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April 4, 2007

VIA FACSIMILE AND HAND DELIVERY

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

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 2007N-0123
Docket No. 2007P-0116
ANDA No. 78-081: Amlodipine Besylate Tablets, 2.5 mg, 5 mg and 10 mg

Dear Sirs:

On behalf of Mutual Pharmaceutical Company, Inc., we submit this letter in response to: (1) FDA's March 28, 2007 letter, soliciting comments with respect to several questions that FDA is considering regarding the approval of abbreviated new drug applications for amlodipine besylate products; (2) the March 25, 2007 letter from Pfizer relating to the Apotex amlodipine ANDA, Docket No. 2007N-0123; and (3) the March 26, 2007 letter from Mylan Pharmaceuticals Inc. relating to all pending amlodipine ANDAs, Docket No. 2007P-0116. It is Mutual's view that the Federal Circuit's decision invalidating Pfizer's U.S. Patent No. 4,879,303 ("the '303 patent") is not effective until the Federal Circuit's mandate issues, that all applicants with unapproved ANDAs containing Paragraph IV certifications are required to amend their applications to include Paragraph II certifications to the expired '303 patent, and that those unapproved ANDAs remain subject to Pfizer's pediatric exclusivity period and cannot be approved until it expires on September 25, 2007. Alternatively, if FDA concludes that unapproved ANDAs may retain Paragraph IV certifications, approval of such ANDAs would be delayed by Mylan's 180-day exclusivity period. The clear directives of the Hatch-Waxman Amendments, FDA's own regulations and guidance, and prior court decisions require this result.

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The Federal Circuit Decision Is Not Effective Until the Mandate Issues

For purposes of determining the applicability of pediatric exclusivity for the '303 patent, and thus for determining the eligibility of ANDAs for approval, the '303 patent is valid until the Federal Circuit issues its mandate invalidating it. The Federal Rules of Appellate Procedure and FDA's own prior guidance support this outcome.

A court of appeals' judgment is not final until a mandate issues, and the parties' obligations with respect to that judgment do not become fixed until that time. Fed. R. App. P. 41 advisory committee's note (1998) (Subdivision (c)) (Exhibit A). A mandate is effective when issued, but issuance will be stayed upon the timely filing of a petition for rehearing until the disposition of the petition. Fed. R. App. 41(c), (d)(1). Although the Federal Circuit ruled that the '303 patent is invalid three days before the patent expired, the mandate from the Federal Circuit has not issued. In fact, it will not issue at least until the time to file a petition for rehearing expires. Fed. R. App. P. 41(b). Here, the deadline for Pfizer to file a petition for rehearing has not yet lapsed. Because Pfizer has expressed its intent to file a petition for rehearing, it is likely that the issuance of the mandate will be further delayed. See March 25, 2007 Letter from Peter O. Safir to Sheldon T. Bradshaw, Esq. and Elizabeth Dickinson, Esq., Docket No. 2007N-0123, p. 2-3 (Exhibit B). In the meantime, the Federal Circuit's decision is not final.

Because there is a chance that the Federal Circuit's decision could change before it becomes final, FDA should not take any action on the decision until the mandate issues. This course of action is consistent with previous FDA guidance. Specifically, FDA guidance on court decisions and ANDA approvals states that when, as is the case here, a district court decision of infringement is reversed on appeal, the FDA cannot approve the 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." *FDA Guidance for Industry: Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act* at 4 (March 2000) (Exhibit C).

Thus, FDA should not take any action based on the Federal Circuit's March 22, 2007 decision until the Federal Circuit's mandate issues. Doing so would be contrary to FDA's own guidance and the Federal Rules of Appellate Procedure.

*Holders of Unapproved ANDAs Must Amend Paragraph IV
Certifications to Paragraph II Certifications to the Expired '303 Patent*

Because the Federal Circuit's March 22, 2007 decision invalidating the '303 patent is not yet final, the '303 patent expired by its own terms on March 25, 2007. At the moment of its expiration, Paragraph IV certifications to the '303 patent contained in unapproved ANDAs were no longer accurate and no longer valid because the patent to which they related had expired.

Food and Drug Administration

April 4, 2007

Page 3

ANDA applicants with Paragraph IV certifications are therefore required to amend their applications to include Paragraph II certifications to the now-expired '303 patent. If such an amendment is not made, FDA is entitled to treat those remaining Paragraph IV certifications as Paragraph II certifications upon patent expiration.

The Hatch-Waxman Amendments provide that FDA may refuse to approve any application that "contains an untrue statement of material fact." 21 U.S.C. § 355(j)(4)(K). Moreover, FDA's regulations require an ANDA filer to change its patent certification "if, at any time before the effective date of the approval of the application, the applicant learns that the submitted [patent] certification is no longer accurate." 21 C.F.R. § 314.94(a)(12)(viii)(C)(1). Once an ANDA filer's certification becomes "at variance with the legal reality," FDA may either force the ANDA filer to change its certification or treat the certification as automatically changed. Mylan Labs., Inc. v. Thompson, 389 F.3d 1272, 1281-82 (D.C. Cir. 2004).

When dealing with a similar situation involving the fentanyl transdermal patch, FDA properly required an ANDA applicant to change its Paragraph IV certification to a Paragraph II certification when the patent expired prior to final approval of the ANDA. Mylan Labs., 389 F.3d at 1281-82. The D.C. Circuit Court of Appeals affirmed FDA's decision and concluded that, "[o]nce the certification changed to *paragraph II* – whether *de facto* or *de jure* – pediatric exclusivity attached under 21 U.S.C. § 355a(c)(2)(A)(i)." Id.

Similarly, with respect to fluconazole, FDA properly determined that a Paragraph IV certification was no longer valid upon patent expiration where the generic challenger stipulated to a dismissal of the patent lawsuit upon expiration. In affirming FDA's determination, the district court summarized:

More specifically, the Federal Defendants maintain, a Paragraph IV certification states that, in the applicant's view, the patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the ANDA is submitted. See 21 U.S.C. § 355(j)(2)(A)(vii)(IV). A Paragraph II certification states that "such patent has expired." 21 U.S.C. § 355(j)(2)(A)(vii)(II). Section 505(j) provides that an ANDA that contains an untrue statement of material fact cannot be approved. See 21 U.S.C. § 355(j)(4)(K). Therefore, at the "magic moment" of midnight on January 29, 2004 [when the listed patent expired], Ranbaxy's Paragraph IV certification was no longer accurate and no longer valid because the patent to which it related had expired. The Paragraph IV certification either became a Paragraph II certification, or FDA was entitled to treat it as a Paragraph II certification, because the patent had expired. Alternatively, Ranbaxy was required to amend the Paragraph IV certification to provide accurate information, namely, the expiration of the patent, the lack of which made the Paragraph IV

certification invalid and non-approvable and left as the only option available a Paragraph II certification.

Ranbaxy Labs. Ltd. v. FDA, 307 F. Supp. 2d 15, 20 (D.D.C. 2004), aff'd without opinion, 2004 U.S. App. LEXIS 8311 (D.C. Cir. 2004).

Thus, at the “magic moment” of midnight on March 25, 2007, all Paragraph IV certifications to the ‘303 patent contained in unapproved ANDAs were no longer accurate and either automatically became Paragraph II certifications or the ANDA applicants were required to amend their Paragraph IV certifications to Paragraph II certifications. No matter the mechanism, the result is clear – all unapproved ANDAs that contained Paragraph IV certifications to the ‘303 patent must be treated as though they contain Paragraph II certifications to the expired ‘303 patent.

Pfizer’s Pediatric Exclusivity Bars ANDA Approvals Until September 25, 2007

By providing an economic incentive for drug manufacturers to invest in conducting safety and efficacy studies of drugs in pediatric patients, Congress recognized that pediatric populations are “therapeutic orphans,” and that pediatric studies “pose ethical and moral issues” and are difficult to conduct. S. Rep. No. 105-43, at 51 (1997). Pediatric exclusivity was created to ensure that more drugs were studied and therefore made safely available to pediatric patients who need them. Congress’ grant of an additional six months of marketing exclusivity to a drug manufacturer that performs pediatric studies elevated the goal of obtaining more drugs that are safe for pediatric use over the goal of accelerating the availability of generic competition to those drugs. See S. Rep. No. 107-79, at 11 (2001) (“By granting drug manufacturers a 6-month extension of market exclusivity for a drug upon satisfactory completion of requested pediatric studies of the product and delaying the availability of lower cost generic alternatives, the bill will make those prescription drugs . . . more expensive There would also be cost savings . . . by, for example, the reduced need for hospitalization of children and reduced error in medicating children.”).

After the NDA holder conducts the necessary pediatric studies, the pediatric exclusivity provisions provide that the NDA holder’s patent exclusivity will be extended by a period of six months. 21 U.S.C. § 355a. Specifically, the statute states that, when the ANDA contains a Paragraph II or Paragraph III certification to a listed patent, the period during which the submitted ANDA may not be approved is extended “by a period of six months after the date the patent expires (including any patent extensions).” 21 U.S.C. § 355a(c)(2)(A). If the drug is the subject of a Paragraph IV certification to a listed patent, pediatric exclusivity only applies if “in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed.” 21 U.S.C. § 355a(c)(2)(B).

At the moment that the '303 patent expired on March 25, 2007, it was valid and infringed. Paragraph IV certifications in pending ANDAs became inaccurate upon patent expiration and must be converted to or treated as Paragraph II certifications. By the terms of Section 355a, Pfizer's pediatric exclusivity attached when the '303 patent expired, and pending ANDAs containing Paragraph II or Paragraph III certifications cannot be approved until September 25, 2007 – six months after the patent expired. It is only after Pfizer's pediatric exclusivity expires that FDA can then grant final approvals to the pending ANDAs (assuming those ANDAs meet approval requirements).

This result is consistent with the letter and intent of the statute, and should not change if the Federal Circuit issues its mandate invalidating the '303 patent during Pfizer's pediatric exclusivity period. At the moment when the availability of pediatric exclusivity was determined, the '303 patent was valid and infringed. Pending ANDAs now must properly contain either Paragraph II or Paragraph III certifications, and ANDAs containing Paragraph II or Paragraph III certifications are subject to Pfizer's pediatric exclusivity by the terms of the statute. There is no mechanism, in the statute or otherwise, to rescind Pfizer's pediatric exclusivity if the patent upon which it is based is invalidated after it expires. Such is the regime enacted by Congress, which elevated the need for drugs to safely treat children over increased generic competition.

Paragraph IV ANDAs Are Subject to Mylan's Exclusivity Period

Alternatively, to the extent that FDA allows unapproved ANDAs to retain Paragraph IV certifications, such ANDAs are subject to Mylan's 180-day exclusivity period. The Hatch-Waxman Amendments unequivocally provide that an ANDA will be subject to the first filer's exclusivity period if it "contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification." 21 U.S.C. § 355(j)(5)(B)(iv).¹ FDA regulations are consistent with the statute. 21 C.F.R. § 314.107(c). Because Mylan submitted the first Paragraph IV certification with respect to amlodipine, all subsequent ANDAs containing a Paragraph IV certification are subject to Mylan's exclusivity period. Short of amending such ANDAs to include Paragraph II certifications, which would be subject to Pfizer's pediatric exclusivity, there is no statutory or regulatory mechanism to defeat Mylan's exclusivity period.

CONCLUSION

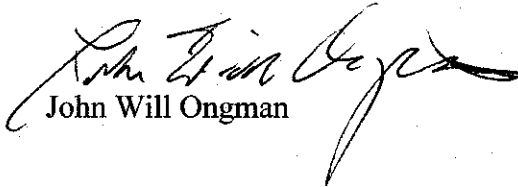
Accordingly, FDA should not give effect to the Federal Circuit's March 22, 2007 order invalidating the '303 patent unless and until the mandate issues, should require all applicants with pending ANDAs containing Paragraph IV certification to change to Paragraph II

¹ The law governing patent certifications and exclusivity issues relating to amlodipine is the pre-MMA law. Pub. L. No. 108-173, § 1102(b)(1), 117 Stat. 2066, 2460 (2003).

Food and Drug Administration
April 4, 2007
Page 6

certifications, and should not approve any ANDAs until Pfizer's pediatric exclusivity expires on September 25, 2007. Alternatively, all pending ANDAs with a Paragraph IV certification should be subject to Mylan's 180-day exclusivity period.

Sincerely,



John Will Ongman