

January 28, 2003

Dear ANDA Applicant for Gabapentin:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Gabapentin Capsules, Tablets, or Oral Solution.

As described in the attached letter addressed to TorPharm and Purepac Pharmaceutical Company, the FDA has removed U.S. Patent No. 5,084,479 (the '479 patent) from the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

Applicants with pending ANDAs for gabapentin drug products must amend their applications, as required by 21 C.F.R. 314.94(a)(12)(viii)(B), to withdraw any prior certification or section viii statement as to this patent.

Please indicate at the top of your cover letter accompanying your submission that it is intended as a "Patent Amendment".

Sincerely yours,

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

ANDA 75-360 Torpharm (Gabapentin Capsules, 100 mg, 300 mg and 400 mg)
ANDA 75-350 Purepac (Gabapentin Capsules, 100 mg, 300 mg and 400 mg)

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for: TorPharm, a Division of Apotex, Inc.
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

January 28, 2003

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Ave.
Elizabeth, NJ 07207

Dear Ms. McDonald and Ms. Janulis:

This letter addresses approval and 180-day exclusivity issues related to your pending abbreviated new drug applications (ANDAs) for gabapentin capsules. Two patents for the reference listed drug, Neurontin (gabapentin) capsules, raise questions of eligibility for 180-day exclusivity under section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act) which were left unresolved after recent litigation. This letter describes FDA's resolution of these novel and complex issues. In resolving these matters, the agency has considered the relevant provisions of the Act; FDA's regulations in 21 C.F.R. § 314; the preambles to those regulations where relevant; *Purepac Pharmaceutical Co. v. Thompson*, No. 02-1657 (D.D.C. Dec. 16, 2002); *Warner-Lambert v. Apotex, Inc.*, No. 02-1073 (Fed. Cir. Jan. 16, 2003); and the submissions made by Torpharm, Purepac, and others on this issue.

U.S. Patent Number 5,084,479

Pfizer Inc., by assignment from Warner-Lambert, Co., is the holder of the approved NDA for Neurontin (gabapentin) capsules, which was originally approved for adjunctive therapy in the treatment of partial seizures associated with epilepsy. At the time of the original NDA submission for the capsules, Warner-Lambert submitted information on patents claiming, *inter alia*, a method of treating certain forms of epilepsy. Shortly after the NDAs were approved, Warner-Lambert submitted information to FDA on U.S. Patent Number 5,084,479 (the '479 patent), claiming a method for using gabapentin to treat neurodegenerative diseases. Warner-Lambert submitted declarations to FDA that the '479 patent covered the method of use of Neurontin, and FDA listed the patent in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

On August 20, 2002, Purepac filed suit against FDA in the United States District Court for the District of Columbia challenging FDA's determination that applicants seeking approval of generic gabapentin were required to submit patent certifications to the '479 patent, on the ground that the '479 patent did not claim a method of use for which a drug product has been approved. *Purepac Pharmaceutical Co. v. Thompson*, No. 02-1657 (D.D.C.)

Right after the conclusion of oral argument on Purepac's motion for summary judgment on December 13, 2002, FDA received a letter from Pfizer addressing Warner-Lambert's submission to FDA of the '479 patent for publication in the Orange Book as protection for the approved Neurontin NDAs. Pfizer's letter states that Warner-Lambert never represented to FDA that the '479 patent claims the approved use of gabapentin to treat epilepsy, nor was the listing intended to convey that it covers the approved use.

On December 16, 2002, the court issued its decision in *Purepac*. Judge Huvelle concluded that the '479 patent does not claim the approved use of gabapentin. *Purepac* slip op. at 24-26.

Because the '479 patent does not claim an approved use of gabapentin, it may not be listed in the Orange Book under FDA's regulations. Based upon the information provided in Pfizer's letter, and upon Judge Huvelle's finding, FDA requested by letter of January 6, 2003, that Pfizer withdraw the '479 patent from the list of patents covering Neurontin. FDA explained that if Pfizer did not withdraw the '479 patent, FDA reserved the right to take any action appropriate to conform the patents listed as protection for Neurontin with the requirements of FDA's regulations and the Act.

By letter of January 8, 2003, Pfizer notified FDA that it "agrees that the '479 patent does not claim methods of use for which Neurontin has been approved" and "reconfirms that neither Pfizer nor Warner-Lambert ever represented to FDA that the '479 patent claimed an approved use." Pfizer's letter also states a number of arguments in support of its listing of the patent.

On January 16, 2003, the Federal Circuit issued a decision regarding the scope of infringement of patents on unapproved uses under 35 U.S.C. § 271(e)(2)(A). *Warner-Lambert Co. v. Apotex Corp.*, Civil No. 02-1073 (Fed. Cir.). The '479 patent was one of the patents at issue in that litigation. On January 17, 2003, Pfizer notified FDA that, based upon the *Warner-Lambert* decision, it was going to withdraw the '479 patent from the Orange Book.

Before FDA withdraws the '479 patent from the Orange Book pursuant to Pfizer's letter, it must make a determination, as required by 21 C.F.R. § 314.94(a)(12)(viii)(B), that the removal of the patent will not affect an applicant's 180-day exclusivity. Torpharm has argued that it is eligible for exclusivity as to the '479 patent because it was the first to file a substantially complete ANDA containing a paragraph IV certification to that patent. Therefore, Torpharm asserts, FDA may not remove the '479 patent from the Orange Book until Torpharm's exclusivity has expired. FDA disagrees with Torpharm. The agency has concluded that 1) Torpharm is not eligible for exclusivity as to the '479 patent, and 2) FDA may therefore remove the '479 patent from the Orange Book.

180-Day Exclusivity as to the '479 Patent

FDA has determined that, under the provisions of section 505(j) of the Act and related FDA regulations, Torpharm is not eligible for 180-day exclusivity as to the '479 patent.

i. Exclusivity

The statutory provision governing 180-day exclusivity reads:

If the application contains a certification described in subclause IV of paragraph (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).

Although this "exclusivity" provision is commonly characterized as granting 180-day exclusivity to the first applicant to submit an ANDA containing a paragraph IV certification, the statute does not provide for that directly. Instead, this end is accomplished by delaying the approval of subsequent ANDAs containing a paragraph IV certification for 180 days after the exclusivity period for the first ("previous") applicant has begun. Thus, if, by the time the first applicant's ANDA is ready for approval, it no longer contains a valid paragraph IV certification, the first applicant is not eligible for exclusivity. Similarly, where subsequent applications do not contain paragraph IV certifications, their approval is not delayed under this statutory provision. Therefore, the Torpharm ANDA and at least one subsequent ANDA would have to contain paragraph IV certifications to the '479 patent for there to be any exclusivity as to this patent.

ii. Paragraph IV Certifications and Section viii Statements

The relevant provisions at section 505(j)(2)(A)(vii) and (viii) state that an ANDA must include:

(vii) 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) of this section –

- (I) that such patent information has not been filed,
- (II) that such patent has expired,
- (III) of the date on which such patent will expire, 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; and

(viii) 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, a statement that the method of use patent does not claim such a use.

(emphases added).

Thus, if an ANDA applicant is seeking approval for a use claimed by a listed patent, the applicant must submit a certification pursuant to section 505(j)(2)(A)(vii). If an ANDA applicant is not seeking approval for a use claimed by a listed patent, it must submit a statement pursuant to section 505(j)(2)(A)(viii). As FDA's preamble to the final rule implementing these provisions noted, the statute distinguishes between ANDAs seeking approval for a use claimed in a patent and ANDAs not seeking approval for a use claimed in a patent. 59 Fed. Reg. 50338, 50347 (October 3, 1994). The two provisions of the statute – and the corresponding implementing regulations at 21 C.F.R. § 314.94(a)(12)(i) – do not overlap. An applicant does not have the option of making a paragraph IV certification in lieu of, or in addition to, a section viii statement; either the ANDA applicant is seeking approval for the use claimed in the patent, or it is not. The character of the patent and of the specific ANDA determine what the applicant must - and may - submit in response to a listed patent.

iii. This Case

FDA has reviewed the statute and its regulations in light of the statements in Pfizer's recent letters, Judge Huvelle's decision in *Purepac*, and the Federal Circuit's decision in *Warner-Lambert*, and determined that neither Torpharm nor subsequent applicants with ANDAs that contain a paragraph IV certification to the '479 patent may retain a paragraph IV certification. In determining whether a paragraph IV certification or section viii statement is appropriate, the relevant factual inquiry is whether the ANDA applicant is seeking approval for a use claimed in the patent. In this case, it is now clear that no ANDA applicant is seeking approval for the use of gabapentin claimed in the '479 patent. As clarified in Pfizer's recent submissions to FDA, and as found by Judge Huvelle and the Federal Circuit, the '479 patent claims the use of gabapentin to treat neurodegenerative diseases. See *Purepac*, slip op. at 24-25; *Warner-Lambert*, slip op. at 2-3. The ANDA applicants are seeking approval for gabapentin products labeled for use in treating epilepsy; not for the treatment of neurodegenerative disease. See *Purepac*, slip op. at 12,14; *Warner-Lambert*, slip op. at 4. Further, as Judge Huvelle noted, "[t]here is no dispute that epilepsy is *not* a neurodegenerative disease." *Purepac*, slip op. at 24, n. 21 (emphasis in the

original). Because the '479 patent claims neurodegenerative disease, and none of the applicants is seeking approval of a gabapentin product for the treatment of neurodegenerative diseases, all of the ANDA applicants for gabapentin would be required to submit a statement pursuant to section 505(j)(2)(A) (viii) -- not a patent certification pursuant to section 505(j)(2)(A)(vii) -- with respect to the '479 patent.

Thus, if the '479 patent were to remain listed in the Orange Book, all ANDA applicants for gabapentin would be required to submit a "section viii statement" to the '479 patent. Once Torpharm submitted a section viii statement to the '479 patent, it would no longer be eligible for exclusivity; once subsequent applicants amended their ANDAs to contain section viii statements, they would no longer be blocked by Torpharm's paragraph IV certification. Because no ANDA applicant for gabapentin, including Torpharm, could maintain a paragraph IV certification to the '479 patent, Torpharm would not be eligible for exclusivity under section 505(j)(5)(B)(iv).¹

Removal of the '479 patent from the Orange Book

As discussed above, FDA has concluded that Torpharm is not eligible for exclusivity as to the '479 patent. Because FDA has made the determination that no applicant is eligible for exclusivity as to the '479 patent, 21 C.F.R. § 314.94 does not prevent its removal from the Orange Book. Accordingly, FDA has removed the patent. Applicants with pending ANDAs for gabapentin must amend their applications, as required by 21 C.F.R. § 314.94(a)(12)(viii)(B), to withdraw any certification or section viii statement as to the '479 patent. As stated in the regulation, once the amendment has been submitted, the ANDA will "no longer be considered to be one containing a certification under [paragraph IV]." *Id. See also Mylan Pharmaceuticals, Inc. v. Henney*, 94 Supp. 2d 36, 56-58 (D.D.C. 2000)(removal of paragraph IV certification terminates eligibility for exclusivity).²

U.S. Patent Number 6,054,482

During the *Purepac* litigation, FDA's position was that, based upon its review of the ANDA records, Purepac was the first to submit an ANDA amendment containing a paragraph IV certification to the '482 patent. Beginning on January 7, 2003, Torpharm submitted to FDA a series of letters analyzing the administrative record related to the Purepac gabapentin capsule ANDA. Based upon its analysis, Torpharm asserted that Torpharm, not Purepac, was first to submit an amendment containing a paragraph IV certification to the '482 patent. The crux of

¹ FDA notes that, even if Torpharm were to refuse to withdraw its paragraph IV certification to the '479 patent, because of Judge Huvelle's decision that the '479 patent doesn't claim a use for which the applicants are seeking approval, FDA would have no basis to prevent subsequent ANDA applicants from amending their paragraph IV certifications for the '479 patent to section viii statements. Once such a change was made, Torpharm's paragraph IV certification would not delay approval of the subsequent ANDA. Although FDA's regulations state, that under certain circumstances, a subsequent applicant may not change its certification to circumvent a first applicant's exclusivity, that approach is premised upon the paragraph IV certification having been an appropriate certification to the listed patent. That is not the case here.

² Note that the withdrawal of the '479 patent from the Orange Book will affect pending ANDAs for all gabapentin drug products (capsule, tablet, and solution). Applicants must amend pending ANDAs accordingly.

Torpharm's argument is that Purepac's ANDA was not complete at the time of submission. Torpharm asserts that, when Purepac's ANDA amendment with the paragraph IV certification to the '482 patent was both sent to (May 25, 2000) and received by (May 26, 2000) FDA, Purepac did not comply with the statute or regulations because it did not indicate that it was sending (or had sent) concurrent notice of the certification to the NDA holder/patent owner. Torpharm argues that it was the first applicant to submit an amended ANDA that meets the statutory notice requirements, and, therefore, it is eligible for 180-day exclusivity.

The agency agrees with Torpharm that, under the Act, an ANDA applicant submitting an amendment containing a paragraph IV certification to a listed patent must provide notice of the submission at the time the amendment is submitted. However, after reviewing the ANDA records, FDA has concluded that Purepac remains eligible for 180-day exclusivity as to the '482 patent. Even after taking into account the delay in notice, Purepac was still the first ANDA applicant to both submit an amended ANDA containing a paragraph IV certification and provide notice of the submission to the NDA holder and patent owner.

The Act has separate provisions addressing notice of a paragraph IV certification when the certification is submitted in an ANDA or in an amendment to an ANDA. Section 505(j)(2)(B)(i) states that "an applicant who makes a [paragraph IV certification] shall include in the application a statement that the applicant will give the notice required by clause (ii)...." In contrast, section 505(j)(2)(B)(iii) states that "if an application is amended to include a [paragraph IV certification], the notice required by clause (ii) shall be given when the amended application is submitted." FDA regulations at 21 C.F.R. §§ 314.94(a)(12)(i) and 314.95(b), and at §§ 314.94(a)(12)(viii) and 314.95(d), respectively, parallel these requirements. An applicant submitting an original ANDA with a paragraph IV certification must provide notice only after receiving acknowledgement from FDA that the ANDA has been received and is sufficiently complete to permit a substantive review. An applicant submitting an ANDA amendment containing a paragraph IV certification must send the notice at the same time it submits the amendment.

FDA's record shows, and correspondence with Purepac confirms, that Purepac did not send the required notice of the paragraph IV certification to the '482 patent until after it had submitted the amendment to FDA. FDA records show that Purepac sent its paragraph IV certification to the '482 patent to FDA on May 25, 2000. It was stamped received by FDA on May 26, 2000. Purepac sent notice of the certification to the NDA holder, Warner-Lambert, on June 13, 2000, the same day it sent notice to the patent owner.

FDA believes that, to resolve the question of who is eligible for 180-day exclusivity in this case, it must look to the fundamental requirements for submission of an ANDA amendment. This entails looking at the requirements of the statute and the regulations, and the date those requirements were met. As discussed above, the statute makes the first applicant to submit a paragraph IV certification to a patent eligible for exclusivity, and it also requires that the ANDA applicant give notice when the ANDA is submitted. Because Purepac did not give notice when it submitted the amendment to FDA, FDA will not treat the original receipt date as the relevant date for exclusivity purposes. Instead, the agency will look to the date that Purepac actually sent the required notice, since this is the date upon which Purepac effectively met the statutory

requirements by having both submitted a paragraph IV certification and sent notice of the submission. This date is June 13, 2000.

Torpharm, in turn, sent its amendment with the paragraph IV certification to the '482 patent to FDA on June 13, 2000. It was stamped received on June 16, 2000. Torpharm sent notice of the paragraph IV certification to Warner-Lambert by letter dated June 12, 2000, which was sent on June 13, 2000. Therefore, the date upon which Torpharm had both submitted its amendment to FDA and sent the required notice was June 16, 2000. Because this date is later than the June 13, 2000, date applicable to Purepac, Purepac remains eligible for 180-day exclusivity as to the '482 patent exclusivity.

In making this decision, FDA has rejected Purepac's argument that the 2½ week time lag between submission of the ANDA amendment and sending of the notice should be disregarded because it was a reasonable period for preparing and sending the detailed statement of factual and legal basis required by the statute. The statute clearly contemplates that an ANDA applicant will have determined whether its product infringes a listed patent – or whether that patent is infringed - before it submits a patent certification, not after, since it is precisely this analysis that is the basis for the paragraph IV certification itself.³

FDA also rejects Torpharm's argument that this conclusion gives Purepac some reward for having submitted its amendment without sending the notice. The agency's calculations are based upon when – in the case of both Torpharm and Purepac – the agency had received the ANDA amendment and notice of the paragraph IV certification had been sent.

Sufficiency of Notice Re the '482 patent

The regulations require that notice of a paragraph IV certification be sent to both the NDA holder and the patent owner. 21 C.F.R. § 314.95(a). There is no dispute that both applicants gave notice to the NDA holder, Parke Davis/Warner Lambert. Purepac's notice was received by Parke Davis on June 14, 2000; Torpharm's notice was received on June 15, 2000 by both Parke Davis and Warner-Lambert. However, both Purepac and Torpharm have raised questions about the adequacy and timing of notice to the patent owner, Godecke Aktiengesellschaft (Godecke), a Germany company. Purepac has documented that it sent notice to Godecke on June 13, 2000, which was received on June 26, 2000. Torpharm did not send notice directly to Godecke. Torpharm argues that, under 21 C.F.R. § 314.95(a)(1), notice to Warner-Lambert is sufficient because Warner-Lambert is identified in the patent declarations for the '482 patent as the U.S. agent for Godecke. FDA agrees. Because Warner-Lambert is the agent for Godecke, notice to Warner-Lambert is sufficient. Moreover, notice to Warner-Lambert is sufficient notice for both Purepac and Torpharm. The 30 month stays are calculated from the date notice was received by Warner-Lambert. Therefore, the 30 month stays on approval of the Purepac and Torpharm

³ As noted above, an ANDA applicant may wait to send the notice of a paragraph IV certification in an original ANDA because FDA must determine whether the application is sufficiently complete to permit a substantive review. Once that determination has been made, however, an applicant must send the notice. 21 C.F.R. § 314.95(b).

ANDAs with respect to the '482 patent expired on December 14, 2002, and December 15, 2002, respectively.

Shared Exclusivity

Judge Huvelle's December 16, 2002, decision finding that Purepac properly submitted a section viii statement to the '479 patent remanded to the agency the question whether Torpharm still had a claim to immediate approval and/or 180-day exclusivity for its gabapentin capsule ANDA. The court noted that "FDA has not decided whether it could, or would, approve Torpharm's application with a paragraph IV certification to the '479 patent even if the Court were to direct the agency to accept Purepac's application with a section viii statement." *Purepac*, slip op. at 34-35. The court determined it was appropriate to let FDA sort out the "considerable complexities" of this matter. *Id.* Even though Judge Huvelle did not directly decide the question of shared exclusivity, the fundamental basis of her decision effectively decided the matter.

Judge Huvelle's finding that Purepac's section viii statement was appropriate **because the '479 patent does not claim a use for which Purepac – or Torpharm – was seeking approval** was fatal to any claim Torpharm had to exclusivity. It is possible the court could have found a different basis for permitting Purepac's section viii statement that would have given the agency more discretion in making an exclusivity decision. However, given the court's specific conclusions and subsequent events, FDA believes it has little choice but to find that no applicant is eligible for 180-day exclusivity as to the patent and delist the '479 patent. With no possibility of blocking exclusivities, as described in the November 2001 letter regarding omeprazole ANDAs, there is no possibility that Torpharm and Purepac will have shared exclusivity for gabapentin capsules. Only the '482 patent remains relevant for exclusivity purposes. Purepac is eligible for 180-day exclusivity as to that patent. Therefore, Torpharm, and other ANDA applicants for gabapentin capsules, must wait for final approval until the end of Purepac's exclusivity period, which will be triggered by either commercial marketing of gabapentin capsules, or by a court decision finding the '482 patent invalid or not infringed, whichever comes first.

FDA is aware that the outcome in this case may seem inequitable. Torpharm submitted a paragraph IV certification to a listed patent as required by FDA. Moreover, it successfully defended a hard-fought patent infringement case, which established important new parameters for litigation under 35 U.S.C. § 271(e)(2). However, there is no guarantee in the statute that, even in such compelling circumstances, an ANDA applicant will benefit from exclusivity. The value of exclusivity appears to be a function of timing, strategy, and luck. In Torpharm's case, exclusivity was lost to Purepac's successful defense of its section viii statement to the '479 patent.

This is not a tentative approval or approval letter for any ANDA. Tentative approval and approval status will be communicated separately to each applicant. A copy of this letter will be sent to all applicants with pending ANDAs for gabapentin capsules.

If you have questions regarding these issues, please contact Ms. Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, (301) 827-5845.

Sincerely yours,

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

cc: Timothy H. Gilbert, counsel for Torpharm/Apotex
Arthur Y. Tsien, counsel for Torpharm/Apotex
William A. Rakoczy, counsel for Torpharm/Apotex
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