

Exhibit B



Re: U.S. Patent No. 5,256,664
Nefazadone Hydrochloride Tablets

Food and Drug Administration
Rockville MD 20857

JUL 31 2003

Dear ANDA Applicant for Nefazodone Hydrochloride Tablets:

This letter addresses the status of U.S. Patent No. 5,256,664 ('664 patent), which has been listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). Bristol-Myers Squibb (Bristol) submitted this patent to FDA for listing in the Orange Book as a protection for the drug product Serzone (nefazodone hydrochloride tablets). On April 4, 2003, Bristol requested that FDA remove the '664 patent from the Orange Book listing for Serzone (NDA 20-152). FDA is removing the '664 patent from the Orange Book.

The Federal Food, Drug, and Cosmetic Act (the act) places the responsibility for submitting patent information for new drugs on the new drug application (NDA) applicant. Section 505(b)(1) and (c)(2). The act further directs that FDA publish the submitted patent information, *id.*, and update that information every thirty days, section 505(j)(7)(A)(iii). FDA anticipated in its regulations that NDA applicants would, on occasion, correct patent information by withdrawing or amending that information. 21 CFR 314.53(f)

FDA regulations describe one limited situation in which the agency will maintain a patent listing even after the NDA holder requests FDA remove it from the Orange Book. This exception is described in 21 CFR 314.94(a)(12), which provides that

a patent that is the subject of a lawsuit under [21 CFR 314.107(c)] shall not be removed from the list until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended.

FDA interprets this regulation to mean that, if the listed patent has been the subject of a lawsuit as a result of the paragraph IV certification submitted by the "previous" applicant under section 505(j)(5)(B)(iv), and that applicant's ANDA contains an appropriate paragraph IV certification, FDA will not remove that patent until relevant patent litigation has been resolved and either 1) an ANDA applicant prevails and exclusivity is triggered by the court decision finding the patent invalid or not infringed, or 2) the first ANDA applicant loses the lawsuit and changes its certification to a paragraph III. This interpretation conforms to the regulatory scheme at the time the regulation was promulgated, whereby an ANDA applicant had to have been sued – and ultimately prevail – to earn its exclusivity. *See* 21 CFR 314.107(c) (1998)(the applicant submitting the first application must successfully defend against a suit for patent infringement). Although FDA amended some of its regulations as a result of *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998) to remove the "successful defense" requirement for

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exclusivity, 63 Fed. Reg. 59710 (Nov. 5, 1998), FDA retained the requirement of a lawsuit having been filed in this context. The statutory language that the court found controlling in *Mova*, section 505(j)(5)(B)(iv), is not directly applicable to this circumstance. Instead, the only applicable statutory provision generally gives control over patent listings to the NDA holder. Section 505(b)(1) and (c)(2). FDA's interpretation of the regulation -- limiting the exception to patent delisting to instances where NDA holder or patent owner has sued the ANDA applicant as a result of the paragraph IV certification -- is consistent with this statutory provision and the overall regulatory scheme. Under the circumstances, FDA has maintained a reasonable balance between allowing NDA applicants to correct patent listings and protecting the incentive for ANDA applicants who are sued as a result of a patent certification and bear the cost of that litigation.

No nefazodone ANDA applicant was sued as a result of its paragraph IV certification to the '664 patent. Thus, 21 CFR 314.107(c) is not a bar to removal of the patent from the Orange Book. See July 31, 2002, letter from Gary Buehler, Director, Office of Generic Drugs, to Apotex Corporation regarding delisting U.S. Patent No. 6,063, 927 for Paxil. (enclosed).

The agency considered and rejected whether, alternatively, it is required to maintain the '664 patent in the Orange Book because at least one ANDA was submitted containing a paragraph IV certification, in spite of the fact that no applicant was sued. Under FDA's current interpretation of section 505(j)(5)(B)(iv), the first ANDA applicant to submit a paragraph IV certification to a patent need not be sued as a result of that certification to be eligible for 180 days of exclusivity. 21 CFR 314.107(c)(2003); *Purepac v. Friedman*, 162 F.3d 1201 (D.C.Cir. 1998). However, the agency does not believe that because an ANDA applicant may be eligible for exclusivity merely by submitting a paragraph IV patent challenge, the FDA must maintain the patent listing when no litigation results from that certification and the NDA holder requests that the patent be removed from the list. Moreover, even if FDA were to believe that it would be reasonable to leave the patent in the Orange Book, as a matter of equity based on the broad eligibility for exclusivity under the current regulations, the statutory language giving control over patent listings to the NDA holder, and the very limited exception in the regulations, mitigate against doing so.¹

Therefore, FDA is removing the '664 patent from the Orange Book as a protection for Serzone (nefazodone hydrochloride tablets). The '664 patent will not serve as the basis for 180-day exclusivity for any ANDA referencing Serzone. Please amend your ANDA accordingly, as described at 21 CFR 314.94(a)(12)(viii)(C).

¹ Similarly, under FDA's regulations, an ANDA applicant also will not maintain its eligibility for exclusivity beyond the expiration of the patent, even if the applicant has vigorously defended patent litigation resulting from its paragraph IV certification. 21 CFR 314.94(a)(12)(viii); *Dr. Reddy's Laboratories, Inc., et al. v. Thompson, et al.*, No. 02-452, slip op at 27-39 (D.N.J. July 17, 2003).

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If you have any questions regarding this letter, please contact Ms. Cecelia Parise, Regulatory Policy Advisor, Office of Generic Drugs, at 301-827-5845.

Sincerely,



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

Enclosure: July 30, 2003, letter to Apotex Corp.

cc: Daniel E. Troy, OCC



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

ANDA 75-356

Food and Drug Administration
Rockville MD 20857

JUL 30 2003

Apotex Corporation
Attention: Marcy Macdonald
U.S. Agent for Torpharm
616 Heathrow Drive
Lincolnshire, Illinois 60069

Sent by Facsimile and U.S. Mail

Dear Ms. Macdonald:

This is in reference to your abbreviated new drug application (ANDA) dated March 31, 1998, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Paroxetine Hydrochloride Tablets 10 mg, 20 mg, 30 mg, and 40 mg. Specifically, this letter addresses the matter of 180-day exclusivity under section 505(j)(5)(B)(iv) of the Act for ANDAs referencing Paxil®, manufactured by GlaxoSmithKline (GSK).

As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book), multiple patents are listed for this drug product. The patent numbers and expiration dates of the patents listed in the Orange Book are as follows:

U.S. Patent No. 4,721,723	expiration (with pediatric exclusivity)	June 29, 2007
U.S. Patent No. 5,789,449	"	July 6, 2009
U.S. Patent No. 5,872,132	"	November 19, 2015
U.S. Patent No. 5,900,423	"	November 19, 2015
U.S. Patent No. 6,063,927	"	October 23, 2019
U.S. Patent No. 6,080,759	"	November 19, 2015
U.S. Patent No. 6,113,944	"	June 14, 2015
U.S. Patent No. 6,121,291	"	September 17, 2017
U.S. Patent No. 6,133,289	"	November 19, 2015
U.S. Patent No. 6,172,233	"	July 15, 2018

(Note: Patents will be referred to in this letter by the last three digits of the patent number.)

We have reviewed the submissions, including original applications and amendments, for the ANDAs referencing Paxil, and have determined that different applicants have been the first to submit paragraph IV certifications for these patents. Torpharm was the first to submit paragraph IV certifications for all four strengths as to the '723 patent, the '759 patent, the '289 patent, and the '233 patent, and as to the '291 patent for the 10 mg, 20 mg, and 30 mg strengths. Different ANDA applicants were the first to submit paragraph IV certifications as to the other listed patents and for other strengths.

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Torpharm
Paroxetine Hydrochloride Tablets
180-day Exclusivity

As you may be aware, in a limited number of cases, FDA has addressed the situation in which different ANDA applicants were first to submit patent challenges as to different listed patents. FDA has adopted the "shared exclusivity" approach to address eligibility for 180-day exclusivity in these circumstances.

The facts related to the Paroxetine Hydrochloride ANDAs present many of the same issues as were addressed by FDA in its application of the shared exclusivity approach to approval of ANDAs for omeprazole delayed-release capsules in November 2001. As explained below, the same general principles apply to the Paroxetine ANDAs.

Background

The statutory provision governing 180-day exclusivity reads:

If the application contains a certification described in subclause IV of paragraph (j)(2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification, the application shall be made effective not earlier than one hundred and eighty days after -

- (I) the date the Secretary receives notice from the applicant under the previous application of first commercial marketing of the drug under the previous application, or
- (II) the date of a decision of a 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).¹

FDA's regulations at 21 CFR § 314.107(c)(1) & (2) address the beginning of 180-day exclusivity as follows:

¹ The referenced provision governing paragraph IV certifications at section 505(j)(2)(a)(vii)(IV) states that an ANDA must contain

a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c)...

(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.

If an abbreviated new drug application contains a certification that a relevant patent is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted containing a certification that the same patent was invalid, unenforceable, or would not be infringed, approval of the subsequent abbreviated new drug application will be made effective no sooner than 180 days from whichever of the following dates is earlier:

- (i) The date the applicant submitting the first application first commences commercial marketing of its drug product; or
- (ii) The date of a decision of the court holding the relevant patent invalid, unenforceable, or not infringed.

The "applicant submitting the first application" is the applicant that submits an application that is both substantially complete and contains a certification that the patent was invalid, unenforceable, or not infringed prior to the submission of any other application for the same listed drug that is both substantially complete and contains the same certification.

In an August 2, 1999, response to petitions from two generic drug firms addressing this issue with respect to approval of ANDAs for cisplatin, FDA stated that these regulations must be interpreted, at least in the situation with cisplatin, to make eligibility for 180-day exclusivity based on who submitted the first paragraph IV certification for each listed patent. (Docket No. 99P-1271/PSA1 and PSA2). Therefore, in cases where multiple patents are listed, multiple applicants may be eligible for periods of exclusivity for a single drug product. Based upon the statements in the petition response, and FDA's actions in approving ANDAs for cisplatin, the agency's approach had been to use a patent-based analysis in determining eligibility for exclusivity. In other words, the first applicant with a paragraph IV certification for each listed patent was separately eligible for 180-day exclusivity based on that patent. Note that, in the case of cisplatin, one of the patents upon which eligibility for exclusivity was based had expired by the time any of the ANDAs eligible for exclusivity could be approved, so the agency's interpretation did not result in a delay in approvals of ANDAs.

Exclusivity Stand-Off

The agency has recognized, however, that if eligibility for exclusivity is patent-based, without regard to the facts and circumstances of specific applications, the agency could be prevented from approving ANDAs referencing a particular drug product by multiple conflicting exclusivities, which is inconsistent with the purpose and operation of the statute. This issue is discussed in some detail in the preamble to the proposed rule addressing changes to the ANDA approval regulations. 64 Fed. Reg. 42873, 42875-6 (August 6, 1999); *withdrawn* 67 Fed. Reg. 66593 (Nov. 1, 2002).

The situation with omeprazole ANDAs referencing Prilosec illustrated how untenable the patent-based multiple exclusivity approach could be in certain situations, when there are multiple

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patents listed for the listed drug and different first applicants for these patents. Under the patent-by-patent approach described in the cisplatin petition response, different ANDA applicants would have been eligible for exclusivity with respect to different patents listed for the reference listed drug. Absent a regulatory solution, these different exclusivity periods would have blocked approval of omeprazole ANDAs indefinitely.

An exclusivity stand-off whereby each ANDA applicant's approval is delayed indefinitely would be so at odds with both the narrow purpose of the 180-day exclusivity provision and the broader purposes of 1984 Drug Price Competition and Patent Term Restoration Act (the Hatch-Waxman Amendments) as to be absurd. Court decisions, including Mova Pharmaceutical Corp., v. Shalala, 140 F.3d 1060, 1074 (D.C.Cir. 1998), observe that the 180-day exclusivity period is intended as a reward to the ANDA applicant who challenges a listed patent. Such a challenge may make it possible for generic drugs to be approved before the expiration date of the challenged patent. The exclusivity stand-off would prevent the ANDA applicants who are eligible for the exclusivity from benefiting in any meaningful way from the exclusivity, and could substantially and indefinitely delay the availability of lower cost drugs for consumers. In that case, the eligible first ANDA applicants would be hamstrung by the very provision intended to provide them a benefit, and competition would be stifled by the very provision intended to encourage it. The only beneficiary of this interpretation would be the innovator who – despite the expiration of 30-month stays on ANDA approval – would see an indefinite extension of its monopoly market in a manner inconsistent with the intent of the Hatch-Waxman Amendments.

Regulatory Solution

To avoid results that cannot be reconciled with the purposes of the 180-day exclusivity provision in particular and the Hatch-Waxman Amendments in general, the agency has sought an approach to 180-day exclusivity that both hews as closely as possible to statutory language and is consistent with the goals of the legislation. It seems clear that Congress did not anticipate, and therefore did not address, this factual situation in drafting the 180-day exclusivity provisions of the Act, and FDA certainly did not contemplate it in promulgating the regulations now in effect. As noted in the cisplatin petition response, these regulations were adopted when the agency interpreted the statute to require that an ANDA applicant be sued and win its patent litigation to qualify for exclusivity. The chances of two applicants, each of whom was first for a different patent, winning their patent litigation was extremely low.²

The text of the Act does not address the situation in which two ANDA applicants' eligibility for exclusivity will create a stand-off in approvals, and the legislative history is similarly unilluminating. Accordingly, the agency has the discretion to construe the statute reasonably to further the purposes of the statute. Alternatively, even if the statutory language could be interpreted to result in an exclusivity stand-off, such an interpretation would be inconsistent with the purpose of the statute, inconsistent with agency policy, and the agency should reject it for producing an absurd result.

² In the years from 1984 to 1998, only three ANDA applicants qualified for 180-day exclusivity. Since the Mova decision in 1999, over 70 ANDAs have received 180 days of exclusivity.

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Once the interpretation resulting in the exclusivity stand-off is rejected, the choice appears to be between rewarding all applicants who submitted a first paragraph IV ANDA by giving them all the shared chance to market during the exclusivity period, or rewarding the very first applicant to challenge any listed patent by giving that applicant the entire exclusivity period to itself.

Under the usual application of the 180-day exclusivity provision, the agency would approve the ANDA eligible for exclusivity whenever it was ready for approval, and the exclusivity would begin to run, independent of the approval, with the commercial marketing of that drug product or with a court decision on the patent, whichever was first. However, when two or more applicants have exclusivity as to different patents that effectively blocks one another, the approval of the eligible ANDAs (and thus the possibility of the commercial marketing trigger coming into play) cannot occur without some resolution of the stand-off. The agency reviewed two approaches to resolving the question of which ANDA(s) may be approved - and when - in cases where different applicants are first to submit paragraph IV certifications to different patents.

FDA determined that when approval of an ANDA eligible for exclusivity is blocked by another applicant's eligibility for exclusivity, the applicants that are eligible for the 180-day period of generic drug exclusivity may share the same exclusivity period. An approach that shares the exclusivity among all of the first ANDA applicants ("shared exclusivity") would reward the first applicants to submit a paragraph IV certification with respect to any listed patent, and is therefore consistent with the most natural reading of the statutory text, which refers to the paragraph IV certification for the patent. The general approach to shared exclusivity is as follows:

When different applicants have submitted first paragraph IV ANDAs for different listed patents, FDA will approve the ANDAs that are first for any listed patent as soon as they are otherwise eligible for approval. That is, if it is only another applicant's eligibility for 180-day exclusivity as to a different patent that would block approval for an applicant that is itself eligible for 180 days of exclusivity, FDA will approve the ANDA. Exclusivity for all the ANDAs eligible for exclusivity at that time will be shared, and it will be triggered by the earlier of either first commercial marketing of any first applicant or a court decision on any one of the patents that qualified any applicant for exclusivity.³ During that "shared" exclusivity period, FDA may approve any ANDA eligible for exclusivity, but no other ANDAs.

Obviously, this approach may deprive any one applicant of the chance to be the sole competitor to the NDA holder. But the exclusivity is already structured in such a way that eligibility for exclusivity does not guarantee 180 days as the sole marketed generic drug (i.e., the court decision trigger could start exclusivity before an ANDA is approved, or uncertainty over the patent could result in no marketing of an approved product until an affirmance in the Federal

³ FDA has been asked to clarify which court decisions on which patents may begin the running of "shared" exclusivity. FDA intends that exclusivity could be triggered by a court decision on any of the patents that qualify an ANDA applicant for exclusivity as of the time of the application of the shared exclusivity: that is, at the time an applicant eligible for 180-day exclusivity is ready for final approval except for another applicant's eligibility for 180-day exclusivity as to another patent.

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Circuit of a district court win). A shared exclusivity approach will limit the number of ANDAs approved during the exclusivity period to the number of "first" applicants. Moreover, it may give each first applicant some part of the benefit from removing the multiple patents as barriers to approval, when any one of those patents could have delayed approval of ANDAs. There is also a clear benefit to consumers if FDA were to approve more than one ANDA: with multiple ANDAs approved and eligible for exclusivity, it is more likely that the exclusivity period will be triggered more quickly and at least one of the generic drugs will reach the market during the exclusivity period. Past experience has shown that first generics who are the sole applicants eligible for exclusivity often find it in their interest not to begin the exclusivity period.

FDA rejected a "one first applicant" approach, which would give all the exclusivity to the very first ANDA applicant to submit a patent challenge to any patent listed for the innovator drug. FDA would approve only the ANDA of the applicant who submitted the first paragraph IV certification for any patent, regardless of the patent for which it was submitted. That applicant's exclusivity would then begin to run with first marketing or a court decision on the patent that is the subject of the first certification. During the exclusivity period the agency would approve no other ANDA for the listed drug. When the exclusivity expired, all subsequent applicants would be eligible for approval if they otherwise met the approval requirements.

The one first applicant approach would reward the first applicant to begin to clear the path to ANDA approvals by challenging a listed patent. However, the agency believes that this approach would be less consistent with the statutory language than the shared exclusivity option, because this approach would be based upon a challenge to only one listed patent (the one for which the earliest paragraph IV certification was submitted). As noted above, the statute appears to apply exclusivity specifically with respect to an ANDA containing a paragraph IV certification for a patent for which a previous paragraph IV certification has been received for the same patent. Also, although promptness in challenging patents listed early in the Orange Book is important, it is certainly not adequate to remove the barriers to approval posed by later listed patents. Finally, by vesting the power to begin the exclusivity and the marketing of the drug in the hands of only one applicant, this approach would hold the potential for delays in the approval of generic drugs because there may be no court decision on this particular patent and the sole first applicant might not begin commercial marketing of its drug product. As a result, the 180-day exclusivity period would not begin to run, and the availability of multiple generic drugs could be substantially delayed.

Thus, the agency has adopted the shared exclusivity approach as more consistent with the statutory language, and with the intent of both the 180-day exclusivity provision and the Hatch-Waxman Amendments. FDA has now applied this approach on several occasions.

Shared 180-Day Exclusivity and Paroxetine Hydrochloride Tablets

Shared exclusivity applies to Paroxetine Hydrochloride ANDAs because different applicants are eligible for 180-day exclusivity as to different listed patents.

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TorPharm
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The agency has determined that TorPharm's ANDA was the first substantially complete ANDA containing a paragraph IV certification for all four strengths as to the '723 patent, the '759 patent, the '289 patent, and the '233 patent, and as to the '291 patent for the 10 mg, 20 mg, and 30 mg strengths. Different ANDA applicants were first to submit paragraph IV certifications as to the other listed patents and strengths.

Therefore, FDA has determined that it will approve your ANDA, and the ANDAs of other applicants also eligible for 180-day exclusivity, as soon as they are otherwise eligible for approval (i.e., all patents with a paragraph III certification have expired, no 30-month stay, ANDA meets other 505(j) approval requirements, etc.). Approval of an ANDA will not trigger the beginning of exclusivity. Exclusivity will begin to run with 1) the first commercial marketing of the drug product by any sponsor eligible for 180-day exclusivity, or 2) a court decision on any of the patents as to which any applicant qualified for the 180-day exclusivity, whichever comes first. During the 180-day exclusivity period, only those applicants eligible for exclusivity may be approved. Once the 180 days of exclusivity expire, FDA may approve any other ANDAs for Paroxetine Hydrochloride that are otherwise eligible for approval.

Status of the TorPharm ANDA

FDA has determined that there is one remaining 30-month stay, relating to the '233 patent, applicable to TorPharm's ANDA. As you know, by letter of July 1, 2003, GSK requested that FDA remove the '927, '759, and '233 patents from the Orange Book. Thus, GSK has effectively abandoned its claim to that 30-month stay. There are no other barriers to approval of TorPharm's ANDA and that ANDA is being approved today by separate approval letter.

Pursuant to 21 C.F.R. § 314.94(a)(12)(viii)(B), FDA will not remove a patent from the Orange Book that has been the subject of relevant patent litigation until the agency has determined that no ANDA applicant is eligible for 180-day exclusivity as to that patent. TorPharm is eligible for 180-day exclusivity as to the '759 and '233 patents. Therefore, FDA will not remove those patents from the Orange Book until the 180-day exclusivity period has expired.⁴ There has been no relevant litigation as to the '927 patent, and therefore the '927 patent is being withdrawn from the Orange Book, and will not serve as a basis for exclusivity. If TorPharm were to relinquish its eligibility for 180-day exclusivity as to the '759 and '233 patents, those patents would be removed from the Orange Book immediately.

⁴ Although FDA reached a different outcome recently in deciding to immediately delist a method of use patent (the '479 patent) for gabapentin, that situation involved different circumstances. In the gabapentin case, the patent holder essentially admitted to FDA that it had violated FDA regulations in submitting the patent for listing that did not claim an approved use. Further, the court in *Purepac Pharm. Co. v. Thompson*, 238 F. Supp. 2d 191(D.D.C. 2002) found that the '479 patent had been improperly submitted and enjoined FDA from refusing to approve any ANDA solely on the ground that it contained a section viii statement to the '479 patent. For reasons explained in the gabapentin administrative decisions and litigation, those circumstances led FDA to immediately delist the patent. However, those circumstances are not present in this case.

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Please note that a letter containing substantially the same information is being sent to the other ANDA applicants eligible to share the 180-day exclusivity for Paroxetine Hydrochloride. If you have any questions regarding this letter, please contact Ms. Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 301-827-5845.

Sincerely,



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

cc: Daniel E. Troy, OCC

