DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

Marc A. Goshko
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RE: Docket No. 2007N-0389
ANDA 77-165: Granisetron Hydrochloride Injection, 1 mg/mL

Dear Mr. Goshko:

This is in response to your letter dated September 28, 2007 (Teva Letter), in which you assert that abbreviated new drug application (ANDA) 77-165 is entitled to 180-day generic drug exclusivity. This ANDA is for Granisetron Hydrochloride Injection in 1 milligram/1 milliLiter single dose vials. It was submitted by SICOR Pharmaceuticals, Inc., now Teva Parenteral Medicines, Inc. (Teva), and was received for filing on June 1, 2004. The reference listed drug for this ANDA is Kytril Injection (Kytril), the new drug application (NDA) for which is held by Hoffman-LaRoche, Inc. As explained in this letter, it is the Agency's position that Teva is entitled to 180-day exclusivity with respect to ANDA 77-165. The Teva ANDA was approved on December 31, 2007, and Teva was granted 180-day exclusivity at that time.

Teva's ANDA 77-165 was the first ANDA for this drug product containing a paragraph IV certification to a listed patent for Kytril. Because this ANDA was submitted after December 8, 2003, the 180-day exclusivity for ANDAs referencing Kytril is governed by section 505(j)(5)(D) of the Federal Food, Drug, and Cosmetic Act (FFDCA or Act), as amended by the provisions of Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (the MMA), Pub. L. 108-173, 117 Stat. 2066 (Dec. 8, 2003). *See* section 1102(b) of the MMA. FDA has not promulgated regulations implementing these new statutory provisions; until it does so, it will regulate directly from the statute in determining whether ANDA applicants are entitled to exclusivity.[1]

[1] It is FDA's practice to make decisions on eligibility for 180-day exclusivity only in the context of specific ANDAs that are otherwise eligible for approval. This approach is based on the multiple factors that may influence eligibility for exclusivity or forfeiture up to the time an application is ready for approval (e.g., patent expiration, patent delisting, failure to obtain a tentative approval within 30 months, withdrawal of ANDA) and could thus render a premature eligibility determination incorrect. When the agency must make an approval decision for an ANDA, it will inform the applicant that it is either 1) a first applicant and entitled to exclusivity, 2) a first applicant that has forfeited its exclusivity, or 3) eligible only for a tentative approval because one or more first applicants are eligible for 180-day exclusivity. It is possible that an ANDA applicant could be informed upon approval that it is a "first applicant" eligible for 180-day exclusivity pursuant to section 505(j)(5)(B)(iv), but later forfeit that exclusivity under section 505(j)(5)(D). FDA will consider whether there has been a forfeiture of 180-day exclusivity when approval of a subsequent ANDA may be blocked by a first applicant's exclusivity.

The MMA established a new set of forfeiture events under which an applicant previously eligible for 180-day exclusivity could lose that eligibility. These provisions are quite complex and, because of the value of 180-day exclusivity, are of substantial interest to regulated industry. In recognition of this interest, and to obtain the benefit of comment from interested parties on the interpretation and application of the new provisions in specific factual settings, we are establishing public dockets to receive comments on certain complex MMA issues. The Teva Letter raised issues regarding forfeiture of 180-day exclusivity that, while product specific, also could have a significant effect on exclusivity for other products. We established a docket on October 11, 2007, to permit public comment on the issues raised by the Teva Letter. We received comments from four interested parties. Three of these (Sun Pharmaceuticals, Ltd., Ranbaxy, Inc., and Baxter Healthcare Corporation (Baxter)[2]) agreed that Teva was eligible for 180-day exclusivity; one (Olsson Frank Weeda (OFW)) believed that Teva has forfeited its exclusivity.

In considering the applicability of the MMA forfeiture and exclusivity provisions to the granisetron ANDAs, we have considered the views of Teva and the other parties submitting comments.

I. STATUTORY AND REGULATORY BACKGROUND

Under the 1984 Hatch-Waxman Amendments (Hatch-Waxman Amendments) to the Act, an NDA applicant must submit information for each patent that claims the drug or method of using the drug that is the subject of the NDA and for which "a claim of patent infringement could reasonably be asserted if a person not licensed by the patent owner engaged in the manufacture, use, or sale of the drug." Sections 505(b)(1) and (c)(2). FDA publishes this patent information in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

An applicant must include in its ANDA one of the following certifications with respect to each listed patent for the listed drug it references:

> (I) that such patent information has not been filed (a paragraph I certification),
> (II) that such patent has expired (a paragraph II certification),
> (III) of the date on which such patent will expire (a paragraph III certification), or
> (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (a paragraph IV certification).

Section 505(j)(2)(A)(vii).[3] See also 21 CFR 314.94(a)(12)(i)(A). An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and the patent owner notice of its patent certification, including a description of the legal and factual basis for its

[2] Baxter acknowledges that it shares Teva's interest in this matter because it is the first filer with respect to a different granisetron injection product, and has the identical risk of forfeiture as described in the Teva Letter. The other parties who submitted comments did not identify what, if any, interest they have in the outcome.

[3] The Act provides only one circumstance in which an ANDA applicant need not certify to a listed patent: "if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection," the applicant can submit "a statement that the method of use patent does not claim such a use" (a section viii statement). Section 505(j)(2)(A)(viii); see also 21 CFR 314.94(a)(12)(iv).

assertion that the patent is invalid or not infringed. Section 505(j)(2)(B). Should the NDA holder or patent owner initiate a patent infringement action against the ANDA applicant within 45 days of receiving the required notice, approval of the ANDA will be stayed for 30 months from the date of the notice or such shorter or longer time as the court might order. Section 505(j)(5)(B)(iii).

The MMA exclusivity provisions, like those in the Hatch-Waxman Amendments, provide the first applicant(s) to submit a paragraph IV certification challenging a patent - and thus undertake the risk of litigation - an incentive in the form of the opportunity to be the only generic drug manufacturer to compete with the innovator for a 180-day period. The requirements for obtaining and retaining this 180-day exclusivity period are described at sections 505(j)(5)(B)(iv) and 505(j)(5)(D) of the Act.

Section 505(j)(5)(D) describes a significant new feature of 180-day exclusivity under the MMA in the form of a set of conditions under which an ANDA applicant loses - or forfeits - eligibility for 180-day exclusivity. Only one of these possible forfeiture events is at issue in this matter, i.e., the "failure to market" event, which appears in the Act as follows:

> (I) FAILURE TO MARKET .--The first applicant fails to market the drug by the later of--
>
> (aa) the earlier of the date that is--
>
> (AA) 75 days after the date on which the approval of the application of the first applicant is made effective under subparagraph (B)(iii); or
>
> (BB) 30 months after the date of submission of the application of the first applicant; or
>
> (bb) with respect to the first applicant or any other applicant (which other applicant has received tentative approval), the date that is 75 days after the date as of which, as to each of the patents with respect to which the first applicant submitted and lawfully maintained a certification qualifying the first applicant for the 180-day exclusivity period under subparagraph (B)(iv), at least 1 of the following has occurred:
>
> (AA) In an infringement action brought against that applicant with respect to the patent or in a declaratory judgment action brought by that applicant with respect to the patent, a court enters a final decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the patent is invalid or not infringed.
>
> (BB) In an infringement action or a declaratory judgment action described in subitem (AA), a court signs a settlement order or consent decree that enters a final judgment that includes a finding that the patent is invalid or not infringed.
>
> (CC) The patent information submitted under subsection (b) or (c) is withdrawn by the holder of the application approved under subsection (b).

Section 505(j)(5)(D)(i)(I).

II. FACTUAL BACKGROUND

Teva is eligible for 180-day exclusivity for granisetron hydrochloride injection 1 mg/mL, because it was a "first applicant," as described in section 505(j)(5)(D)(iv)(II)(bb). Teva's ANDA was received for filing on June 1, 2004. At that time it contained a paragraph III certification to U.S. Patent No. 4,886,808 ('808 patent); a section viii statement to a method-of-use patent, U.S. Patent No. 5,953,340 ('340 patent); and a paragraph IV certification to U.S. Patent No. 6,294,548 patent ('548 patent). Teva provided notice of the certification to the NDA holder and patent owner as required. The paragraph IV certification to the '548 patent qualified Teva as the sole first applicant eligible for 180-day exclusivity.

There are two features of Teva's patent certifications that, operating together, raise the question of Teva's possible forfeiture of its 180-day exclusivity. The first is that ANDA 77-165 was received for filing on June 1, 2004, which is almost 43 months before the December 29, 2007 expiration date of the '808 patent. The paragraph III certification to the '808 patent meant that FDA could not approve the ANDA before the date the '808 patent was due to expire, regardless of Teva's success in its paragraph IV certification challenge to the '548 patent. The second factor is that neither Teva nor any subsequent applicant was sued as a result of its paragraph IV certification to the '548 patent, or has yet brought a declaratory judgment action regarding that patent, and the '548 patent remains listed in the Orange Book.

III. DISCUSSION

Application of the "failure to market" forfeiture provisions in section 505(j)(5)(D)(i)(I) requires a series of earlier-of/later-of analyses. The statute directs that a forfeiture event occurs when the first applicant fails to market the drug by the later of two dates. One of these dates is calculated under subpart (aa) by determining the earlier of a date that is either, under subitem (AA), 75 days after the first applicant's ANDA is approved or, under subitem (BB), 30 months after the date of submission of the first applicant's ANDA.[4] Teva's ANDA was approved on December 31, 2007, so the 75-day period under (AA) would expire on March 15, 2008. The relevant date under subitem (BB) is 30 months after the date of submission of Teva's ANDA, or December 1, 2006. Because the date under (BB) is earlier than the March 15, 2008 date under (AA), the "30 month from submission date" of December 1, 2006, is the applicable date under the subpart (aa) analysis.

The statute then directs that FDA look to the "later of" the December 1, 2006 date or a date under subpart (bb) of section 505(j)(5)(D)(i)(I). Subpart (bb) identifies three events that, if occurring as to a first applicant or any other applicant, could start a 75-day period leading to forfeiture. These events include, very generally, when (a) a court enters a final decision that the patent is

[4] Section 505(j)(5)(D)(i)(I)(aa)(BB) states that the 30 month period should be calculated from the date of "the submission of the application of the first applicant." In applying the MMA 180-day exclusivity provisions, FDA will consider the date an ANDA containing a paragraph IV certification is submitted to be the date the agency considers the ANDA to have been "received" pursuant to 21 CFR 314.101(b). Both this regulation and the definition of "first applicant" at section 505(j)(5)(B)(iv)(II)(bb) of the Act require that the ANDA containing the paragraph IV certification be substantially complete, meaning it is sufficiently complete to permit a substantive review. When an ANDA containing a paragraph IV certification is determined, upon review, to have been substantially complete as of the day it was submitted to FDA, it will be considered to be received as of the date it was submitted (i.e., date-stamped by the appropriate FDA mail-room).

invalid or not infringed, (b) a court signs a settlement order or consent decree entering final judgment that includes a finding that the patent is invalid or not infringed, or (c) the patent information for the listed drug is withdrawn by the NDA holder. To date, no action for infringement of the '548 patent has been brought against Teva or any subsequent applicant, nor has any granisetron ANDA applicant brought a declaratory judgment action regarding infringement of the '548 patent in an attempt to gain patent certainty and initiate the 75-day period leading to forfeiture. Therefore, no court has entered a final judgment of invalidity or non-infringement, and no court has signed a settlement order or consent decree entering final judgment of invalidity or non-infringement. The holder of the reference listed drug also has not requested that the patent be withdrawn from the Orange Book. Thus, none of the events contemplated in the statute's "later of" construct has occurred. Moreover, there is no pending litigation that could lead to a final judgment or decision that would start the 75-day forfeiture period.

The question posed by this set of circumstances is whether, when no "later" event as identified under subpart (bb) has occurred at the time the agency makes its exclusivity determination, forfeiture of 180-day exclusivity occurs when the applicant fails to market the drug by the applicable date under subpart (aa).[5]

We find that under the plain language of the statute, 180-day exclusivity is not forfeited for failure to market when an event under subpart (aa) has occurred, but - as in this case - none of the events in subpart (bb) has occurred. The "failure to market" provision results in forfeiture when there are two dates on the basis of which FDA may identify the "later" event as described in section 505(j)(5)(D)(i)(I). The provision does not effect a forfeiture when an event under subpart (aa) has occurred, but no event under subpart (bb) has yet occurred.

This is not a situation in which it would be impossible for a later event to occur. Although at the time FDA made its exclusivity decision, there was no litigation regarding the '548 patent pending that could result in a forfeiture event under subitem (AA) or (BB) of subpart (bb), there was nevertheless the possibility that either an additional ANDA applicant would be sued as a result of a paragraph IV certification to the patent or one of the applicants would bring a declaratory judgment action against the NDA holder or patent owner. Either of these actions could result in a forfeiture event. In addition, the patent could be withdrawn by the NDA holder, resulting in a forfeiture event under subitem (CC). Because at least one of the events described in subpart (bb) could still have occurred and, if it did, would necessarily occur "later" than December 1, 2006, Teva did not forfeit its exclusivity.[6]

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[5] We note that in this matter, there is no allegation that Teva has "parked" its exclusivity (where it would serve as an effective barrier against approval of any subsequent ANDAs referencing the same listed drug) as a result of settlement of patent litigation with the NDA holder and/or patent owner. Teva's failure to obtain final approval and trigger its exclusivity with commercial marketing before December 31, 2007, as anticipated under section 505(j)(5)(B)(iv)(I), appears to have been a function solely of its paragraph III certification to a patent that expired December 29, 2007, more than three years after the ANDA was submitted.

[6] Inherent in the structure of the "failure to market" forfeiture provisions is the possibility that a first applicant would be able to enter into a settlement agreement with the NDA holder or patent owner in which a court does not enter a final judgment of invalidity or non-infringement (i.e., without a forfeiture event under subpart (bb) occurring), and that subsequent applicants would be unable to initiate a forfeiture with a declaratory judgment action. This inability to force a forfeiture of 180-day exclusivity could result in delays in the approval of otherwise approvable ANDAs owned by applicants that would market their generic drugs if they could but obtain approval. This potential scenario is not one for which the statute currently provides a remedy.

The comment submitted by OFW disagrees with this interpretation of the "failure to market" forfeiture provision. It asserts that FDA should base its forfeiture decision on the state of events as of a specific date, without regard to the possibility that certain relevant events may occur in the future. OFW argues that, if on the date when a subsequent ANDA would be eligible for final approval but for the first applicant's 180-day exclusivity, "there is no ***actually*** pending patent litigation, no final court decision that the patent is invalid or not infringed, and the patent remains in the Orange Book," then subpart (bb) should be "disregarded completely" and only the events in subpart (aa) should be considered. OFW Letter, at 3.

The comments from OFW apparently concede that, if there is patent litigation pending, it would be premature for FDA to make a forfeiture decision solely on the grounds that a subsequent ANDA would be eligible for final approval but for 180-day exclusivity. When patent litigation is pending, OFW notes, the Agency cannot make a forfeiture determination until the litigation is resolved and the agency can ascertain whether a forfeiture event in subpart (bb) has occurred.

Whatever appeal OFW's proposal might have for a hypothetical exclusivity forfeiture program, it is not consistent with the statutory language in section 505(j)(5)(D)(i)(I). The MMA could have employed the approach suggested by OFW, in which the agency determines - at the time a subsequent ANDA is ready for approval - whether any of certain events have occurred. It did not. Instead, the scheme Congress adopted expressly directs that, even if an earlier event has occurred, the Agency await the occurrence of one of certain "later" events before finding a forfeiture of exclusivity. Section 505(j)(5)(D)(i)(I). By including the declaratory judgment mechanism as a means for initiating a forfeiture, Congress may have intended to provide subsequent applicants with an effective tool for clearing the path to final ANDA approval. As OFW notes, whether declaratory judgments will prove to be an effective means for establishing patent certainty - and forcing forfeiture of exclusivity - remains to be seen. Nevertheless, the Agency may not read out of the statute the forfeiture provisions that rely on an ANDA applicant's success in patent litigation.[7]

Although the structure of the 180-day exclusivity and forfeiture provisions may give rise to concerns about parking of exclusivity, and the premature review of ANDAs, neither of these is a factor in the current granisetron matter. Teva has not parked its exclusivity (indeed, it actively pursued final approval and initiated commercial marketing promptly upon approval), and it submitted its ANDA only three and a half years before the expiration of the patent to which it filed a paragraph III certification. This timing is entirely reasonable.

[7] The OFW comment raises a point that has been a source of some concern to the Agency irrespective of the forfeiture provisions, and that is that the "race" to earn 180-day exclusivity by submitting the first ANDA to challenge a patent may result in the submission of ANDAs that may also contain one or more paragraph III certifications to patents that do not expire until well into the future and that will preclude approval of the application for many years. We have received ANDAs for which, based on the patent expiration dates and corresponding certifications, the sponsor has no intention to obtain approval and market the generic drug for 12 years or more. OFW is correct when it notes that this practice may result in agency resources being committed to unnecessary reviews. There is the very real possibility that events will occur in the years between initial review and patent expiration such that the sponsor ultimately will decide not to obtain approval of and market the generic drug product. See OFW Letter, at 7-8. Furthermore, should the sponsor seek final approval after the lapse of many years from initial review and tentative approval, the ANDA would almost certainly have to be reviewed a second time before a final approval could issue.

IV. CONCLUSION

For the reasons discussed above, the Agency has determined that Teva is entitled to 180-day exclusivity with respect to ANDA 77-165.

If you have any questions regarding this correspondence, please contact Cecelia M. Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 240-276-9310.

Sincerely yours,

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: Docket No. 2007N-0389
Winston & Strawn LLP, Counsel for Sun Pharmaceuticals, Ltd.
David Adams, Counsel for Ranbaxy, Inc.
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/s/

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