ANDA 74-732 March 21, 2002

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Sent by Facsimile and U.S. Mail

Dear Mr. Sisto:

This is in reference to your abbreviated new drug application (ANDA) dated August 17, 1995, for Tamoxifen Citrate Tablets, 10 mg, and your supplemental application dated September 26, 2000, for an additional strength, Tamoxifen Citrate Tablets, 20 mg, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act (Act).

The listed drug product referenced in your application is NDA 17-970, Nolvadex® (Tamoxifen Citrate) Tablets, AstraZeneca Pharmaceuticals, LP. This drug product is subject to a period of protection by U.S. Patent No. 4,536,516 ('516 patent), which expires on August 20, 2002. You originally filed a certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '516 patent was invalid, not infringed or unenforceable. You notified the NDA applicant and patent owner of this certification and were sued for patent infringement. Your ANDA was approved on June 26, 2000, at the termination of the 30-month stay under section 505(j)(5)(B)(iii). No decision in the patent infringement litigation had been rendered at that time. In addition, a supplemental application for Tamoxifen Citrate Tablets, 20 mg was submitted on September 26, 200, pursuant to section 505(j) of the Act, and it included a PIV certification to the ‘516 patent.

On March 9, 2001, you notified FDA that Mylan had settled its patent litigation with AstraZeneca and as a result you were amending your supplemental application to include a patent certification under section 505(j)(2)(A)(vii)(III) of the Act to the '516 patent for Tamoxifen Citrate Tablets, 20 mg. Subsequently on August 2, 2001, you also amended your application to include a patent certification under section 505(j)(2)(A)(vii)(III) of the Act to the '516 patent for Tamoxifen Citrate Tablets 10 mg. A "paragraph III" certification states the date on which the patent will expire. Until the matter involving the '516 patent, the agency had never received a request to change a patent certification for an approved ANDA from a paragraph IV to a paragraph III. Pursuant to section 505(j)(5)(B)(ii) of the Act, if an ANDA contains a paragraph III certification, approval may be made effective on the date certified under paragraph III.

Mylan's submission of a paragraph III certification means that the Mylan ANDA 74-732 is converted to tentative approval status and may be finally approved when the '516 patent expires. Although section 505(j) does not expressly provide for a change in approval status based upon the ANDA applicant's resolution of patent litigation, provisions of the 1984 Drug Price Competition and Patent Term Restoration Act codified in the Patent Code give courts the authority to order the date of approval of an ANDA to be no earlier than the date of expiration of the infringed patent is described at 35 U.S.C. 271(e)(4). The legislative history of Hatch-Waxman makes it clear FDA may change the approval status of an approved ANDA based upon the outcome of patent infringement litigation:

> If the infringing party has not begun commercial marketing of the drug, injunctive relief may be granted to prevent any commercial activity with the drug and the FDA would be mandated to make the effective date of any approved ANDA not earlier than the expiration date of the infringed patent. . . . *In the case where an ANDA had been approved, the order would mandate a change in the effective date.*
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> If the infringing party has begun commercial marketing of the drug, damages and other monetary relief and injunctive relief may be awarded . . . . In addition, *the FDA would be mandated to change the effective date of the approved ANDA to the expiration date of the infringed patent*.

H.R. Rep. No. 857, 98th Cong., 2d Sess., part 1, at 46 (1984) (emphasis added).

Moreover, conversion of the Mylan ANDA approval to tentative approval is the only approach that gives Mylan's submission of a paragraph III certification after approval of its ANDA any regulatory effect. Based upon Mylan's submissions to FDA, this outcome appears both consistent with Mylan's settlement of the patent litigation and its intent in submitting a paragraph III certification for an already approved ANDA.[1]

Therefore, this letter is to inform you that, in light of your change in your certification to the '516 patent from paragraph IV to paragraph III, the final approval given to Mylan Pharmaceuticals Inc.'s ANDA 74-732 on June 26, 2000, including all amendments and supplements thereto, is hereby converted to a tentative approval. In order to further

[1] FDA is aware of the recent district court decision discussing whether the court would withdraw approval of an ANDA to give effect to the provision at section 505(j)(5)(B)(iii) of the Act which permits a court to lengthen the 30-month stay. *Minnesota Mining and Manufacturing Co., et al. v. Alphapharm Pty, Ltd.*, No. 99-13 (D.Minn. March 7, 2002). In that matter, the court determined it would not extend the 30-month stay and withdraw approval of the ANDA, citing among its reasons that there was no claim the ANDA was improperly approved and FDA was not a party to the litigation. Slip op. at 5. The agency does not believe this decision is relevant to the change in the tamoxifen ANDA approval status because, *inter alia*, there is clear authority under 35 USC 271(e)(4) for a court to order a delay in the ANDA effective approval date when infringement has been found, and when a tamoxifen ANDA applicant has changed its patent certification to a paragraph III, it has indicated directly to FDA that approval should be granted at the expiration of the patent.

clarify the FDA's letter to Mylan dated April 4, 2001, regarding the supplemental new drug application for Tamoxifen Citrate Tablets, 20 mg, submitted on September 26, 2000, this supplement is also considered to be tentatively approved.

The agency notes as well that, should AstraZeneca receive pediatric exclusivity under section 505A of the Act for studies in response to FDA's Written Request for pediatric studies of tamoxifen citrate, the approval status of the Mylan ANDA will be important to the extent of exclusivity protection AstraZeneca receives. Section 505A provides that if a sponsor submits pediatric studies that respond to a Written Request and the drug studied is subject to a listed patent for which a paragraph III certification has been submitted, FDA will extend the period during which it will not approve the ANDA by six months after the date the patent expires. Section 505A(c)(2)(A)(ii). Mylan has submitted a paragraph III certification to the '516 patent. Should AstraZeneca submit studies that qualify for pediatric exclusivity, tentative approval status for Mylan will permit FDA to delay final approval of this ANDA containing paragraph III certifications until expiration of the six-month exclusivity period, as described in section 505A.

The agency notes that, based upon the information you have presented to date, the drug products described in your ANDA are safe and effective for use as recommended in the submitted labeling. Therefore, as noted, the application is **tentatively approved.** This determination is based upon information available to the agency at this time, i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug products, and is subject to change on the basis of new information that may come to our attention.

Because the agency is granting a **tentative approval** for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the agency whether circumstances have or have not arisen that may affect the effective date of final approval. To reactivate your application, please submit an amendment prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final printed labeling, chemistry, manufacturing, and controls data as appropriate. Please note that this amendment should be submitted even if none of these changes were made. The amendment should be designated clearly in your cover letter as a **MINOR AMENDMENT**. In addition to this amendment, the agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above. Any changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to agency review before final approval of the application will be made.

The drug products that are the subject of this abbreviated application may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery or introduction into interstate commerce of this drug before the effective final

approval date is prohibited under section 301(d) of the Act. Also, until the agency issues the final approval letter, these drug products will not be listed in the Orange Book.

Please contact Cecelia Parise, R.Ph., Regulatory Policy Advisor to the Director, Office of Generic Drugs, at (301) 827-5845, for further information regarding this issue.

Sincerely yours,

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