TEVA PARENTERAL MEDICINES

BY VIA FED EX

Gary J. Buehler
Director, Office of Generic Drugs
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
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September 28, 2007

RE: ANDA NO. 77-165: GRANISETRON HYDROCHLORIDE INJECTION, 1mg/mL 1mL VIALS (EQUIVALENT TO 1mg/mL KYTRIL®)

Dear Dr. Buehler:

We are writing to request that FDA confirm that Teva Parenteral Medicines, Inc. (formerly SICOR Pharmaceuticals, Inc.) ("Teva") is entitled to 180-day exclusivity for its generic granisetron hydrochloride injection drug product ("granisetron") that is the subject of the above application.

As set forth below, the plain language and structure of the Hatch-Waxman Act compel the conclusion that Teva is entitled to 180-day exclusivity because Teva is the first applicant that submitted a substantially complete paragraph IV ANDA for the generic granisetron drug product referenced above. The fact that Teva has not yet marketed its generic granisetron does not alter that conclusion. Teva's exclusivity has not been forfeited under the failure-to-market provision set forth in 21 U.S.C. § 355(j)(5)(D)(i)(I)(aa), because there is a continuing possibility of ANDA-based patent litigation that could result in a "later" forfeiture event under 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb). This plain-language interpretation of the Act is especially appropriate in this case, where Teva's failure to commence commercial marketing is based solely on the existence of a blocking patent—and not on its own lack of diligence in securing final marketing approval from the Agency.

Given the pharmaceutical industry's strong interest in FDA's interpretation of the forfeiture provisions contained in 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), Teva hereby authorizes the Agency to share this letter with, and solicit comments from, those pharmaceutical manufacturers who will be impacted directly by the Agency's resolution of the issue presented here.

Relevant Background

Granisetron is an antinauseant and antiemetic agent. Injectable granisetron drug products are currently marketed by Hoffmann-La Roche Inc. ("Roche") under the brand name Kytril®. Roche has listed three patents as claiming injectable granisetron in the

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Orange Book: U.S. Patent No. 4,886,808 (the "'808 patent"), which is scheduled to expire on December 29, 2007; U.S. Patent No. 5,952,340 (the "'340 patent"), which is scheduled to expire on September 14, 2016; and U.S. Patent No. 6,294,548 (the "'548 patent"), which is scheduled to expire on May 4, 2019. *See Approved Drug Products With Therapeutic Equivalence Evaluations* ADA-66 (27th ed. 2007).

On May 28, 2004, Teva submitted ANDA No. 77-165 seeking approval to market a generic injectable granisetron drug product in 1mg/mL single-dose vials. Teva's ANDA contained a paragraph III certification to the earliest-expiring granisetron patent (the '808 patent), a section 505(j)(2)(a)(viii) method-of-use certification to the next expiring patent (the '340 patent), and a paragraph IV certification to the latest-expiring patent (the '548 patent). FDA received Teva's ANDA on June 1, 2004. *See* Letter from C. Bina to R. Lowe, July 30, 2004 at 1 (attached as Exh. 1). As the first substantially complete granisetron ANDA containing a paragraph IV certification to one or more of the patents listed as claiming injectable granisetron, Teva's ANDA laid the groundwork for generic competition on this drug to commence ***more than a decade*** before the '548 patent's expiration in May 2019.

Despite the fact that Teva committed a technical act of patent infringement by submitting its paragraph IV ANDA to the Agency, *see Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990); 35 U.S.C. § 271(e)(2)(A), Roche has never initiated a patent infringement action against Teva (or any subsequent applicant for generic granisetron drug products). Nonetheless, Teva (like any subsequent paragraph IV applicant for generic granisetron) remains subject to the possibility of a patent infringement suit by Roche, and it retains the statutory right to file a declaratory judgment action seeking patent certainty under 21 U.S.C. § 355(j)(5)(C) and 35 U.S.C § 271(e)(5). That is so because the only limitation on ANDA-based patent claims is the doctrine of laches, which presumptively—but not invariably—applies after six years. *See A.C. Aukerman Co. v. R.L. Chaides Const. Co.*, 960 F.2d 1020, 1035 (Fed. Cir. 1992) (*en banc*).[1] The ongoing possibility of such litigation in turn gives rise to a continuing possibility of a court decision holding that the Kytril® '548 patent is invalid or not infringed, a settlement approval or consent decree that includes a finding that such patent is invalid or not infringed, or, if such litigation produces a counterclaim seeking to compel Roche to delist the Kytril® '548 patent under 21 U.S.C. § 355(j)(5)(C)(ii)(I), a court order requiring Roche to do so. *See* 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb).

On August 16, 2005, FDA tentatively approved Teva's ANDA. *See* Letter from G. Buehler to R. Lowe, Aug. 16, 2005, at 1 (attached as Exhibit 2). However, FDA has not granted final approval to the ANDA—and Teva thus has not begun to market generic

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[1] Though 35 U.S.C. § 286 similarly imposes a six-year statutory limitation on a patentee's ability to recover monetary damages for infringement, it does not otherwise bar suits seeking injunctive or declaratory relief. *See Teva Pharms. USA, Inc. v. Novartis Pharms. Corp.* ["*Famvir*"], 482 F.3d 1330, 1341 (Fed. Cir. 2007) (citing *A.C. Aukerman*, 960 F.2d at 1030, for the proposition "that § 286 is 'not a statute of limitations in the sense of barring a suit for infringement' but rather a 'limit to recovery to damages for infringing acts committed within six years of the date of the filing of the infringement action'") (internal ellipsis omitted)).

granisetron—because Teva's ANDA included a paragraph III certification to the '808 patent. *See id.* at 1, 2; *see also* 21 U.S.C. § 355(j)(5)(B)(ii) (precluding FDA from granting final approval to an ANDA that contains a paragraph III certification until "the date certified under [paragraph] (III)"). Teva expects that FDA will grant prompt final approval to its ANDA when the '808 patent expires on December 29, 2007, and intends to begin immediate commercial marketing of its generic granisetron drug products at that time.

Argument

As modified by the MMA, the Hatch-Waxman Act establishes an expedited FDA approval process for generic drugs and creates significant incentives for manufacturers to develop affordable generic alternatives. To that end, the statute authorizes FDA to promptly approve a proposed generic drug product if its manufacturer demonstrates that the proposed drug product is bio- and therapeutically equivalent to a "listed drug" that previously has been deemed safe and effective.

In order to secure FDA approval, an applicant must submit an abbreviated new drug application ("ANDA") that demonstrates the bio- and therapeutic equivalence of its proposed generic drug product to the reference listed drug. *See* 21 U.S.C. § 355(j) (2003). The statute also requires the applicant to make a "certification" regarding each patent that the NDA holder has listed as claiming the reference listed drug. *Id.* § 355(j)(2)(a)(vii). Of the various certifications an applicant might include in its filing, the most important is a "paragraph IV" certification. Such certifications assert that a given patent is invalid or will not be infringed by the proposed generic drug product, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), and therefore indicate that the applicant either has developed a viable legal challenge to the validity of a competition-blocking patent or has engineered a non-infringing pathway around such a patent.

In order to help clear the "patent thicket" and speed the onset of market competition, the statute rewards applicants who submit paragraph IV certifications. Congress recognized that the first generic drug company to engineer a generic pathway bears significant research and legal costs when they attack a patent directly or design their way around it. Congress also recognized that the first ANDA filer faces a significant risk that it will be sued for patent infringement. To encourage generic manufacturers to assume those risks, Congress chose to reward the "first applicant" who "submits a substantially complete application that contains and lawfully maintains a [paragraph IV] certification" with eligibility for a "180-day exclusivity period" during which it holds the right to market the generic product without competition from other generic manufacturers. 21 U.S.C. § 355(j)(5)(B)(iv); *see also Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 879 (D.C. Cir. 2004); *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1064 (D.C. Cir. 1998); *Sandoz, Inc. v. FDA*, 439 F. Supp. 2d 26, 29 (D.D.C. 2006).

That is precisely what Teva did here. On May 28, 2004, Teva submitted the first substantially complete ANDA for generic injectable granisetron drug products that contained a paragraph IV certification to one or more of the patents Roche listed in the

Orange Book as claiming Kytril®. As such, Teva earned eligibility for 180-day exclusivity. 21 U.S.C. § 355(j)(5)(B)(iv)(I).

Teva's eligibility for 180-day exclusivity remains intact despite the fact that the MMA now provides for a "forfeiture" of marketing exclusivity when the first applicant fails to market its drug products within certain specified timeframes. *See* 21 U.S.C. § 355(j)(5)(D)(i)(I). In particular, the statute deems a first applicant's 180-day exclusivity period to be forfeited if that

> 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)*** ... 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 [a paragraph IV certification], at least 1 of the following has occurred:
>
> > (AA) ... a court enters a final decision ... that the patent is invalid or not infringed.
> >
> > (BB) ... 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) of this section is withdrawn by the [NDA] holder.

Id. (emphases added).

Even though the 30-month period set forth in 21 U.S.C. § 355(j)(5)(D)(i)(I)(aa)(BB) expired on or about November 28, 2006—nearly one year before Teva even was eligible to begin marketing its generic granisetron drug products—the plain text and structure of the statute compel the conclusion that Teva remains fully entitled to its 180-day exclusivity period for generic granisetron.

That is so because the statute provides that a first applicant's exclusivity is forfeited ***only*** upon "***the later of***" two potential events (or "forfeiture triggers"). While one of those events has occurred in this case (30 months have passed since Teva submitted the first paragraph IV ANDA for generic granisetron, *see* 21 U.S.C.

§ 355(j)(5)(D)(i)(I)(aa)(BB)), there is an ongoing possibility that a "***later***" forfeiture event could be triggered under section 355(j)(5)(D)(i)(I)(bb). As a result, any decision to divest Teva of its exclusivity for generic granisetron would violate the statute's plain text and structure.

More specifically, the statute establishes two distinct groupings (or "baskets") of potential forfeiture triggers; creates a process for selecting one trigger from each basket; and then deems the first applicant's exclusivity forfeited only after the "***later***" of those two potential forfeiture triggers occurs. To that end, the first basket, which is established by subsection (aa) of section 355(j)(5)(D)(i)(I), includes two potential forfeiture triggers and directs the Agency to assess which occurs "earlier":

> ***(aa)***
>
> > (AA) the date that is 75 days after FDA grants final approval to the first applicant's ANDA, *id.* § 355(j)(5)(D)(i)(I)(aa)(AA); or
> >
> > (BB) the date that is 30 months after the first applicant submitted its ANDA to the Agency, *id.* § 355(j)(5)(D)(i)(I)(aa)(BB)....

The timing of the first potential forfeiture trigger in this basket is contingent on many factors, including the type and number of certifications contained in the ANDA, the timing of litigation (if any) arising out of the ANDA, and the applicant's own diligence in responding to inquiries from the Agency about the ANDA. But the timing of the second potential forfeiture trigger in this basket is fixed: FDA merely needs to note to the date the applicant submitted its exclusivity-qualifying paragraph IV certification to the Agency and add 30 months. Because the first basket thus (1) includes a fixed forfeiture trigger and (2) requires the Agency to determine which of two potential forfeiture triggers occurs first, ***the first basket inevitably will produce a determinate result***: the first applicant will either secure final approval of its ANDA within 30 months, in which case the date that is 75 days after the date of that final approval will serve as the controlling forfeiture trigger for purposes of the first basket; or the applicant will not secure final approval within 30 months, in which case the date of the 30-month deadline will serve as the controlling forfeiture trigger for purposes of the first basket.

In sharp contrast to the first basket, the second basket, which is established by subsection (bb) of section 355(j)(5)(D)(i)(I) and separated from the first basket by the word "or," ***inevitably will produce a contingent result.*** That is so because each of the three potential forfeiture triggers contained in that basket is dependant on events that may or may not occur:

> ***"or"***
>
> ***(bb)***
>
> > (AA) the patentee and/or NDA holder files a patent infringement lawsuit against one or more paragraph IV applicants, and/or one or more of the paragraph IV applicants files a declaratory judgment

> action against the NDA holder, and the court overseeing such litigation enters a final judgment holding that each and every one of the exclusivity-qualifying patents is invalid or not infringed, *id.* § 355(j)(5)(D)(i)(I)(bb)(AA);
>
> ***or***
>
> (BB) the patentee and/or NDA holder files a patent infringement lawsuit against one or more paragraph IV applicants, and/or one or more of the paragraph IV applicants files a declaratory judgment action against the NDA holder, and the court overseeing such litigation approves a settlement or enters a consent decree declaring that each and every one of the exclusivity-qualifying patents is invalid or not infringed, *id.* § 355(j)(5)(D)(i)(I)(bb)(BB);
>
> ***or***
>
> (CC) the patentee and/or NDA holder files a patent infringement lawsuit against one or more paragraph IV applicants; pursuant to 21 U.S.C. § 355(j)(5)(C)(ii)(I), one or more of the applicants files a counterclaim action seeking to compel the NDA holder to delist and/or correct 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 withdraws all such patent information pursuant to the court's order, *id.* § 355(j)(5)(D)(i)(I)(bb)(CC).

The key point here is straightforward. The plain language and structure of the statute require FDA to determine which is ***"the later of"*** (1) a determinate forfeiture trigger, which comes from the first basket, "***or***" (2) a contingent forfeiture trigger, which comes from the second basket. But there is no conceivable way for FDA to determine which of those 2 potential forfeiture triggers occurs "***later***" until (a) one of the contingencies that could give rise to a forfeiture trigger the second basket has occurred, or (b) none of those contingencies can occur. After all, it is impossible to know whether a contingent event has occurred before it does occur—and twice as hard to determine that such an event will not occur until it no longer can occur.

In other words, so long as the second basket remains "open," the fact that the first basket may have been "closed" has no bearing on the first applicant's eligibility for exclusivity. Until ***both*** baskets have been "closed," it is impossible to determine which potential forfeiture trigger—the applicable one from the two choices provided in the first basket, or the applicable one from the three choices provided in the second basket—occurs "***later,***" and thus results in a forfeiture of the first applicant's entitlement to exclusivity.

That is precisely the case here, where the second basket unquestionably remains "open." Roche has not sued Teva (or any subsequent applicant for generic granisetron),

but it could initiate suit against Teva (or any subsequent applicant) at any time. Any such lawsuit could result in the entry of a final court decision holding that the '548 patent is invalid or not infringed by Teva's (or some subsequent applicant's) generic granisetron drug products, or in a court order compelling the delisting of that patent, and thus could give rise to a "***later***" forfeiture event from the second basket, *see id.* § 355(j)(5)(D)(i)(I)(bb)(AA)-(BB). In such litigation, Teva (or some subsequent applicant) could also opt to settle with Roche and secure the entry of a settlement order or consent decree that includes a finding that the '548 patent is invalid or not infringed by Teva's (or some subsequent applicant's) generic granisetron drug products. That, too, would give rise to a "***later***" forfeiture event from the second basket. *See id.* § 355(j)(5)(D)(i)(I)(bb)(BB).

Moreover, Teva (or any subsequent applicant for generic granisetron) could at any time choose to initiate a declaratory judgment action against Roche pursuant to 21 U.S.C. § 355(j)(5)(C) and 35 U.S.C § 271(e)(5). Indeed, given the Supreme Court's recent decision in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. ---, 127 S. Ct. 764, 774 n.11 (2007) (invalidating the Federal Circuit's "reasonable apprehension of imminent suit" test for Article III jurisdiction over declaratory judgment actions), and the Federal Circuit's subsequent implementation of that decision in the *Famvir* case, *see* 482 F.3d at 1340, the possibility of such an action is more realistic than ever. Again, any such litigation could result in a court decision, settlement order, or consent decree that speaks to the (in)validity and/or (non-)infringement of the claimed '548 patent, and thereby could give rise to a "***later***" forfeiture event from the second basket. *See* 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(AA)-(BB).

The bottom line here is that so long as these contingencies remain in play, the plain language and structure of § 355(j)(5)(D)(i)(I) provide that the passage of 30 months since Teva submitted its ANDA is insufficient on its own to result in the forfeiture of Teva's 180-day exclusivity for generic granisetron. Short of gazing into a crystal ball, there simply is no conceivable mechanism for determining whether these contingencies will come to pass, and thus whether any such occurrence is (or would be) "***later***" than the passage of 30 months since Teva submitted its path-breaking paragraph IV ANDA for generic granisetron. Teva thus remains fully entitled to its 180-day exclusivity period.

Other provisions of the statute confirm that Congress meant what it said in § 355(j)(5)(D)(i)(I). Indeed, interpreting § 355(j)(5)(D)(i)(I) to mandate forfeiture based solely upon an applicant's failure to commence commercial marketing within 30 months would render superfluous the "failure to obtain tentative approval" trigger set forth in 21 U.S.C § 355(j)(5)(D)(i)(IV).

That subsection provides for forfeiture where the first filer "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." *Id.* (emphasis added). This forfeiture trigger thus specifically contemplates cases in which an applicant could maintain its eligibility for 180-day exclusivity ***despite*** the passage of 30 months after its ANDA is filed; otherwise, the

exception for cases in which FDA changes the requirements for approval would be meaningless.

If, however, the first applicant automatically forfeits its 180-day exclusivity whenever it fails to commence marketing within 30 months of submitting its ANDA (and regardless of whether there is any ongoing possibility of a forfeiture event from the second basket), then § 355(j)(5)(D)(i)(IV) would simply replicate § 355(j)(5)(D)(i)(I)(aa)(BB). After all, exclusivity would be forfeited without respect to whether FDA has changed the requirements for approval, and there effectively would be no difference between an applicant's failure to obtain final approval within 30 months and its failure to obtain tentative approval within 30 months.

That is not how Congress wrote the statute, and given that every "statute should be construed so that effect is given to all its provisions, so that no part will be inoperative or superfluous, void or insignificant," *Hibbs v. Winn*, 542 U.S. 88, 101 (2004) (quotation omitted), FDA is obligated to avoid interpreting what Congress did write in a manner that would render § 355(j)(5)(D)(i)(IV) a nullity. The only way to do so is to recognize that the tentative approval trigger represents a clear congressional expectation that 180-day exclusivity must remain intact where, as here, the second basket remains "open."

Beyond the plain language and structure of § 355(j)(5)(D)(i)(I) and the statute as whole, strong policy considerations bolster Teva's interpretation of the statute. Congress enacted the MMA's forfeiture provisions largely to prevent exclusivity-eligible applicants from holding up generic market competition, and thereby depriving consumers of prompt access to safe and affordable generic medicines, by unduly delaying market entry or otherwise "parking" their exclusivity. *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).

The problem here, however, is not that Teva has unduly delayed the onset of generic market competition by waiting ***too long*** to market its products; it is that Teva did not wait ***long enough*** to submit its path-breaking paragraph IV ANDA. After all, the only reason Teva has not already begun marketing generic granisetron is because it submitted its ANDA in May 2004, and a legitimate blocking patent precludes FDA from granting final approval until December 29, 2007. *See* 21 U.S.C. § 355(j)(5)(B)(ii). In other words, if Teva had simply waited another year to challenge Roche's patent, this letter would not have been necessary. Congress could not possibly have intended to punish first applicants for challenging weak patents ***too soon***; the whole point of the exclusivity reward is to stimulate faster patent challenges—and more of them—in order to speed the entry of generic drugs into the market. *See, e.g., Andrx Pharms., Inc. v. Biovail Corp. Int'l*, 256 F.3d 799, 809 (D.C. Cir. 2001); *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991).

That is precisely what Teva's paragraph IV application will accomplish. When the '808 patent expires on December 29, 2007, Teva intends to commence immediate commercial marketing—***nearly 12 years before the scheduled expiration of the '548 patent in May 2019***. That remarkable outcome is possible only because Teva undertook

the effort and expense of identifying vulnerabilities in the '548 patent, challenging the patent, and then accepting the risk that it would be sued for patent infringement by filing the first application containing a paragraph IV challenge to the '548 patent. Again, those are the very investments and risks that 180-day exclusivity is designed to reward, *see, e.g.*, *Sandoz, Inc. v. FDA*, 439 F. Supp. 2d 26, 29, 33-34 (D.D.C. 2006); *Mylan Pharms., Inc. v. Shalala*, 81 F. Supp. 2d 30, 44 (D.D.C. 2000), and it would be incredibly perverse to punish Teva for doing exactly what Congress intended.

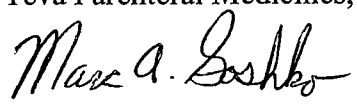
Indeed, adopting a contrary interpretation of the statute inevitably would slow the development and marketing of generic drugs, in direct contravention of the broader statutory goals—and the very purpose of the forfeiture triggers. After all, if a manufacturer can be deemed to have forfeited its exclusivity by filing its ANDA more than 30 months prior to the expiration of a legitimate blocking patent, it will delay filing its ANDA until that time. That, of course, will discourage the prompt resolution of patent disputes and lead to delays in the advent of generic market competition—especially in those cases where the brand manufacturer promptly sues the first applicant for patent infringement and later secures an extension of the automatic thirty-month stay under 21 U.S.C. § 355(j)(5)(B)(iii). There is no basis for thinking that Congress intended to punish generic applicants for filing early patent challenges, and FDA should not countenance an interpretation of the statute that would produce such an absurd result.

Conclusion

For the foregoing reasons, the Agency should confirm that Teva remains entitled to 180-day exclusivity for its generic granisetron hydrochloride injection drug products.

Because the '808 patent is scheduled to expire on December 29, 2007 and Teva expects to receive its final approval on that date, Teva respectfully requests that FDA issue its final decision on this matter no later than December 1, 2007. 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.



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