DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 28 2003

Daniel J. Tomasch, Esq.
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666 Fifth Ave.
New York, NY 10103

Dear Mr. Tomasch:

This responds to your letter of May 23, 2003, on behalf of Alcon Laboratories, Inc., regarding 180-day exclusivity under Section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act with respect to the patents listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) as protection for Allergan's Alphagan (brimonidine tartrate) Ophthalmic Solution. Alcon has a pending ANDA for brimonidine, as does Bausch & Lomb.

Alcon's position is that no 180-day exclusivity should attach to any of the patents listed for brimonidine, because certain court decisions have found that none of those patents claim approved uses of Alphagan, and thus they should not have been listed in the Orange Book. More importantly, given the posture of this matter, Alcon argues that no party is eligible for 180-day exclusivity for U.S. Patent No. 6,465,464 ('464 patent). FDA has reviewed your submission and disagrees with your analysis.

I. Background on Brimonidine Patent Litigation.

Your letter cites recent private patent litigation as a basis for denying 180-day exclusivity as to the '464 patent for brimonidine. Allergan initially obtained U.S. Patents 6,194,415 ('415 patent) and 6,248,741 ('741 patent) which claimed a method of using brimonidine as a neuroprotective agent to treat glaucoma. After Alcon and Bausch & Lomb filed ANDAs for brimonidine with paragraph IV certifications to the '415 and '741 patents, Allergan separately sued Alcon and Bausch & Lomb for patent infringement in the U.S. District Court for the Central District of California. On May 8, 2002, the court granted summary judgment to Alcon. *Allergan, Inc. v. Alcon Laboratories, Inc.*, 200 F. Supp. 2d 1219, 1223 (C.D. Cal. 2002) (*Allergan I*). Shortly thereafter, in a June 4, 2002, Order, the court granted summary judgment to Bausch & Lomb, referencing its May 8, 2002, Order granting summary judgment to Alcon.

On March 28, 2003, the Federal Circuit affirmed the decision of the district court. *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322 (Fed. Cir. 2003). On May 22, 2003, the Federal Circuit denied Allergan's petition for rehearing *en banc*.

After the district court decision on the '415 and '741 patents was issued and while the appeal was pending, Allergan listed the '464 patent, which also covered the use of brimonidine for

Attachment C

neuroprotection. This patent was also the subject of paragraph IV certifications by both Alcon and Bausch & Lomb. Allergan filed patent infringement litigation in the U.S. District Court for the District of Delaware. Alcon and Bausch & Lomb filed a declaratory judgment action in the U.S. District Court for the Central District of California. The Delaware court granted the ANDA applicants' motion to transfer the patent infringement case to California. On March 20, 2003, the California court entered an Order and decision finding that the '464 patent was not infringed under either 35 U.S.C. 271(e)(2) or 271(b) for the same reasons as in *Allergan I. Alcon Labs., Inc. v. Allergan, Inc.*, 02-1192 (C.D. Cal. March 20, 2003) ("*Allergan II*").

II. Eligibility for 180-Day Exclusivity is Based on Each Patent.

Alcon contends that because *Allergan II* was decided on the same principles as *Allergan I*, any exclusivity should have been awarded to Alcon after it won summary judgment in *Allergan I*. Thomasch letter at 2. That argument is contrary to FDA's longstanding position that the first ANDA to submit a paragraph IV certification for each of the patents listed in the Orange Book for a drug product has been, or is, eligible for 180-day exclusivity as to that patent. In responding to a 1999 citizen petition related to approval of ANDAs for the drug product cisplatin, FDA construed the pertinent regulations, 21 C.F.R. § 314.107(c)(1) & (2), and determined that eligibility for 180-day exclusivity would be based on who filed the first paragraph IV certification for each listed patent. Under FDA regulations, a "subsequent" ANDA with a paragraph IV certification relating to the "same patent" as a previous ANDA paragraph IV certification is not eligible for approval until the first ANDA's exclusivity has run. 21 CFR § 314.107(c)(1).

The regulation's reference to the "same patent" as opposed to "any" patent or "all patents related to the same drug" means that eligibility for exclusivity is based upon the particular patent at issue and not the drug product as a whole. As a result, multiple applicants may be eligible for periods of exclusivity for a single drug product. The agency has referred to this approach to determining eligibility for exclusivity as a "patent-by-patent" or "patent-based" analysis. That is, the first applicant with a paragraph IV certification for each listed patent is separately eligible for 180-day exclusivity based on that patent.

The only patent currently relevant to 180-day exclusivity and the timing of brimonidine ANDA approvals is the '464 patent. In a May 21, 2003, letter, FDA informed Alcon, Bausch & Lomb, and Allergan that the May 8, 2002, and June 4, 2002, decisions involving the '415 patent and '741 patent were court decisions of non-infringement for purposes of permitting ANDA approval. The first of these decisions would also have triggered the running of exclusivity under section 505(j)(5)(B)(iv)(II) for the '415 and '741 patents. The 180-day exclusivity period as to those patents has thus expired.

Accordingly, the first ANDA applicant to submit a paragraph IV certification to each of the patents has been eligible for 180-day exclusivity as to that patent, and exclusivity based on the '464 patent is not foreclosed by the earlier decisions on the '415 and '741 patents.

III. The Facts Involving Exclusivity for Gabapentin Were Significantly Different.

Alcon argues that the facts regarding the patents for brimonidine are the same as those related to the '479 patent for gabapentin, which was at issue *in Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003), *Purepac Pharm. Co. v. Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002), and *TorPharm, Inc. v. Thompson*, Civil Action No. 03-0254 (D.D.C. April 25, 2003) (*Purepac* and *TorPharm* have been consolidated on appeal, which is pending in the D.C. Circuit).

A. Background on Gabapentin

Purepac and TorPharm submitted ANDAs for gabapentin, and the innovator Warner-Lambert sued them both. With respect to one method of use patent (the '479 patent), the Federal Circuit found that TorPharm did not infringe the patent because it was not seeking approval for the use claimed in the patent. *Warner-Lambert Co.*, 316 F.3d 1348.

In the meantime, Purepac had filed a section viii statement for the '479 gabapentin patent, that is, a statement that a method-of-use patent submitted in connection with an NDA does not claim any use of the drug product for which the applicant is seeking approval, pursuant to 21 U.S.C. § 355(j)(2)(A)(viii); 21 C.F.R. § 314.94(a)(12)(iii). When FDA told Purepac that its section viii statement was improper and it would not approve its ANDA, Purepac sued FDA (and TorPharm intervened) seeking to require FDA to approve its ANDA and not approve an ANDA that contained a paragraph IV certification to that patent. During that litigation, the innovator essentially admitted to FDA that it had violated FDA regulations in submitting the patent for listing that did not claim an approved use.

The district court determined that the patent did not claim an approved use of the drug, and an ANDA applicant could therefore submit a section viii statement as to that patent. *Purepac Pharm. Co.*, 238 F. Supp. 2d 191. In subsequent administrative proceedings, FDA determined that no ANDA applicant was eligible for 180-day exclusivity as to the '479 patent. As the agency described in a January 28, 2003, letter to the ANDA applicants, because the patent owner had informed FDA directly that the '479 patent did not claim an approved use of gabapentin, and because the *Purepac* court had specifically found that an ANDA applicant could submit a section viii statement to the patent, no ANDA applicant could maintain a paragraph IV certification as to the '479 patent and no one would be eligible for 180-day exclusivity as to that patent. *See* January 28, 2003 letter from Gary Buehler to Apotex Corp. and Purepac Pharmaceutical Co. (attached).

TorPharm challenged this decision as inconsistent with FDA's treatment of 180-day exclusivity for a patent listed for mirtazapine. In the case of mirtazapine, a district court had found in private patent infringement litigation that the listed patent claimed only unapproved uses of mirtazipine. *Organon, Inc. and Akzo Nobel N.V. v. Teva Pharmaceuticals, Inc.*, C.A. 01-2682 (Dec. 18, 2002 D.N.J.); *appeal docketed*, CA 03-1218 (Fed. Cir.). Nevertheless, FDA granted the first mirtazipine ANDA applicant to file a paragraph IV certification to that patent 180-day exclusivity. As described in a February 24, 2003 letter to Tim Gilbert, counsel for

Apotex/TorPharm (attached), FDA's practice under section 505(j)(5)(B)(iv) and 21 C.F.R. § 314.107(c) is to grant 180-day exclusivity to the ANDA applicant that was first to file a valid paragraph IV certification to a listed patent, and for that exclusivity to be triggered, in certain cases, by a court decision in litigation resulting from a paragraph IV certification finding the patent invalid or not infringed. It would be unreasonable, and contrary to FDA regulations and practice, to either remove challenged patents from the Orange Book or require a change from paragraph IV certification to section viii statement for the ANDA applicants on the basis of a district court decision of non-infringement, where that decision was the result of the ANDA applicant's submission of a paragraph IV certification and successful litigation of the patent claim. To do so would vitiate the 180-day exclusivity. Thus, the agency would not rely on a favorable decision obtained by an ANDA applicant in paragraph IV litigation to eliminate that applicant's exclusivity. Gabapentin, however, involved additional circumstances other than the court decision in paragraph IV litigation.

TorPharm sued FDA and Purepac intervened. The district court upheld FDA's decisions contained in the January 28 and February 24, 2003, letters. *TorPharm, Inc. v. Thompson*, Civil Action No. 03-0254 (D.D.C. April 25, 2003). The court explained why a decision in the underlying paragraph IV litigation that the patent did not claim an approved use would not vitiate exclusivity:

> If a judicial determination of non-infringement in patent litigation triggered by the use of a paragraph IV certification comes to serve as a basis for the subsequent FDA determination that the patent in question should no longer be listed – and therefore that a paragraph IV certification, and its corresponding promise of exclusivity, is no longer appropriate – the incentive structure created by the Hatch-Waxman Amendments would be turned on its head... It would be cruelly ironic, and perverse, to use an ANDA applicant's success in such an infringement action as the basis for denying exclusivity to that applicant.

TorPharm, slip opinion at n. 15. The court noted that the agency's decision to delist the patent in gabapentin was compelled by the court's earlier decision in *Purepac* (which was not paragraph IV litigation) that required FDA to accept Purepac's section viii statement, rather than the result of the *Warner-Lambert* decision in the patent litigation.

B. Comparison of Gabapentin and Brimonidine.

Alcon argues that the gabapentin outcome controls the outcome in brimonidine, and no ANDA applicant is eligible for 180-day exclusivity as to the '464 patent. Alcon cites the court's finding in *Allergan II* that the '464 patent does not claim an approved use for Alphagan. Alcon asserts that the *Allergan II* decision "implicitly recognizes that the '464 Patent, since it does not cover 'an approved or pending use of the new drug' (21 C.F.R. § 314.53(b)), should not have been listed in the Orange Book." Thomasch letter at 8.

As explained above, a court decision in private patent litigation finding that a listed patent does not claim an approved use for the listed drug *does not* render the first ANDA applicant to file a

paragraph IV certification as to that patent ineligible for exclusivity. The facts involved in the mirtazapine case resemble those involved for brimonidine in that there was a decision in the paragraph IV litigation that the patent did not claim an approved use. Thus, the reasoning underlying the agency's treatment of the mirtazapine patent applies as well to the concerns Alcon has raised regarding the '464 patent for brimonidine.

The circumstances surrounding the gabapentin patent were different in that there had been an admission by the patent holder to FDA that the '479 patent does not claim an approved use, and a district court decision in a case brought against FDA in which the court expressly found that a section viii statement is the correct submission for the listed patent. Neither the *Purepac* court's narrow decision based on unique factual circumstances involving gabapentin, nor FDA's decision regarding exclusivity as to the '479 gabapentin patent required a change in established FDA practice regarding 180-day exclusivity. As the *TorPharm* court held in distinguishing the gabapentin and mirtazapine, "[w]hatever similarities may exist . . . , one crucial difference remains: in the [mirtazapine] case, there was no court decision requiring the FDA to accept a section viii statement with respect to the patent in question." 2003 WL 1957490 at 14.

Alcon further asserts that, in light of *Purepac* and *Warner-Lambert*, Alcon and Bausch & Lomb should have been permitted to submit section viii statements to the '464 patent. Bausch & Lomb should not be permitted to benefit from an improperly submitted paragraph IV certification. Thus, the paragraph IV certifications should be deemed to be section viii statements and no exclusivity should attach.

FDA understands that Alcon and Bausch & Lomb may well have believed that the '464, '415, and '741 patents should not have been listed in the Orange Book. However, the patents were submitted to the agency accompanied by the declaration required by 21 CFR §314.53, and the patents remain in the Orange Book. As the agency has stated repeatedly, an ANDA applicant may not submit a section viii statement unless it "carves out" its labeling to correspond to a listed method of use patent. If the ANDA proposes to duplicate the innovator's label, it must certify to the listed use patents. The district court's narrow decision in *Purepac* on the specific facts in the gabapentin case has not changed the agency's practice. Thus, whatever their views on the propriety of the listing of the brimonidine use patents, including the '464 patent, Alcon and Bausch & Lomb were required to submit paragraph IV certifications, rather than section viii statements.

Furthermore, as FDA stated in the mirtazipine case, it would be unreasonable to either remove challenged patents from the Orange Book or require a change from paragraph IV certification to section viii statement for the ANDA applicants on the basis of a district court decision of non-infringement, where that decision was the result of the ANDA applicant's submission of a paragraph IV certification and successful litigation of the patent claim. Unlike gabapentin, there has been no court decision requiring FDA to accept section viii statements for one or more of the brimonidine patents.

Moreover, both applicants submitted paragraph IV certifications and there is no reason to retroactively deem them otherwise. Whether or not the applicants believe they would file paragraph IV certifications today, based on the current state of the law, is simply irrelevant. Therefore, the courts' decisions in the underlying paragraph IV litigation that the '415, '741 and '464 patents do not claim approved uses of brimonidine do not eliminate exclusivity on those patents.

IV. The Date of FDA Receipt of the Hard-Copy of the Paragraph IV Certification Governs Exclusivity.

Finally, your letter briefly raised the question of whether the date of a facsimile submission from Alcon would serve for calculating when Alcon submitted its paragraph IV certification to the '464 patent. FDA has reviewed its regulations and practices, and has determined that it relies only on the date stamped copy of a paragraph IV certification submitted to the addresses described in 21 CFR § 314.440. Items submitted through the addresses listed in the regulation are date stamped upon submission. FDA relies on the date stamped document submitted to these addresses for determining when a paragraph IV certification was submitted. The regulation does not provide for submission by facsimile. Facsimile copies have not been and are not used by the Office of Generic Drugs for determining receipt dates for patent certifications. Therefore, the date stamp on Alcon's paragraph IV certification submitted in hard copy to the address in 21 CFR § 314.440 will control for purposes of determining eligibility for 180-day exclusivity.

Sincerely,

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

Enclosures:
1. January 28, 2003 Letter to Apotex & Purepac
2. February 24, 20003 Letter to Gilbert

cc: Elizabeth Dickinson, Associate Chief Counsel for Drugs
Thomas Scarlett, Counsel for Bausch & Lomb