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VIA ELECTRONIC AND U.S. MAIL **April 5, 2007**

Gary J. Buehler
Director
Office of Generic Drugs, HFD-600
U.S. Food and Drug Administration
7519 Standish Place
Rockville, MD 20855

Re: 2007N-0123: Amlodipine ANDAs

Dear Mr. Buehler:

On March 29, 2007, FDA opened a public docket and solicited comments on regulatory issues relating to the approval of abbreviated new drug applications (ANDAs) for amlodipine besylate products. FDA's inquiries primarily concern the present and possible future effects of a Federal Circuit panel opinion stating that Pfizer's patent 4,879,303 ("the '303 Patent") is invalid. *Pfizer Inc. v. Apotex Inc.*, No. 2006-1261 (Fed. Cir. March 22, 2007) ("*Apotex* panel opinion"). Pfizer submits this letter in response to FDA's request for comments. As explained below, it is Pfizer's view that the March 22 *Apotex* panel opinion has no present effect on any unapproved amlodipine ANDA. Thus, all unapproved amlodipine ANDAs remain subject to Pfizer's pediatric exclusivity. Pfizer's comments also discuss possible future developments in the *Apotex* case, and how they may affect pediatric exclusivity.

I. FDA's Questions 1 and 2

Questions 1 and 2 in FDA's March 29 letter ask about the impact of the *Apotex* panel opinion on Pfizer's pediatric exclusivity for amlodipine, including what effect the panel opinion had on the legal status of Pfizer's '303 patent, and whether, in the wake of the *Apotex* panel opinion, pediatric exclusivity continues to bar approval of unapproved amlodipine ANDAs. As explained below, the *Apotex* panel opinion did not change the status of Pfizer's '303 patent or Pfizer's pediatric exclusivity for amlodipine. Thus, at this time, pediatric exclusivity continues to bar approval of all unapproved amlodipine ANDAs.

A. The Apotex panel opinion did not render the '303 patent invalid

Under the Federal Rules of Appellate Procedure, an opinion issued by a panel, such as the March 22 *Apotex* panel opinion, becomes final and is effectuated only through a mandate. A

court of appeals' judgment or order is not final until issuance of the mandate. Only "at that time [do] the parties' obligations become fixed." F.R.A.P. 41, Adv. Comm. Notes (1998 Amendments). The issuance of a mandate, moreover, is not automatic. A mandate cannot issue, for example, before disposition of a timely petition for rehearing or rehearing *en banc*. F.R.A.P. 41(b). "The mandate is effective when issued." F.R.A.P. 41(c).

Pfizer will file a timely petition for rehearing and rehearing *en banc* on April 5. *See* F.R.A.P. 40(a) (providing that Pfizer has 14 days following the March 22 ruling in which to seek rehearing). Pfizer's petition will raise several significant issues concerning the March 22 panel opinion, including that the opinion departs from and therefore conflicts with long-standing Supreme Court and Federal Circuit precedent on dispositive issues concerning the validity of the '303 patent, and that it improperly overruled trial court factual determinations. Because of the significance of these errors, Pfizer expects that several *amici* will file briefs supporting Pfizer's petition for rehearing.

If the petition is granted, the mandate will not issue until there is a final decision by the court of appeals following a rehearing that rejects or adopts the opinion of the panel. F.R.A.P. 41(d)(1). If the petition is denied, the mandate will issue "7 calendar days after entry of an order denying a timely petition for panel rehearing" unless the court decides to shorten or extend the time. F.R.A.P. 41(b). Because no mandate has yet issued, the *Apotex* panel opinion has no effect on the legal status of the '303 patent. Therefore, as of this time, the patent is properly listed in FDA's Orange Book.[1]

FDA has recognized that a court of appeals panel opinion has no legal effect until a mandate issues. FDA's policy has been that, in paragraph IV litigation, where a panel of the Federal Circuit issues an opinion that a patent is invalid, unenforceable or not infringed, the agency cannot approve a pending ANDA until "the date the district court issues a judgment that the patent is invalid, unenforceable, or not infringed pursuant to a mandate issued by a court of appeals." *See* FDA Guidance, *Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act* (March 2000) ¶ IV.A. (emphasis added).[2] This approach reflects sound policy. FDA action based on a panel opinion and prior to issuance of the mandate would subvert the appellate processes,

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[1] The validity of the '303 patent was litigated in four separate cases (involving Mylan, Apotex, Synthon, and Dr. Reddy's), all of which resulted in district court judgments of validity and infringement. On March 26, 2007, the Federal Circuit entered a stay pending appeal of the judgment in the *Mylan* case. On March 29, 2007, the *Apotex* district court similarly lifted its judgment (effective April 3), pending resolution of the appeal in that case. Neither of these actions constituted or reflected a final judgment that the '303 patent is invalid.

[2] This March 2000 guidance has been superseded in part by the Medicare Prescription Drug Improvement and Modernization Act of 2003 (MMA). *See* FDA Draft Guidance, *Listed Drugs, 30-Month Stays, and Approval of ANDAs and 505(b)(2) Applications Under Hatch-Waxman, As Amended by the Medicare Prescription Drug Improvement and Modernization Act of 2003* (October 2004) ¶ II.B.4. As discussed in Pfizer's letter of March 25, 2007, however, FDA's basic reasoning in the March 2000 guidance -- that an appellate reversal of a district court ruling should not be given effect by FDA before the mandate issues from the appeals court -- remains applicable here.

including rehearings, that are intended to ensure the correctness and finality of appellate rulings. The Federal Rules of Appellate Procedure expressly permit the Federal Circuit, either in a panel rehearing or sitting *en banc*, to revisit the panel's decision upon a timely petition. FDA should respect the role of the Federal Circuit in deciding the underlying patent dispute -- and the patentholder's right of review -- and not take any action at least until the appellate process has been completed and "the parties' obligations become fixed." F.R.A.P. 41, Adv. Comm. Notes (1998 Amendments).

B. The Apotex panel opinion did not alter Pfizer's pediatric exclusivity for amlodipine

Under the rule established in *Ranbaxy Labs. Ltd. v. FDA*, 307 F.Supp.2d 15 (D. D.C. 2004), *aff'd*, 96 Fed. Appx. 1 (D.C. Cir. 2004), the "critical event" for pediatric exclusivity is "the expiration of the patent" that is the subject of a paragraph IV certification. 307 F.Supp.2d at 19. Where, as here, a patent expires while an ANDA is not yet approved, the Paragraph IV certification becomes a paragraph II certification as of the date of patent expiration. *See id.* at 21. The same rationale applies regardless of whether the holder of an unapproved ANDA filed a paragraph IV or a paragraph III certification prior to patent expiry.

Because the '303 patent has expired, Pfizer's pediatric exclusivity for amlodipine bars approval of all of the unapproved amlodipine ANDAs. At the date of expiration, March 25, 2007, any ANDA with a paragraph IV certification "either converted as a matter of law to Paragraph II certification or became inaccurate." In either event, pediatric exclusivity attached by operation of law from the date of patent expiration, under the statutory provision governing pediatric exclusivity in the context of paragraph II certifications. *See id.* (*citing* 21 U.S.C. 355a(c)(2)(A)(i)). *See also* Federal Defendants' Memorandum In Opposition to Plaintiffs' Motions For Preliminary Injunction and Summary Judgment and In Support Of Cross-Motion For Summary Judgment (July 8, 2004), *filed in Mylan Labs. Inc. v. Thompson*, D. D.C. Case No. 04-1049 ("FDA Duragesic Brief"), at 36 ("If a drug is the subject of a Paragraph II certification, and pediatric studies were submitted prior to the expiration of the patent, then the statute mandates that 'the period during which an [ANDA] may not be approved . . . shall be extended by a period of six months after the date the patent expires'") (quoting 21 U.S.C. 355a(c)(2)(A)) (emphasis in original).

II. FDA's Questions 3 and 4

Questions 3 and 4 in FDA's March 29 letter ask about possible future developments in the patent litigation involving amlodipine generics. Specifically, FDA asks whether Pfizer would be obligated to delist the '303 patent "[i]f and when the *Apotex* panel opinion is 'implemented'" -- by which we assume FDA means, "if and when the panel opinion is effectuated by issuance of a mandate." FDA also asks whether, if a mandate were to issue, FDA could treat the patent as delisted as a matter of law.

FDA has acknowledged, and courts have confirmed, that patent listings are properly controlled by patentholders, who are in the best position to determine whether a patent meets the legal criteria for listing. *See Apotex v. Thompson*, 347 F.3d 1335, 1347-48 (Fed. Cir. 2003) (deferring to FDA's argument that "[o]nce the NDA holder submits [listing] information to the FDA, the agency's sole responsibility . . . is to 'publish it'" (*quoting* 21 U.S.C. § 355(c)(2)); *see*

also aaiPharma v. Thompson, 296 F.3d 227, 238 (4th Cir. 2002). Thus, FDA cannot and should not delist the '303 patent unless and until Pfizer authorizes that delisting.

When the Federal Circuit rules on Pfizer's petition for rehearing and rehearing *en banc*, Pfizer will fully evaluate the Federal Circuit's ruling to determine its legal obligations. If the Federal Circuit grants rehearing, Pfizer likely would take the position that the '303 patent should remain listed, in which case pediatric exclusivity should continue to apply. If the Federal Circuit denies the petition for rehearing, Pfizer will consider whether it has further options for judicial review (such as filing a petition for *certiorari* and a motion to stay the mandate, *see* F.R.A.P. 41(d)(2)). At the same time, Pfizer also will consider very carefully and expeditiously its obligations with respect to the patent listing, including any obligation to delist the patent. Regardless, FDA cannot delist the '303 patent without Pfizer's authorization.

III. FDA's Question 5

Pfizer takes no position on the triggering of 180-day exclusivity in this case.

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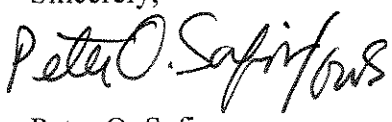
We trust that this letter addresses the questions you raised on March 29. Please contact me if you have any further questions.

Sincerely,



Peter O. Safir

cc: Jeffrey B. Chasnow
Pfizer, Inc.