DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 24 2003

Gilbert's
Attention: Mr. Tim Gilbert
49 Wellington Street East
Toronto, Canada M5E 1C9

OGD Control # 03-107

Dear Mr. Gilbert:

This responds to your January 31, 2003, letter regarding FDA's treatment of ANDAs for mirtazapine in light of the agency's January 28, 2003, decision regarding 180-day exclusivity for pending ANDAs for gabapentin. Both the gabapentin and mirtazapine ANDAs raise questions related to whether an ANDA applicant may be eligible for 180-day exclusivity under section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act) with respect to a patent that does not claim an approved use of the listed drug. Your concern is that FDA is treating these ANDAs - which you believe are similarly situated - in an inconsistent fashion. The agency has reviewed the record concerning the gabapentin and mirtazapine ANDAs, and your analysis, and has concluded that the decisions are warranted by the facts and are not inconsistent.

The agency is aware that on February 14, 2003, Torpharm sued FDA in the U.S. District Court for the District of Columbia over FDA's decisions related to the approval of gabapentin ANDAs. This response to your January 31, 2003, letter is being issued subsequent to that lawsuit. However, you should be aware that the agency had prepared its response regarding the differences between the gabapentin and mirtazapine situations before the February 14, 2003, lawsuit was filed. A February 13, 2003, letter from Organon requesting delisting of the '099 patent delayed issuance of the letter while the agency considered the effect, if any, of this request on 180-day exclusivity. The agency revised its letter to address the delisting issue, as described below.

As you know, FDA has determined that no gabapentin ANDA applicant is eligible for 180-day exclusivity as to U.S. Patent Number 5,084,479 (the '479 patent). FDA's determination that no ANDA applicant is eligible for 180-day exclusivity as to the '479 patent was based upon its conclusion that no applicant could legally maintain its paragraph IV certification as to that patent (and thus the patent could be removed from the Orange Book). This outcome is a consequence of the representation by Pfizer, Inc., the holder of the approved NDA for gabapentin capsules and the '479 patent, to FDA on December 13, 2002, disavowing any claim that the '479 patent covered the approved use of gabapentin – epilepsy (as opposed to the unapproved use – neurodegenerative diseases). This representation was confirmed in later correspondence with Pfizer, as well as in the findings of Judge Huvelle in *Purepac Pharmaceutical Co. v. Thompson*, No. 02-1657 (D.D.C. Dec. 16, 2002). The Federal Circuit also confirmed that the '479 patent

Attachment B

does not claim an approved use of gabapentin in *Warner-Lambert v. Apotex, Inc.*, No. 02-1073 (Fed. Cir. Jan. 16, 2003).

The mirtazapine situation is materially different. As you note, a district court has found in private patent infringement litigation that U.S. Patent No. 5,977,099 (the '099 patent) claims only an unapproved use for mirtazapine, not an approved use for which the ANDA applicants were seeking approval. *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.). In addition, on February 13, 2003, counsel for Organon notified FDA that, although Organon still believes the '099 patent meets the requirements of section 505(b) of the Act for listing in the Orange Book, "[n]onetheless, Organon herewith requests the '099 patent be removed from the Orange Book." However, unlike with the '479 gabapentin patent, there has been no admission by the patent holder to FDA that the patent does not claim an approved use. Likewise, there has been no litigation involving FDA in which the court has expressly found that a section viii statement is the correct submission for the listed patent.

You argue that the gabapentin and mirtazapine situations are nevertheless the same and require the same outcome. Your position is that, to be consistent, FDA either 1) must require all mirtazapine ANDA applicants to now change existing paragraph IV certifications under section 505(j)(2)(A)(vii) to the '099 patent to section viii statements under section 505(j)(2)(A)(viii), and deny any applicant 180-day exclusivity as to that patent, or 2) must reverse its decision that no gabapentin ANDA applicant is eligible for 180-day exclusivity as to the '479 patent.

FDA disagrees. These are not analogous situations, and do not require the same regulatory treatment. As Judge Huvelle noted, the gabapentin situation involved "unique factual circumstances" that warranted special treatment by the court. In that case, the court found – in part on the basis of the use statements addressing the scope of the '479 patent - that the NDA sponsor never intended to assert that the '479 patent claims the approved use of the listed drug. In addition, as the court noted, Pfizer admitted as much in its December 13, 2002, letter to FDA. Therefore, the district court found that an ANDA applicant was entitled to file a section viii statement to that patent. In the mirtazapine case, we have no such admission to FDA by the NDA sponsor, and no specific court decision regarding the submission of a section viii statement.

Neither Judge Huvelle's narrow decision based on unique factual circumstances nor FDA's January 28, 2003, decision requires a change in established FDA practice regarding 180-day exclusivity. 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. If the triggering court decision finds the patent invalid, FDA will leave the patent in the Orange Book for 180 days to give the first applicant the benefit of its exclusivity. 21 C.F.R. 314.94(a)(12)(viii); 59 Fed. Reg. 50338, 50348 (Oct. 3, 1994). As FDA explained in its rulemaking, to permit removal of the patent immediately upon a court decision of patent invalidity would deprive the first applicant of the benefit for which it is eligible by being first to challenge the patent. *Id.* Similarly, it would be unreasonable to either remove the '099 patent

from the Orange Book, as requested by Organon, or require a change from paragraph IV certification to section viii statement for mirtazapine 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. In the normal course, FDA would require ANDA applicants with paragraph IV certifications to maintain the certification and leave the patent in the Orange Book for the 180-day period beginning with the court decision, even when the patent holder requests that the patent be removed from the Orange Book, as has happened with Organon.[1]

In the gabapentin case, Torpharm prevailed on January 16, 2003, in its paragraph IV litigation on the '479 patent in *Warner-Lambert* and thus might appear to be entitled to exclusivity. Thus, although Pfizer notified FDA on January 17, 2003, that it agreed to withdraw the '479 patent, FDA reexamined, in its January 28 letter, Torpharm's entitlement to 180-day exclusivity on that patent before delisting it. See 21 C.F.R. § 314.94 (a)(12)(viii)(B). As noted in FDA's January 28 letter, Pfizer clarified in its December 13 letter that the '479 patent claims the use of gabapentin to treat neurodegenerative diseases, not epilepsy. All of the relevant ANDAs seek approval for gabapentin products labeled for use in treating epilepsy. In light of Pfizer's December 13 clarification, no gabapentin ANDA applicant could retain a paragraph IV certification to the '479 patent. This conclusion was consistent with Judge Huvelle's findings. As FDA pointed out in its January 28 letter, if the '479 patent had remained in the Orange Book, Judge Huvelle's decision would have enabled every gabapentin ANDA applicant to submit a section viii statement to that patent. Thus, even if Torpharm could retain its paragraph IV certification, every other ANDA applicant could change a paragraph IV certification to a section viii statement, and thus deny Torpharm any exclusivity.

Therefore, the agency reaffirms that no ANDA applicants are eligible for exclusivity as to the now delisted '479 patent for gabapentin. Moreover, the '099 patent will remain in the Orange Book for the 180-day period following the district court decision, and mirtazapine ANDA applicants remain eligible for exclusivity as to that patent.

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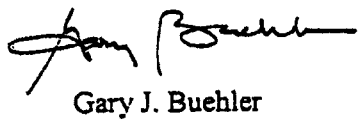
[1] The mirtazapine ANDAs are governed by the "new" definition of the court decision trigger, which is described in FDA's Guidance *Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act*, March 2000. As to mirtazapine, the December 18, 2002, district court decision in *Organon v. Teva* triggers the running of exclusivity. In contrast, if any gabapentin ANDA applicant were eligible for exclusivity as to the '479 patent, such exclusivity would have been triggered by the *Warner-Lambert* appellate decision, as the gabapentin ANDAs are governed by the "old" definition of court decision as described in the guidance.

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

cc: Marcy Macdonald, U.S. Agent for TorPharm/Apotex
Arthur Y. Tsien, counsel for Torpharm/Apotex
William A. Rakoczy, counsel for Torpharm/Apotex
Charles J. Raubicheck, counsel for Purepac
Andrew M Berdon, counsel for Purepac
Daniel E. Troy, OCC