)(5)(D)(i)(IV)—that is, where the Agency, rather than the applicant, bears responsibility for the applicant's failure to obtain a timely approval.

To effectuate Congress's intent in these circumstances, then, we believe that this trigger can and should be applied where the first applicant bears primary responsibility for failing to gain an approvable file within thirty months of submitting its exclusivity-qualifying paragraph IV certification—even if the applicant was not technically eligible for tentative approval in the first instance.[1]

That appears to be the case here. As the Request makes clear, the Agency has not tentatively approved the first applicant's ANDA and it has not finally approved the applicant's ANDA. Teva is not aware of any post-submission "change in or a review of the requirements for approval," 21 U.S.C. § 355(j)(5)(D)(i)(IV), the Agency's Request does not disclose that there has been any such change or review, and given that there are no exclusivities or other similar barriers to immediate approval, the only apparent

[1] It is no answer that the failure-to-market trigger set forth in 21 U.S.C. § 355(j)(5)(D)(i)(I) obviates the need to apply the tentative-approval trigger in this manner in order to effectuate congressional intent. A discussion of this point is set forth in our granisetron hydrochloride letter (FDA Docket No. 2007N-0389).

explanation for the applicant's inability to secure final approval by this late date is that its file does not meet "the statutory standards for manufacturing and controls, labeling, and ... bioequivalence." 21 C.F.R. § 314.105(c). Provided that the first applicant bears primary responsibility for those deficiencies—and the Request gives no indication that that is not the case—the Agency thus should hold that the applicant has forfeited its eligibility for 180-day exclusivity under 21 U.S.C. § 355(j)(5)(D)(i)(IV).

## II. BECAUSE NO APPLICANT IS ELIGIBLE FOR 180-DAY EXCLUSIVITY, FDA MAY DELIST THE '769 PATENT.

As a consequence of the fact that the first applicant has forfeited its eligibility for exclusivity, there is no barrier to delisting the '769 patent from the Orange Book. As the D.C. Circuit's decision in the simvastatin case made clear, the "'precise question at issue' [in that case was] whether the FDA may delist a patent ... after a generic manufacturer has filed ... a paragraph IV certification *so that the effect of delisting is to deprive the applicant of a period of marketing exclusivity*." *Ranbaxy*, 469 F.3d at 125 (emphasis added). The D.C. Circuit resolved that question at *Chevron* step one, holding that FDA's acquiescence in a brand manufacturer's delisting request under those circumstances was inconsistent with the text of the Act, because it effectively "add[s] to the statutory requirements for exclusivity," *id.*; the structure of the Act, because it precludes "the generic manufacturer [from] initiat[ing] a period of marketing exclusivity," *id.*; and the policies of the Act, because it "diminishes the incentive for a manufacturer of generic drugs to challenge a patent listed in the Orange Book." *Id.* at 126.

It goes almost without saying that the above considerations do not apply once a first applicant has forfeited its eligibility for 180-day exclusivity. After all, where the first applicant is no longer eligible for exclusivity, delisting does not itself preclude the applicant from initiating its exclusivity period—the applicant's antecedent forfeiture does. Delisting does not meaningfully add to the requirements for exclusivity, since there is no exclusivity following a forfeiture. And delisting does not diminish the incentive for submitting a paragraph IV certification, because delisting is contingent on the occurrence of an antecedent forfeiture event, as set forth elsewhere in the statute. In these circumstances—where an applicant already has forfeited its exclusivity—we see no barrier to the Agency's acquiescence in a brand manufacturer's request to delist a patent.

That having been said, we wish to make clear that nothing in section 505(j)(5)(D)(i)(I)(bb)(CC) of the Act authorizes the Agency to delist patents where an applicant has submitted an exclusivity-qualifying paragraph IV certification and *remains* eligible for 180-day marketing exclusivity. To be sure, that subsection of the Act does suggest that listed patents can be "withdrawn by the [NDA] holder." 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(CC). But snippets of statutory text cannot be read in isolation; statutes must be read as a whole, and "[t]he plainness or ambiguity of statutory language is determined by reference [not only] to the language itself, [but to] the specific context in which that language is used, and the broader context of the statute as a whole." *Robinson v. Shell Oil Co.*, 519 U.S. 337, 341 (1997).

In this case, it is clear that this provision of the statute is linked to section 505(j)(5)(c)(ii)(I) of the Act. That provision now provides—for the first time—that ANDA applicants who are sued by the NDA holder may "assert a counterclaim seeking an order requiring the holder to correct or delete [listed] patent information." 21 U.S.C. § 355(j)(5)(c)(ii)(I). Until that provision of the Act was added by the MMA, applicants had few means to secure the removal of an improperly listed patent. FDA played only a ministerial role in maintaining the Orange Book, and an applicant's only mechanism for forcing the removal of an illegitimately listed patent was an independent antitrust action. *See, e.g., aaiPharma Inc. v. Thompson*, 296 F.3d 227, 236, 243 n.8 (4th Cir. 2002); *Andrx Pharm., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1373-74 (Fed. Cir. 2002); *In re Buspirone Patent Litig.*, 185 F. Supp. 2d 363 (S.D.N.Y. 2002)). With the addition of section 505(j)(5)(c)(ii)(I) to the statute, then, paragraph IV applicants now can seek relief *within* the Hatch-Waxman framework, and if successful, can obtain a judicial "order requiring the [NDA] holder to correct or delete the patent" from the Orange Book. 21 U.S.C. § 355(j)(5)(c)(ii)(I).

Interpreted in light of that statutory context, the clear purpose of section 505(j)(5)(D)(i)(I)(bb)(CC) of the Act is *not* to enable brand manufacturers to delist patents at will and thereby deprive paragraph IV applicants of their eligibility for exclusivity. Instead, it is to ensure that a paragraph IV applicant who secures a judicial "order requiring the [NDA] holder to correct or delete the patent" from the Orange Book does not "park" its exclusivity after the NDA holder complies with that order by delisting the patent information from the Orange Book.

In this case, of course, Bayer's request to delist the '769 patent was not prompted by a judicial order entered pursuant to section 505(j)(5)(c)(ii)(I) of the Act, and but for the fact that the first applicant for generic Acarbose tablets appears to have forfeited its cligibility for exclusivity under section 505(j)(5)(D)(i)(IV) of the Act, FDA otherwise would be bound to reject Bayer's April 16, 2007 request to delist the '769 patent.

**Conclusion**

For the foregoing reasons, the Agency should hold that the first applicant has forfeited its eligibility for 180-day exclusivity under 21 U.S.C. § 355(j)(5)(D)(i)(IV), and thus may permit Bayer to delist the '769 patent from the Orange Book because doing so would not deprive any applicant of its eligibility for exclusivity. In the event you have any questions or require additional information regarding this matter, please contact me by telephone (215-293-6403) or fax (215-293-6499).

Sincerely,
Teva Parenteral Medicines, Inc.

Marc A. Goshko

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