DEPARTMENT OF HEALTH & HUMAN SERVICES

ANDA 76-719, Amlodipine Besylate Tablets, 2.5 mg, 5 mg, and 10 mg.

SENT BY FACSIMILE AND U.S. MAIL

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Apotex Corp.
Attention: Kiran Krishnan
Project Leader, Regulatory Affairs
U.S. Agent for: Apotex Inc.
2400 N. Commerce Parkway, Suite 400
Weston, FL 33326

Dear Madam:

This letter references your abbreviated new drug application for amlodipine besylate tablets submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and received on April 14, 2003, and also your correspondence dated May 1, 2007 submitted on behalf of Apotex by Welsh and Katz, LTD.

This letter responds to your letter of May 1, 2007, regarding the timing of the potential approval of your client Apotex Inc.'s abbreviated new drug application (ANDA) for amlodipine besylate tablets (amlodipine). Issues related to the timing of the approvals of the amlodipine ANDAs submitted by Apotex and others have been the subject of a administrative decision issued on April 18, 2007, FDA Letter Decision (Apr. 18, 2007) (available at http://www.fda.gov/ohrms/dockets/dockets/07n0123/07n-0123-let0002-vol1.pdf) (hereinafter, FDA Decision), which in turn has been challenged and reviewed by the Federal District Court for the District of Columbia. *Mylan Labs., Inc. v. Leavitt*, 2007 U.S. Dist. LEXIS 31170 (D.D.C. April 30, 2007).

In your letter, you inform FDA regarding a development in the patent litigation between Apotex and Pfizer Inc., the NDA holder for amlodipine besylate tablets, which Pfizer markets under the name Norvasc. In January 2006, the Federal District Court for the Northern District of Illinois held Pfizer's Patent No. 4,879,303 ('303 patent) was valid and infringed. *Pfizer, Inc. v. Apotex, Inc*, No. 03C 5289, 2006 U.S. Dist. LEXIS 95778 (N.D. Ill. January 24, 2006). On March 22, 2007, the Federal Circuit issued an opinion reversing the district court decision, finding that Apotex's amlodipine besylate tablets did not infringe claims 1-3 of the '303 patent because those claims were invalid for obviousness. *Pfizer, Inc. v. Apotex, Inc.*, No. 2006-1261, 2007 U.S. App. LEXIS 6623 (Mar. 22, 2007) (hereinafter, *Apotex* Opinion). Pfizer has moved for reconsideration of that opinion, and the mandate has not yet issued. In your letter, you formally notify FDA that, on March 29, 2007, the Illinois district court lifted (effective as of April 3, 2007) the injunction on Apotex marketing its amlodipine product. *Pfizer, Inc. v. Apotex, Inc*, No.

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03C 5289 (N.D. Ill. March 29, 2007) (attached to your letter as Exhibit A and, hereinafter, March 29 Order).[1]

You requested in your May 1 letter that, based on the March 29 Order and the reasoning in the FDA Decision, FDA immediately approve Apotex's amlodipine ANDA. You asked FDA to issue its response by close of business on May 2. The agency declined to respond within that timeframe, and, on May 3, 2007, you moved for reconsideration in the D.C. federal district court of that court's April 30 decision.

In this letter, FDA declines to immediately approve Apotex's amlodipine ANDA. We address the arguments made in your letter to the agency, upon which you have elaborated in your submission to the D.C. federal district court.

In its April 18 administrative decision, FDA explained that, after the '303 patent expired on March 25, 2007, Apotex's paragraph IV certification to that patent converted to a paragraph II certification, and Apotex's ANDA became subject to Pfizer's pediatric exclusivity:

> It has been FDA's longstanding view, that, when a patent expires before pending patent litigation is resolved, ANDA applicants who have not received final effective approval are required under Hatch-Waxman, to change their paragraph III and paragraph IV certifications to paragraph II certifications. Because, upon patent expiry, all ANDA applicants are presumed to have paragraph II certifications, the paragraph II provision of the pediatric exclusivity statute, 21 U.S.C. § 355a(c)(2)(A)(i), would control. The D.C. Circuit has upheld this approach in two recent decisions. *See Mylan Labs., Inc. v. Thompson*, 332 F. Supp. 2d 106, 124 (D.D.C. 2004), *aff'd*, 389 F.3d 1272 (D.C. Cir. 2004); *Ranbaxy Labs., Ltd. v. FDA*, 307 F. Supp. 2d 15 (D.D.C. 2004) *aff'd*, 2004 U.S. App. LEXIS 8311 (D.C. Cir. April 26, 2004). . . . When the '303 patent expired on March 25, 2007, all of the unapproved ANDAs were required to change (or deemed to have changed) to paragraph II certifications and became subject to Pfizer's pediatric exclusivity at that time. That is their status during the period before the mandate issues.

FDA Decision at 8-9.

Nevertheless, the three day window between the issuance of the *Apotex* Opinion and the expiration of the '303 patent presented a new factual scenario that FDA had not previously considered in which an ANDA applicant (here Apotex) obtained an opinion that the patent is invalid before the patent expired, and may obtain a final determination that the patent is invalid, but only *after* the patent expired. FDA explained that "the implicit meaning and logical interpretation of [21 U.S.C. §] 355a(c)(2)(B)" is that "if in paragraph IV litigation a court determines that a patent is invalid or not infringed, pediatric exclusivity will not bar approval of

[1] It should be noted that, at the time FDA issued its April 18, 2007 administrative decision in this matter, Apotex had not informed FDA of the March 29 Order, and this development was not known to FDA. This information first came to FDA's attention when Apotex submitted it to the D.C. district court as an attachment to Apotex's April 27 reply brief.

that applicant's ANDA." FDA Decision at 8. Accordingly, FDA determined that, even though Apotex's paragraph IV certification was converted to a paragraph II certification at the time of patent expiration and Apotex is now subject to pediatric exclusivity, the language of section 355a(c)(2)(B) "creates an exception to the application of the Hatch-Waxman certification provisions." FDA Decision at 9. FDA found that exception because "the statute manifests a clear Congressional intent that pediatric exclusivity not block the approval of an ANDA where the ANDA applicant has prevailed in the paragraph IV patent litigation." *Id*. This means that if and when there is a final court determination in the patent litigation between Pfizer and Apotex that the relevant claims of the '303 patent are invalid, Apotex's ANDA will not be blocked by Pfizer's pediatric exclusivity.

The issuance of the March 29 Order by the Illinois district court does not change the result under the above analysis or entitle Apotex to immediate approval. Pediatric exclusivity will continue to bar approval of Apotex's ANDA until Apotex affirmatively wins its patent litigation, with a final effective decision that the patent is invalid or not infringed. The March 29 Order is not a final effective decision that the patent is invalid or not infringed. Lifting the injunction does not by itself convert the original Illinois district court finding the '303 patent is valid and infringed into a finding that the patent is invalid or not infringed. Either the Illinois district court's original judgment that the patent is valid and infringed remains in effect until the mandate issues,[1] or, at best, the lifting of the injunction nullified that court's initial decision so that there is in effect no district court judgment. Under either scenario, Apotex has not obtained a final effective court determination that the patent is invalid such that pediatric exclusivity has ceased to bar approval of Apotex's ANDA.

Apotex argues that, because FDA noted in its April 18 administrative decision that it "applies a [district court patent] decision, unless it is stayed, in determining issues related to ANDA approval," FDA should now conclude that, Apotex, as the beneficiary of the lifted injunction, should be entitled to immediate approval. Apotex May 1 Letter at 2; Apotex Reconsideration Brief at 4-5. However, that argument does not follow logically from FDA's construction of the statute and the relevant facts. FDA made that statement in the context of discussing the timing of the effectiveness of a Federal Circuit decision that reverses a district court patent judgment. FDA never stated expressly or implied that where district court determined that an ANDA applicant, such as Apotex, infringed a valid patent, enjoined the applicant from marketing, and

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[1] Although Apotex claims that the lifting of the injunction vacated the district court's judgment, Apotex's Memorandum in Support of Emergency Motion for Reconsideration at 4 n.2 and 6, FDA does not believe that Apotex's conclusion is correct. Apotex has not provided any documentation with its letter to FDA or its brief filed with the D.C. district court that such vacatur has occurred or any legal authority that vacatur should be presumed. Indeed, a comparison of the final judgment entered by the Illinois district court, Pfizer, Inc. v. Apotex, No. 03C 5289, 2006 U.S. Dist. LEXIS 95778 (N.D. Ill. January 24, 2006), and the March 29 Order reveals that there are other parts of the judgment that appear to be unaffected by the lifting of the stay. In addition, although Rule 62(c) of the Federal Rules of Civil Procedure provides that a district court may suspend an injunction during the pendency of an appeal, "[t]he rule authorizes the suspension, modification, restoration or grant of injunction, not the dissolution of an injunction already granted." Coastal Corp. v. Texas Eastern Corp., 869 F.2d 817, 819-821 (5th Cir. 1989). Because the filing of an appeal generally, with a few limited exceptions that do not appear to be applicable here, divests a district court of jurisdiction until the district court receives the mandate of the court of appeals, see Fundicao Tupy S.A. v. United States, 841 F.2d 1101, 1103-04 (Fed. Cir. 1988), it is questionable whether the Illinois district court had the authority to vacate its judgment before the mandate issued.

subsequently lifted that injunction, the lifting of the injunction, by itself, would constitute an affirmative court determination of patent invalidity such that pediatric exclusivity would no longer bar final approval.

Apotex further argues that FDA has acted inconsistently because Mylan and Apotex were in "identical" situations vis-à-vis unfavorable district court patent decisions. Apotex May 1 Letter at 1; Apotex Reconsideration Brief at 4. Apotex fails to note, however, that the questions arose in different legal and factual contexts. As explained in our preliminary injunction opposition brief in the D.C. district court litigation, the issues related to the Mylan ANDA concerned whether its final approval should be converted to a tentative approval because of the unfavorable patent decision. See FDA Opp. Brief at 37-39 (April 26, 2007). In *Mylan (fentanyl)*, the D.C. Circuit upheld FDA's determination, that when an ANDA applicant received final approval of its ANDA prior to expiration of the relevant patent but, subsequently, loses its patent litigation with a court order that resets the effective date of ANDA approval to a date no earlier than the date of patent expiry and enjoins the ANDA applicant from marketing its product until the patent expires, FDA is required to convert the final approval to a tentative approval. *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1277-78 (D.C. Cir. 2004). Then, when the patent expired, the tentatively approved ANDA would be subject to pediatric exclusivity, even though it would not have been subject to that exclusivity had the ANDA remained finally approved. *Id*. Here, however, before FDA acted on the order issued by the district court in Mylan's amlodipine patent litigation resetting the effective date of Mylan's ANDA approval and enjoining marketing, Mylan received a stay of the district court's decision from the Federal Circuit. *Pfizer Inc. v. Mylan Labs., Inc.*, No. 2007-1194 (Mar. 23, 2007). After that stay, FDA had no basis to convert the approval status of Mylan's ANDA from approved to tentatively approved. Thus, Mylan's final approval remained effective.

Apotex, however, has never received final approval of its ANDA, so the legal analysis relating to when FDA will convert a final approval to a tentative approval has no application to Apotex. Instead, Apotex is asserting that the lifting of the injunction in its district court patent case entitles it to different relief altogether -- the termination of pediatric exclusivity based on an affirmative patent court victory. As noted above, FDA believes that in the circumstances at issue here, Apotex must "win" its patent litigation with an affirmative determination of invalidity or non-infringement to qualify for this limited exception. In contrast, Mylan had to "not lose" its patent litigation in order to maintain its final effective approval. Mylan was able to satisfy this lower standard; Apotex has not yet met the higher one. Thus, Apotex is incorrect in arguing that the situations are identical; they involve legally and factually distinct questions.

Accordingly, the issuance of the March 29 Order does not require FDA to change any of the conclusions reached in its April 18, 2007 administrative decision.

A copy of this letter will be placed on public display in the Dockets Management Branch, Room 1061, Mail Stop HFA-305, 5630 Fishers Lane, Rockville, MD 20852.

If you have any questions regarding this letter, please contact Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 240-275-9319.

Sincerely

{See appended electronic signature page}

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

cc: Robert B. Breisblatt
Welsh & Katz, Ltd
120 South Riverside Plaza, 22 Floor
Chicago, IL 60606

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/s/

Gary Buehler

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