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Food and Drug Administration  
Rockville MD 20857

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FEB 6 2001

Re: Docket No. 00P-1446/CP1

Dear Ms. Jaskot:

This responds to your citizen petition dated August 9, 2000, requesting the Food and Drug Administration (FDA) to determine (1) that the abbreviated new drug application (ANDA) submitted by Mylan Pharmaceuticals, Inc. (Mylan), for 30-milligram (mg) nifedipine extended-release tablets (ANDA 75-108) is not eligible for 180-day exclusivity or (2) that such exclusivity has expired. Either determination would permit FDA to immediately approve any subsequent ANDA for the same drug. No comments were submitted to the petition docket. For the reasons stated below, your petition is granted.

## I. BACKGROUND

The 1984 Drug Price Competition and Patent Term Restoration Act, otherwise known as the Hatch-Waxman Amendments or Hatch-Waxman, includes a provision giving 180 days of marketing exclusivity to the first generic drug applicant to challenge a listed patent for the innovator drug. This provision, found at section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the statute or Act),<sup>1</sup> has been the subject of considerable litigation and administrative review in recent years, as the courts, industry, and FDA have sought to interpret it in a way that is consistent both with the text and with the legislative goals underlying Hatch-Waxman. A series of federal court decisions beginning with *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060, 1065 (D.C. Cir. 1998), *Granutec, Inc. v. Shalala*, No. 97-1873 and No. 97-1874, 1998 U.S. App. LEXIS 6685 (4th Cir. Apr. 3, 1998), and *Purepac v. Friedman*, 162 F.3d 1201 (D.C. Cir. 1998), and including the recent D.C. Circuit opinion in *Teva Pharmaceuticals USA, Inc. v. FDA*, 182 F.3d 1003 (D.C. Cir. 1999) (*Teva I*), describe acceptable interpretations of the 180-day exclusivity provision, identify potential problems in implementing the statute, and establish certain principles to be used by the Agency in interpreting the statute.

In light of court decisions finding certain FDA regulations inconsistent with the statute, the Agency proposed new regulations in August 1999 to implement the 180-day exclusivity. Since that time, many comments have been submitted, and there have been additional court decisions

<sup>1</sup> 21 U.S.C. 355(j)(5)(B)(iv).

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further interpreting the 180-day exclusivity provision. The Agency has not yet published a final rule on 180-day exclusivity. As described in the June 1998 guidance for industry entitled *180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act*, (1998 Guidance), until new regulations are in place, FDA will address on a case-by-case basis those 180-day exclusivity issues not addressed by the existing regulations. Your petition describes a situation not addressed by FDA's current regulations and thus must be resolved by direct reference to the statute.<sup>2</sup>

## II. THE FACTS

The ANDAs at issue in your petition are for 30-mg extended-release nifedipine tablets. The reference listed drug for these ANDAs is Pfizer's Procardia XL (nifedipine extended-release tablets, 30 mg) (NDA 19-684). At the time ANDAs were submitted for this drug, there were five patents listed for Procardia in the *Approved Drug Products With Therapeutic Equivalence Evaluations* (Orange Book).<sup>3</sup> Mylan submitted the first ANDA 75-108 (submitted 4/8/97, received 5/27/97) with a paragraph IV patent certification challenging all five of the listed patents. Other ANDA applicants also submitted certifications challenging the listed patents. As a result of its certification and notice to the NDA holder (Pfizer) and patent owner (Bayer AG), Mylan was sued for patent infringement in the U.S. District Court for the Western District of PA on July 18, 1997. Mylan notified FDA of the filing of this lawsuit, and final approval of the Mylan ANDA was delayed for 30 months. The 30-month stay expired before a decision was rendered in the Mylan/Pfizer patent litigation. FDA gave Mylan final approval to market its 30-mg extended-release nifedipine tablets on December 17, 1999.

Although its ANDA was approved over a year ago, Mylan has not marketed the nifedipine tablets approved in its application. Instead, Mylan announced on March 2, 2000, it had entered into a settlement with Pfizer. The settlement terminated the patent infringement litigation before the district court issued a decision.<sup>4</sup> Under the terms of the agreement, Mylan obtained a license to market three strengths of Pfizer's extended-release nifedipine tablets, rather than the Mylan product approved by FDA on December 17, 1999. Mylan has not amended its patent certification as a result of the settlement.

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<sup>2</sup> *Teva I* describes FDA's responsibilities in regulating directly from the statute. Specifically, the court cautions that the Agency must explain the basis for its application of the statute, and interpret the statute to avoid absurd results and to further congressional intent (182 F.3d at 1011).

<sup>3</sup> U.S. Patent Nos. 5,264,446 (expires 11/23/2010), 4,783,337 (expires 9/16/2003), 4,765,989 (expires 9/16/03), 4,612,008 (expires 9/16/03) and 4,327,725 (expired 11/25/00).

<sup>4</sup> Shortly after Mylan and Pfizer settled their patent dispute, the patent owner, Bayer AG, and Mylan also settled their dispute, and those claims were dismissed by order entered in 97-CV-1309 on March 22, 2000, in the U.S. District Court for the Western District of PA.

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The question you raise in your petition is whether Mylan is eligible for exclusivity, and if so, whether the exclusivity has already been triggered. If Mylan is eligible for exclusivity and that exclusivity has not begun to run, subsequent applicants will have to wait until the end of exclusivity triggered either by Mylan's marketing or by a court decision in litigation over this drug product finding the patent invalid or not infringed, or until the patent expires. Once the exclusivity has run its 180-day course, subsequent ANDAs may be approved.

You state that because Mylan settled its litigation with Pfizer and is no longer challenging the patent, Mylan no longer qualifies for 180-day exclusivity (Petition at 2). In the alternative, you propose that FDA find Mylan eligible for exclusivity, and that the exclusivity began either on the effective date of the Mylan/Pfizer agreement, or on the date Mylan began to market the licensed nifedipine tablets (*Id.*). As more fully described below, FDA finds that both positions have merit. Under either position, there is no longer a 180-day exclusivity bar to approval of ANDAs for 30-mg extended-release nifedipine tablets.

### III. STATUTE AND REGULATIONS

The 180-day generic drug exclusivity provision is one component of the complex patent listing and certification scheme included in the Hatch-Waxman Amendments. These amendments balance the dual goals of encouraging and protecting innovation in drug development and expediting the approval of low-cost generic drugs. The Hatch-Waxman Amendments require innovator companies to submit information on patents claiming the approved drug product (section 505(b)(1) and (c)(2)). FDA publishes this information in the Orange Book. An ANDA must include a patent certification to each patent listed in the Orange Book for the innovator drug. There are four types of patent certification. The two certifications relevant to your petition are a *paragraph III* certification, which seeks approval of the ANDA on the date the patent expires, and a *paragraph IV* certification, which states that the "patent is invalid or will not be infringed by the manufacture, use, or sale of the [drug described in the ANDA]" (section 505(j)(2)(A)(vii)).

The filing of a paragraph IV certification (1) indicates that the ANDA applicant seeks to market its product before the expiration of a listed patent and (2) begins a process in which issues of patent protection may be resolved in patent litigation. The ANDA applicant notifies the NDA holder and patent owner that the ANDA applicant has submitted an ANDA and of the grounds for its belief that the generic drug will not infringe the listed patent(s) (section 505(j)(2)(B)(i) and (ii)). The NDA holder and patent owner then have 45 days to file a suit for patent infringement against the ANDA applicant (section 505(j)(5)(B)(iii)). If such a suit is filed, FDA cannot approve the ANDA for 30 months (or a shorter or longer period ordered by the court) (*Id.*).

The 180-day exclusivity acts as an incentive for the first ANDA applicant to challenge a listed patent. The statutory provision establishing this exclusivity reads:

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If the application contains a [paragraph IV certification] and is for a drug for which a previous application has been submitted under this subsection containing<sup>5</sup> such a certification, the application shall be made effective not earlier than one hundred eighty days after —

(I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or

(II) the date of the decision of the court in action described in clause (ii) holding the patent which is the subject of the certification to be invalid or not infringed.

whichever is earlier.

(section 505(j)((5)(B)(iv))

Only an application containing a paragraph IV certification may be eligible for exclusivity. FDA regulations contain a provision at 21 CFR 314.94(a)(12)(viii) stating that an applicant may amend its patent certification, and if it does so, the application will no longer be considered to contain the previous certification. Under certain circumstances, an ANDA applicant is required to amend its patent certification if the patent is determined to be infringed or if the applicant discovers the submitted certification is no longer correct. If an applicant changes from a paragraph IV certification to a paragraph III certification, the ANDA will no longer be eligible for exclusivity (94 F. Supp.2d at 54-56).

#### IV. DISCUSSION

In the absence of applicable regulations governing this situation, FDA has interpreted the statute given the facts of this matter and taking into account the purposes of the statute. FDA has determined that Mylan's actions have rendered it ineligible for 180-day exclusivity. Alternatively, FDA has determined that any 180-day period of exclusivity has already expired. Either interpretation leads to the same conclusion — that there is no longer a 180-day exclusivity obstacle to FDA approval of subsequent ANDAs for 30-mg extended-release nifedipine tablets.

The facts in this case are similar to those in *Mylan*, 94 F. Supp.2d at 40-42. In *Mylan*, Barr Laboratories submitted the first ANDA with a paragraph IV certification for the drug tamoxifen. The innovator sued Barr as a result of its paragraph IV certification, and Barr won the case at the district court level. Before an appeal was complete, Barr and the innovator entered into an agreement under which Barr obtained a payment from the innovator and a license to market the innovator's tamoxifen product. The patent infringement litigation was dismissed, and Barr

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<sup>5</sup> The public law version of this provision substituted the word *continuing* for the term *containing*. In *Mylan*, the court determined that such substitution was a "scrivener's error" and "the word 'continuing' was intended to be the word 'containing.'" (*Mylan Pharmaceuticals, Inc. v. Henney*, 94 F. Supp.2d 36 (D.D.C. 2000)).

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certification from a paragraph IV to a paragraph III, and thus Mylan has lost its eligibility for exclusivity.

The generic drug approval provisions of the Act contemplate certain events resulting from the filing of a paragraph IV certification. Once an ANDA applicant notifies the NDA holder and patent owner it is challenging a listed patent, one of two things can happen: either the 45-day period lapses without the filing of a lawsuit and the ANDA can be approved immediately under section 505(j)(5)(B)(iii), or the ANDA applicant is sued for patent infringement and the 30-month stay described in section 505(j)(5)(B)(iii) goes into effect. The statute describes the patent litigation as having two possible results: the court decides the patent is invalid or not infringed, or the court decides the patent has been infringed (section 505(j)(5)(B)(iii)(I)-(III)). The statute provides for court decisions made before or after the 30-month period expires and with or without the approval of the ANDA and marketing of the generic product. But the statute appears to contemplate that there will be a decision on the patent status of the drug and does not identify what to do if the litigation is settled without a court decision on the patent. Because the outcome of patent litigation affects the accuracy of a patent certification and thus eligibility for exclusivity, FDA must determine the effect of this settlement on Mylan's patent certification.<sup>7</sup>

The Mylan/Pfizer settlement resulted in the dismissal of the patent infringement litigation, and in Mylan's marketing of a nifedipine product under a license from Pfizer. Details of the settlement have not been made public, so the agency must rely in making its decision on the limited information that is publicly available and, more importantly, upon the parties' actions. Mylan is no longer participating in litigation intended to prove that its product will not infringe the listed patent.<sup>8</sup> Moreover, despite the fact that its ANDA has been approved for more than a year, Mylan has never marketed its own ANDA product. These facts lead FDA to presume that Mylan believes the product described in its ANDA may infringe the listed patent and is therefore waiting until patent expiry before marketing its own product. The appropriate certification for a company that has chosen to wait until a listed patent expires before marketing is a paragraph III certification stating the date of patent expiration. Because FDA considers Mylan's actions in settling the litigation and marketing Pfizer's nifedipine product to have effectively changed Mylan's certification from a paragraph IV to a paragraph III, and because applicants who change from a paragraph IV to a paragraph III are no longer eligible for 180-day exclusivity, Mylan has

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<sup>7</sup> The Agency addressed the issue of settlements of patent litigation in the proposed rule and declined to adopt an approach in which ANDA applicants would be required to notify FDA of settlements that would either render the first applicant ineligible for exclusivity or begin the running of exclusivity. Instead, FDA proposed to adopt a triggering period approach. (See 64 FR 42873 at 42880; August 6, 1999.) FDA has not issued final regulations addressing these issues. Therefore, the Agency is relying on a case-by-case approach to particular situations presented and regulating directly from the statute as necessary. FDA's approach to the 180-day exclusivity issues presented in your petition during this interim period should not affect the rulemaking process (*Teva Pharmaceuticals, USA, Inc. v. FDA*, 2000 WL 1838303 (D.C. Cir. 2000)(*Teva II*)).

<sup>8</sup> This fact alone is not necessarily dispositive on the question of whether — as stated in a paragraph IV certification — the patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which [Mylan's ANDA] was submitted" (section 505(j)(5)((A)(vii)(IV)).

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amended its patent certification from a paragraph IV to a paragraph III. The Barr ANDA is not eligible for approval until the patent expires in August 2002. On these facts, the court found two grounds for immediate approval of tamoxifen ANDAs subsequent to Barr. First, the court held that the district court decision, although later vacated, began the running of Barr's exclusivity under section 505(j)(5)(B) (*Id.* at 54). Second, the court found that under FDA's regulation at 21 CFR 314.94(a)(12)(viii) governing amendments to patent certifications, Barr's change from a paragraph IV certification to a paragraph III certification rendered it ineligible for exclusivity (*Id.* at 56-57).

In the course of reaching its decision, the *Mylan* court identified three factors to consider in interpreting the 180-day exclusivity provision of Hatch-Waxman. First, the statute is to be interpreted in a manner consistent with "the statute's interest in affording market access and incentives for both generic and non-generic makers," and to maintain "an incentive for the parties to fulfill the purposes of Hatch-Waxman" (94 F. Supp.2d at 53). Second, FDA should avoid an interpretation that excessively favors the first generic and the innovator parties' "anticompetitive hold" over the drug. The court observed that "Hatch-Waxman intended to provide an incentive for drug companies to explore new drugs, not a market 'windfall' for crafty, albeit industrious, market players" (*Id.*). Finally FDA should avoid interpreting Hatch-Waxman so the decision on whether a generic applicant is entitled to exclusivity rests entirely in the patent holder's hands (*Id.* at 54).

With these principles in mind, the Agency has looked to the statute to determine when subsequent ANDAs for 30-mg extended-release nifedipine tablets may be approved. Specifically, FDA must determine the effect of the dismissal of patent infringement litigation before a court decision and after approval of an ANDA. FDA must also determine whether the marketing of Pfizer's product, in lieu of Mylan's own, has any effect on exclusivity. Under well-established principles of administrative law, FDA has discretion in addressing these questions where the statute does not directly address the issues presented (*Chevron, USA, Inc v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 843 (1984); *Christensen v. Harris County*, 120 S. Ct. 1655, 1662-63 (2000); 1998 Guidance at 4).

A. Mylan Is No Longer Eligible for Exclusivity

The Agency has reviewed these circumstances and determined that, consistent with the language of the statute, in the absence of an applicable regulation,<sup>6</sup> and applying the factors identified by the courts in *Mylan* and *Teva I*, the Mylan/Pfizer settlement effectively changed Mylan's patent

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<sup>6</sup> FDA regulations regarding patent certifications do not specifically address the circumstances here. The regulations require an ANDA applicant to change its certification from a paragraph IV to a paragraph III when patent litigation determines the patent is infringed. The regulations also require an applicant to amend its certification if, before the ANDA is approved, the applicant learns that the certification is incorrect. The regulations say nothing about amending a patent certification that becomes inaccurate — other than with a finding of infringement — after an ANDA is approved.

lost its eligibility for exclusivity. This interpretation is consistent with the principles articulated by the *Mylan* court: it avoids perpetuating the first generic and innovator parties' "anti-competitive hold" over the drug and allows market access to other generic manufacturers.

B. Mylan's Exclusivity Started to Run with Its Commercial Marketing of the Innovator's Product.

Alternatively, you ask FDA to consider the "deal" struck by Mylan and Pfizer as "commercial marketing" that begins the running of exclusivity under section 505(j)(5)(B)(iv)(I). According to your interpretation, exclusivity would have begun either on March 2, 2000, the day the settlement was announced, or when Mylan began to market nifedipine under the license from Pfizer. FDA believes a compelling argument can be made that commercial marketing began when Mylan began marketing Pfizer's product. The Chairman, CEO, and President of Mylan noted in the March 2, 2000, press release describing the settlement that "we are pleased with this agreement, which positions Mylan as the first company to offer its customers generic extended-release nifedipine products." Mylan thus believed it was beginning the marketing of a generic drug, which is the event described in the statute as beginning the running of exclusivity.

There are two events that can start the running of exclusivity. As set out above, the exclusivity will begin with the first of either the date of a court decision finding the patent invalid or not infringed or "the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application" (section 505(j)(5)(B)(iv)). One issue for FDA, then, is whether the ANDA applicant's marketing of the innovator's drug as a generic constitutes "commercial marketing of the drug under the previous application." Another consideration is whether such an interpretation would be consistent with the goals of 180-day exclusivity. FDA believes both that Mylan's marketing of the Pfizer drug was commercial marketing that began the exclusivity period and that such an interpretation is fully consistent with the goals of Hatch-Waxman.

FDA's interpretation of the "commercial marketing" trigger is governed by the court's approach to the analogous situation in *Teva I*. In that case, the court looked to the practical effect of the statutory terms in the court decision trigger at section 505(j)(5)(B)(iv)(II) in determining what interpretation was appropriate. The court observed that the term *holding* in that provision was used to describe a court action that has preclusive effect on the innovator's right to pursue a patent infringement action, and because a preclusive finding was contemplated by the statute, a dismissal for lack of subject matter jurisdiction was a court decision triggering the beginning of exclusivity. Any other conclusion would have produced absurd results (182 F.3d at 1009). Similarly, in the present case the Agency has determined that the commercial marketing trigger is intended to give the first ANDA applicant with a paragraph IV certification the opportunity to market a generic version of the innovator's drug with no competition for 180 days. Whether Mylan markets the product approved in its ANDA or the product approved in Pfizer's NDA is of little import to the statutory scheme; Mylan has begun commercial marketing of generic

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nifedipine. Permitting Mylan to market nifedipine without triggering the beginning of exclusivity would be inconsistent with the intent of the statutory scheme.

Finally, with respect to those Congress intended to benefit, marketing the drug approved in the Pfizer NDA or the drug approved in the Mylan ANDA has the same effect. The benefit intended by the 180-day exclusivity provision is two-fold. First, as is clear in the legislative history, the consuming public is intended to benefit from ANDA approvals through the prompt availability of lower cost generic drugs. Second, ANDA applicants who speed the availability of generic drugs by challenging patents are given the opportunity to reap the economic benefit of limited competition for a period of 180 days. Interpreting Mylan's marketing of the Pfizer product as beginning the running of exclusivity sets a finite limit on the delay in true market competition for this nifedipine product. Moreover, such an interpretation gives Mylan exactly what the statute seemed to intend — 180 days to reap the economic benefits of being Pfizer's sole competition. To permit Mylan to continue to market a nifedipine product without beginning the exclusivity would harm the consuming public by denying access to multiple safe and effective generic nifedipine products ready for final approval. It would also give Mylan (and Pfizer) a windfall clearly not intended by Congress. According to FDA records, Mylan began marketing the 30-mg extended-release nifedipine tablets under the license from Pfizer approximately 10 months ago, on March 28, 2000. Therefore, Mylan has received the full measure of the intended benefit under Hatch-Waxman.

## V. CONCLUSION

For the reasons stated above, your petition is granted. Under either of the approaches described, there is no longer a 180-day exclusivity obstacle to FDA approval of subsequent ANDAs for 30-mg extended-release nifedipine tablets.

Sincerely yours,



Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research