EXHIBIT B

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

April 18, 2007

Dear ANDA Applicant/Holder for Amlodipine Besylate Tablets:

This letter addresses issues related to the timing of potential approvals of abbreviated new drug applications (ANDAs) that reference Norvasc tablets. This letter construes the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 (known as the Hatch-Waxman Amendments or Hatch-Waxman), codified at 21 U.S.C. §§ 355, 360cc, and 35 U.S.C. §§ 156, 271, 282, and does not necessarily apply to changes made in the Medicare Modernization Act (MMA) of 2003.[1]

As you are aware, Pfizer Inc. (Pfizer) manufactures and markets Norvasc, a besylate salt of amlodipine, indicated for the treatment of hypertension and angina. Pfizer had listed two patents with FDA, asserting that they claim Norvasc and would be infringed by the marketing of generic versions of the product. The later of these patents, Patent No. 4,879,303 ('303 patent), expired on March 25, 2007, so that these patents, by themselves, no longer bar the marketing of generic versions of Pfizer's product. Several companies have submitted ANDAs for approval to market generic versions of Norvasc. Mylan Laboratories, Inc. and Mylan Pharmaceuticals, Inc. (Mylan) filed the first ANDA to market a generic version of Norvasc and had challenged Pfizer's patents by submitting the first "paragraph IV certifications" to those patents with its application. FDA approved Mylan's ANDA in October 2005, and Mylan began marketing its product on March 23, 2007. On or about the same day, Pfizer began marketing a generic version of Norvasc.

Pfizer and Mylan now contend that the approvals of the other ANDAs for amlodipine besylate are blocked by Pfizer's "pediatric exclusivity" until September 25, 2007. Mylan contends, alternatively, that the approvals of its competitors' ANDAs are blocked by Mylan's "180-day marketing exclusivity" until September 19, 2007.[2] Resolution of whether pending ANDAs referencing Norvasc are blocked either by Pfizer's pediatric exclusivity or Mylan's 180-day exclusivity involves a number of legal issues, some of first impression for the agency. Part of the analysis requires FDA to determine the effect of a recent Federal Circuit decision in patent litigation between Pfizer and Apotex Inc. (Apotex), another ANDA applicant for amlodipine besylate who filed a paragraph IV certification after Mylan had submitted its certification. On March 22, 2007, the Federal Circuit ruled that the three claims in the '303 patent that Pfizer asserted that Apotex infringed were invalid as obvious. *Pfizer Inc. v. Apotex, Inc.*, No. 2006-1261, 2007 U.S. App. LEXIS 6623 (March 22, 2007) (the *Apotex* decision).

---

[1] The 1984 Hatch-Waxman provisions govern most issues related to ANDA approval for amlodipine besylate tablets. Although certain provisions of Hatch-Waxman have been superseded by changes made in the MMA, the 180-day exclusivity provisions of the MMA apply only to applications for which the first ANDA with a paragraph IV certification was filed after December 3, 2003. Mylan's ANDA was filed before December 3, 2003, and hence is governed by the pre-MMA provisions with respect to 180-day exclusivity.

[2] Mylan has claimed in its submissions to FDA that its 180-day exclusivity commenced on March 23, 2007 and would expire on September 23, 2007. See Petition for Stay of Action, Docket 2006P-0116 (March 26, 2007) (http://www.fda.gov/ohrms/dockets/dockets/07p0116/07p-0116-psa0001-01-vol1.pdf). However, 180 days after March 23 is September 19.

The questions presented by the pending applications and exclusivity claims include: (1) whether the *Apotex* decision is effective upon issuance of the opinion or upon issuance of the mandate, for purposes of determining the application of Pfizer's pediatric exclusivity; (2) upon the *Apotex* decision becoming effective, whether Pfizer's pediatric exclusivity bars approval of the Apotex ANDA; (3) upon the *Apotex* decision becoming effective, whether Pfizer's pediatric exclusivity bars approvals of the remaining ANDAs; and (4) whether Mylan's eligibility for 180-day exclusivity blocks approval of ANDAs after the expiration of Pfizer's patent. These questions are addressed in turn in the Discussion section below.

Regulatory Background

A. Patent Listing and Certification

The Hatch-Waxman Amendments permit the submission of ANDAs for approval of generic versions of approved drug products. 21 U.S.C. § 355(j). Under the procedure established in Hatch-Waxman, NDA sponsors are required to list patents that protect their approved drug substances, drug products, or approved methods of use, 21 U.S.C. § 355(b)(1); FDA publishes those patents in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the Orange Book); and ANDA applicants are required to certify whether their proposed drug products infringe those listed patents. 21 U.S.C. § 355(j)(2)(A)(vii). As to each patent listed in the Orange Book for the listed drug referenced, an ANDA applicant can certify that 1) such patent information has not been filed (paragraph I certification); 2) the patent has expired (paragraph II certification); 3) the date the patent will expire (paragraph III certification); or 4) the patent is invalid or not infringed by the drug product proposed in the ANDA (paragraph IV certification). *Id.*

In the case of paragraph I and paragraph II certifications, the patent does not serve as a barrier to ANDA approval. A paragraph I or paragraph II certification permits immediate effective approval of the ANDA. 21 U.S.C. § 355(j)(5)(B)(i). If an applicant files a paragraph III certification, approval may be made effective when the patent expires. 21 U.S.C. § 355(j)(5)(B)(ii).

If an applicant seeks to challenge a listed patent and to obtain approval before the patent expires, it must provide a paragraph IV certification certifying that "in the opinion of the applicant and to the best of his knowledge" the patent is "invalid or will not be infringed by the manufacture, use or sale of the [drug described in the ANDA]." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). The applicant with a paragraph IV certification must notify the patent owner and NDA holder of its paragraph IV certification and of the basis of its belief that the patent is invalid or not infringed. 21 U.S.C. § 355(j)(2)(B). The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of infringement. 35 U.S.C. § 271(e)(2)(A). This enables the NDA holder and patent owner to sue the ANDA applicant. If the patent owner or NDA holder brings a patent infringement suit against the ANDA applicant within 45 days after receiving notice of the paragraph IV certification, the suit triggers an automatic stay of FDA approval for 30 months from the date the patent owner or NDA holder received notice of the certification ("30-month stay"). 21 U.S.C. § 355(j)(5)(B)(iii). If the patent owner or NDA holder does not bring suit within 45 days after it has received notice of the paragraph IV certification, the unexpired patent will not, by itself, bar FDA's approval of the ANDA, even if patent litigation is subsequently commenced outside the 45-day period and is ongoing at the time the requirements for approval are met. See *id.*

B. 180-Day Exclusivity

To provide an incentive for ANDA applicants to be the first to challenge a listed patent and remove patent barriers to approval, Congress provided that:

> [I]f the [ANDA] contains a [paragraph IV certification] and is for a drug for which a previous application has been submitted under this subsection . . . [containing] such a certification, the application shall be made effective not earlier than one hundred eighty days after
>
> (I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
> (II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed, whichever is earlier.

21 U.S.C. § 355(j)(5)(B)(iv)(2002).

Although this statutory provision is commonly characterized as granting "180-day exclusivity" to the first applicant to submit an ANDA containing a paragraph IV certification challenging a patent, the statute does not provide for that result directly. Instead, this end is accomplished by delaying the approval of subsequent ANDAs *containing a paragraph IV certification* until 180 days after the exclusivity period for the first ("previous") applicant has been triggered. If the first applicant's ANDA no longer contains a valid paragraph IV certification when it is ready for approval, the first applicant is not eligible for exclusivity. Similarly, when subsequent applicants' ANDAs do not contain paragraph IV certifications, their approval is not delayed under the plain language of this statutory provision.

C. Pediatric Exclusivity

The pediatric exclusivity statute, enacted as part of the Food and Drug Administration Modernization Act (FDAMA) and renewed in the Best Pharmaceuticals for Children Act (BPCA), provides an incentive for NDA sponsors to conduct pediatric studies that FDA has requested. Although this incentive for doing pediatric studies is commonly referred to as "pediatric exclusivity," a grant of pediatric exclusivity alone does not guarantee that an NDA will be free of generic competition while the exclusivity is in effect. Instead, as FDA has opined and the D.C. Circuit has affirmed, the applicability of pediatric exclusivity to prevent approval of a particular applicant's ANDA depends on the outcome of that applicant's patent challenges, if any. See *Mylan Labs., Inc.* v. *Thompson*, 332 F. Supp. 2d 106 (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). Specifically, the statute states that if the approved product has completed the pediatric exclusivity requirements and is subject to

> (i) "a listed patent for which a [paragraph II] certification has been submitted . . . the period during which an application may not be approved under [21 U.S.C. § 355(j)(5)(B)] shall be extended by a period of six months after the patent expires;"
> (ii) "a listed patent for which a [paragraph III] certification has been submitted . . . the period during which an application may not be approved under [21 U.S.C. § 355(j)(5)(B)] shall be extended by a period of six months after the date the patent expires;"

(iii) "a listed patent for which a [paragraph IV] certification has been submitted . . . , and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under [21 U.S.C. § 355(j)(5)(B)] shall be extended by a period of six months after the date the patent expires."

21 U.S.C. § 355a(c)(2)(A)-(B).

Factual Background

On July 31, 1992, FDA approved Pfizer's new drug application (NDA) for amlodipine besylate tablets, which Pfizer began marketing later that year under the brand name Norvasc. Pfizer listed two patents with respect to Norvasc: Patent 4,572,909 ('909 patent), originally due to expire on July 31, 2006, and the '303 patent, originally due to expire on March 25, 2007. Pfizer conducted pediatric studies requested by FDA and, on November 27, 2001, FDA granted Pfizer pediatric exclusivity for Norvasc pursuant to 21 U.S.C. § 355a. Pediatric exclusivity, by delaying approval of ANDAs for six months after the expiration date for a patent, had the potential to block approvals of ANDAs referencing Norvasc until January 31, 2007, with respect to the '909 patent, and until September 25, 2007, with respect to the '303 patent. Because this period with respect to the '909 patent has expired, that patent is no longer relevant to the issues discussed in this letter.

In May 2002, Mylan filed an ANDA for amlodipine besylate, and was the first to file a paragraph IV certification to the '303 patent pursuant to 21 U.S.C. § 355(j)(5)(B)(iv). Pfizer sued Mylan for patent infringement. *Pfizer Inc. v. Mylan Labs. Inc.*, No. 02-cv-1628 (W.D. Pa.). However, because Pfizer did not file its lawsuit within 45 days of receiving notice of Mylan's paragraph IV certification, the filing of the lawsuit did not result in the 30-month stay of approval pursuant to 21 U.S.C. § 355(j)(5)(B)(iii). In October 2005, FDA approved Mylan's ANDA.

In February 2007, the district court in the patent litigation between Mylan and Pfizer entered judgment for Pfizer that Mylan had infringed the '303 patent. *Pfizer Inc. v. Mylan Labs., Inc.*, No. 02-cv-1628, 2007 U.S. Dist. LEXIS 14417 (W.D. Pa. Feb. 27, 2007). On March 16, 2007, the district court amended the judgment and enjoined the approval of Mylan's ANDA until the '303 patent expired. *Id.*, 2007 U.S. Dist. LEXIS 18699 (Mar. 16, 2007).[3] Mylan appealed that judgment and sought a stay of the district court's injunction. The Federal Circuit granted the stay. *Pfizer Inc. v. Mylan Labs., Inc.*, No. 2007-1194 (Mar. 23, 2007). Mylan began marketing its product on March 23, 2007.

Apotex, Inc. (formerly Torpharm, Inc.) filed an ANDA for amlodipine besylate, which contained a paragraph IV certification to the '303 patent. On July 20, 2003, Pfizer sued Apotex for patent infringement. In January 2006, the district court held the patent was valid and infringed. *Pfizer, Inc.* v. *Apotex*, No. 03C 5289, 2006 U.S. Dist. LEXIS 95778 (N.D. Ill. January 29, 2006). The Federal Circuit reversed in the opinion noted above, finding that Apotex's amlodipine besylate

[3] When an NDA holder or patent owner sues the ANDA applicant and wins — that is, the court hearing the patent infringement litigation finds the patent valid and infringed -- the Patent Code provides that "the court shall order the effective date of any approval of the drug * * * involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed." 35 U.S.C. § 271(e)(4)(A).

tablets did not infringe claims 1-3 of the '303 patent because those claims were invalid for obviousness. See *Apotex* decision. The Federal Circuit did not address the validity of the remaining claims of the patent, presumably because those were not claims on which Pfizer had sued Apotex. On April 5, 2007, Pfizer filed a motion in the Federal Circuit, seeking a rehearing and/or rehearing en banc of the *Apotex* decision. This motion stayed issuance of the mandate pending its resolution under Rule 41(d)(1) of the Federal Rules of Appellate Procedure (FRAP).

At midnight on March 25, 2007, the '303 patent expired. Pfizer submitted a letter to FDA dated March 25, 2007, contending that approval of Apotex's ANDA was barred by Pfizer's pediatric exclusivity, at least until the Federal Circuit's mandate issues.

On March 26, 2007, Mylan submitted to FDA a Petition for Stay of Action requesting that the FDA refrain from taking any action to approve any ANDA for amlodipine besylate tables until Mylan's 180-day exclusivity expires. According to Mylan, the 180-day exclusivity for amlodipine besylate tablets had been triggered when it commenced marketing on March 23, and is due to expire on September 19, 2007. Also on March 26, Mylan sued FDA in the U.S. District Court for the District of Columbia, alleging that it was entitled to 180-day exclusivity as to the '303 patent and requesting that the court enjoin FDA from approving additional ANDAs for amlodipine until the merits of its claim for 180-day exclusivity could be heard. *Mylan Labs., Inc.* v. *Leavitt*, CA No. 07-579 (RMU)(D.D.C.).

FDA determined that it was unprepared to immediately resolve all of the legal questions raised by the pending applications and exclusivity claims, and would benefit from soliciting the views and legal arguments of the interested parties. FDA informed the court that it proposed to seek comments to be submitted by April 4, 2007, and to issue its determination by April 11, 2007. The court memorialized FDA's proposal, and enjoined FDA from implementing any ANDA approval decisions, once made, until 5:00 PM on April 13, 2007 to allow the court to review FDA's decisions. *Mylan Labs.*, CA No. 07-579 (RMU), Order (March 26, 2007). FDA subsequently moved the court for an extension of time, until April 18, 2007, to issue its determination, which the court granted.

By letter dated March 28, 2007, FDA requested comments on five specific questions from Pfizer and the ANDA applicants for amlodipine besylate tablets. FDA created a docket for collecting the comments and posting them on the internet, and posted its letter requesting comments to give other interested parties an opportunity to comment on the questions FDA raised. (http://www.fda.gov/ohrms/dockets/dockets/07n0123/07n0123.htm) Several parties expressed a range of opinions on the questions FDA posed. *See id.* After receiving and considering submissions from interested parties, FDA reaches the following conclusions.

Discussion

1. For Purposes of Pediatric Exclusivity, the *Apotex* Decision Will Not be Effective until Issuance of the Mandate.

Under the language of the statute, pediatric exclusivity operates by delaying the approval of an ANDA for six months after a patent expires.[4] The operative subsection of the statute varies

[4] In this case, Mylan's ANDA is not blocked by Pfizer's pediatric exclusivity because its ANDA was already approved in October 2005, and therefore, under the literal terms of the statute, the ANDA's approval cannot be delayed. 21 U.S.C. § 355a(c)(2)(A)-(B). One commenter maintained that FDA should have converted the approval status of Mylan's ANDA to tentative approval after Mylan lost its patent litigation in the district court. See Comments of Synthon Pharmaceuticals, Inc. at 4. However,

according to the certification submitted by the ANDA applicant. When the ANDA applicant, such as Apotex, submits a paragraph IV certification, "if . . . in the patent litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved . . . shall be extended by a period of six months after the date the patent expires . . . ." *See* 21 U.S.C. § 355a(c)(2)(B). As discussed in greater detail below, FDA has previously opined, and concludes below, that this provision means that pediatric exclusivity does *not* apply when the ANDA applicant prevails in its patent challenge -- that the court determines that the patent is *in*valid or would *not* be infringed, and that construction has been acknowledged as appropriate by a court. Accordingly, this provision governs the application of pediatric exclusivity, at least with respect to Apotex.

In determining the effect of the *Apotex* decision on Pfizer's pediatric exclusivity claim, the first issue that FDA must resolve is to ascertain the meaning of the phrase "the court determines" for purposes of the statutory provision quoted above. Specifically, FDA must decide whether the Federal Circuit "determined" invalidity when it issued its opinion or will not "determine" validity or infringement until the mandate issues. Because the Court of Appeal's opinion is not effective until the mandate issues, Pfizer argues that the Federal Circuit will not have determined invalidity until that time. Apotex and others have asserted that the March 22, 2007 date of the issuance of the Federal Circuit opinion is the operative date.

FDA finds that the operative phrase -- "the court determines" -- is ambiguous as to the action it describes. Congress could have been more precise in indicating the action by the court to which it was referring, as it has done in other statutes. Compare, e.g., 26 U.S.C. § 7481(a) (finality is determined "upon mandate" issued by Court of Appeals or Supreme Court) with 21 U.S.C. § 355(j)(5)(B)(iii)(I)(aa)-(bb) (approval "shall be made effective on the date on which the court enters judgment reflecting the decision; or the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed."). Instead, it chose a phrase that, as the comments submitted to FDA reflect, is susceptible to more than one interpretation. On the one hand, the use of the present tense in the word "determines" could suggest that the issuance of the opinion itself is sufficient. Indeed, one dictionary definition of "determine" is "to come to a decision . . . as the result of investigation or reasoning." Webster's Third New International Dictionary (2002) at 616 (definition 1.c). Under this view, a court "determines" validity and infringement when it issues an initial ruling to that effect.

On the other hand, the choice of the word "determines" suggests the fixing or settling of rights and obligations. The dictionary definitions of "determine" include: "to fix conclusively or authoritatively," "to settle a question or controversy about," "to settle or decide by choice of alternatives or possibilities." *Id.* (definitions 1.a, 1.b, and 1.d.). See also Webster's II New Riverside University Dictionary (1994) at 369 ("[t]o end or decide by final, esp. judicial action") (definition 1.b). Under this view, where an appellate court is reversing the district court's judgment below, the parties' rights and obligations continue to be governed by the district court determination until the appellate court issues its mandate effectuating its judgment.

The Federal Rules of Appellate Procedure provide some additional guidance regarding which should be the relevant time frame for determining generally when the Federal Circuit's decision is effective. The rules themselves do not conclusively resolve the issue: FRAP 36 states that a judgment is entered when it is noted on the docket, while FRAP 41(c) states that the mandate is

---

before FDA took such action, the Federal Circuit stayed the district court injunction in that litigation. After that stay, FDA had no basis to convert the approval status of Mylan's ANDA from approved to tentatively approved.

effective when issued. However, the 1998 advisory committee notes to FRAP 41(c) state that "[a] court of appeals judgment or order is not final until issuance of the mandate; at that time the parties' obligations become fixed." These notes have been cited with approval by courts, *Mercer v. Duke Univ.*, 401 F.3d 199, 212 n.7 (4th Cir. 2005); *Stewart Park & Reserve Coalition Inc. v. Slater*, 374 F. Supp. 2d 243, 248 n.5 (N.D.N.Y. 2005); *United States v. Swan*, 327 F. Supp. 2d 1068, 1071-72 (D. Neb. 2004), and no commenters have cited any authority to FDA that would indicate that the advisory committee notes do not state the current rule regarding finality of appellate court decisions.[5] Therefore, under these rules, until the mandate issues, the parties continued to be bound by the district court judgment.

In FDA's view, the phrase "the court determines" in section 355a(c)(2)(B), in the context of a federal court of appeals reversing a district court judgment, should be read as the date the mandate issues for several reasons. When the district court decides a patent issue, FDA applies that decision, unless it is stayed, in determining issues related to ANDA approval. The district court decision continues to control the rights of the parties until the appellate court mandate issues. Thus, the vital date under this scheme is when the rights of the parties become fixed by the decision of the court of appeals, that is, the date the mandate issues. This understanding of the phrase "the court determines" is further supported by the dictionary definitions of "determine" that use the terms "fixing" and "settling," and by the practice under the FRAP, as reflected in the advisory committee notes and as accepted by courts. Furthermore, as a matter of policy, FDA believes that the parties to paragraph IV litigation are best served by a rule that, consistent with the statutory language, errs on the side of greater finality. Such a rule reduces the possibility that an appellate court opinion will be relied on and then overturned (through an adverse opinion after rehearing or rehearing en banc) in very short order. Accordingly, FDA concludes that, in determining the applicability of pediatric exclusivity, this language requires FDA to await issuance of the mandate before giving effect to an appellate court opinion that would overturn a district court's ruling.

In this case, therefore, for purposes of determining the applicability of Pfizer's pediatric exclusivity, FDA will continue to be governed by the district court decision upholding the validity of the patent unless or until the mandate is issued, effectuating the appellate court's judgment.[6] As a result, all of the unapproved ANDAs are currently blocked by Pfizer's pediatric exclusivity. If the mandate does not issue before September 25, 2007, when the pediatric exclusivity expires, Pfizer and Mylan will have no additional competition during the interim period and thus will obtain the full benefit that could be derived under pediatric and 180-day marketing exclusivity. In that event, the remaining issues discussed in this letter will be moot. However, given the possibility that the mandate making the panel decision effective may issue before September 25, 2007, FDA will continue with its analysis.

---

[5] Several commenters have cited an FDA Guidance document issued in March 2000. See, e.g., Mylan Comments at 2; Pfizer comments at 2. FDA is not relying on this guidance document, however, because it relates to a different statutory provision, with different language, context, and purposes.

[6] In this case, the district court found patent validity and infringement and the appellate court opinion found invalidity. Under these circumstances, FDA here declines to give effect to the appellate court's judgment of invalidity until the mandate issues and the patent and pediatric exclusivity attached to the patent block ANDA approvals in the interim. We note, however, that the agency's position on this also suggests that, had the district court found invalidity and the appellate court reached the contrary conclusion of validity and infringement, the converse would also be true: in spite of the appellate court opinion finding validity and infringement, ANDAs could be approved (or could retain their approvals) and neither the patent itself nor pediatric exclusivity would attach to that patent to block such approvals unless and until the mandate issued.

2. Apotex will Cease to be Subject to Pfizer's Exclusivity if the Mandate Issues before September 25, 2007.

This is the first time that FDA has been called upon to determine whether an ANDA applicant is subject to the innovator's pediatric exclusivity when the ANDA applicant has received a *favorable* court decision in its paragraph IV litigation but has not yet obtained final approval when the patent expires. The pediatric exclusivity provisions address several scenarios in terms of the status of the ANDA applications, but there are several scenarios that they fail to address, including this one.

The statute provides that, where the ANDA applicant submits paragraph IV certification, "if . . . in the patent litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved . . . shall be extended by a period of six months after the date the patent expires . . . ." *See* 21 U.S.C. § 355a(c)(2)(B). Based on this language, FDA determines that the converse must also be true - if in paragraph IV litigation a court determines that a patent is *invalid* or *not infringed*, pediatric exclusivity will not bar approval of that applicant's ANDA. This is the implicit meaning and logical interpretation of subsection 355a(c)(2)(B); otherwise, the qualification in that provision regarding the victory for the patent holder in the patent litigation would make no sense and would be superfluous, at least as to any ANDA that did not receive final approval before the patent expired. In addition, this outcome is consistent with the goals of the 180-day exclusivity statute which encourages patent challenges to remove barriers to approval. As noted, FDA had previously opined that this was the logical interpretation of 355a(c)(2)(B), although FDA was not directly applying that interpretation at that time. See *Mylan Labs., Inc.* v. *Thompson*, 332 F. Supp. 2d at 124 (D.D.C. 2004) ("As the FDA has correctly noted in its papers, § 355a(c)(2)(B) would apply 'where an ANDA applicant submits a paragraph IV certification, and prevails in the patent litigation.'")(dicta, citing Federal Defendants' Memorandum in Opposition to Plaintiffs' Motion for Preliminary Injunction and Summary Judgment and In Support of Cross Motion for Summary Judgment at 38 (July 8, 2004)), *aff'd*, 389 F.3d 1272 (D.C. Cir. 2004). FDA therefore concludes that, where an applicant has challenged a patent and has received a decision of invalidity or non-infringement, that applicant will not be subject to the NDA holder's pediatric exclusivity once that decision becomes effective.

FDA has previously been called upon to address other gaps in the pediatric exclusivity provisions. Specifically, the paragraph III and paragraph IV provisions are silent on the applicability of pediatric exclusivity to delay ANDA approvals where an ANDA applicant has a paragraph III or IV certification and has not received final approval at the time the patent expires. In determining the operation of the statute in those circumstances, FDA has relied on the broader certification scheme under Hatch-Waxman.

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).

In considering these earlier determinations regarding the switch to paragraph II certifications with today's decision regarding the non-applicability of pediatric exclusivity to applicants who prevail in patent litigation, FDA determines as follows. 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. However, FDA believes that the language of 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 and therefore creates an exception to the application of the Hatch-Waxman certification provisions. Thus, if and when the mandate finalizing the panel's March 22 decision issues in the *Apotex* case, Apotex's ANDA will not be blocked by Pfizer's pediatric exclusivity.

3. If the Mandate Issues Before the Expiration of Pediatric Exclusivity on September 25, 2007, ANDAs Other than Apotex May Not be Eligible for Immediate Approval.

Although Apotex is the only ANDA applicant to have obtained a favorable decision on the merits against Pfizer in the amlodipine besylate patent litigation, several commenters maintain that all or some of the other ANDAs should not be blocked by Pfizer's pediatric exclusivity because of the *Apotex* decision. Some maintain that, once the patent is declared invalid, it should be presumed delisted from the Orange Book. See Medco Comments at 7. That would mean that no ANDA applicants would be required to maintain their certifications to that patent, and pediatric exclusivity, by its literal terms, would not bar any approvals.

Others maintain that, once a patent is found invalid in litigation against one party, the patent owner is collaterally estopped from asserting infringement claims based on that patent against additional defendants. See, e.g. *Blonder-Tongue Labs., Inc.* v. *University of Ill. Found.*, 402 U.S. 313, 350 (1971). They argue that, applying collateral estoppel, all applicants who submitted paragraph IV certifications should be considered victorious in their individual patent litigation against Pfizer. At that point, they continue, the analysis applied to Apotex's ANDA should be applied to them as well so that their ANDAs would not be blocked by pediatric exclusivity. This would mean, according to at least one commenter, that ANDAs containing paragraph IV certifications at the time of patent expiration would be eligible for approval, while those containing paragraph III certifications would be blocked. See Teva Comments at 11-13.

Other commenters noted, however, that the *Apotex* decision addressed only claims 1-3 of an 11 claim patent. These commenters assert that the patent should stay listed in the Orange Book because some of the claims have not been declared invalid. See Mylan Comments at 1-2; Daiichi Sankyo Inc. Comments at 2. Nevertheless, another commenter maintains that there are no viable claims remaining for these products once claims 1-3 are declared invalid. See Caraco Pharmaceutical Labs, Ltd. at 3.

Patents are required to be listed in FDA's Orange Book if they claim the approved drug substance, approved drug product, or an approved method of use. 21 U.S.C. § 355(b)(1); 21 C.F.R. § 314.53. If the remaining claims do not provide a basis on which to list the patent (i.e., do not claim the approved drug substance, drug product, or an approved method of use), the patent would no longer be eligible for listing in the Orange Book. In such a case, the patent must be withdrawn by Pfizer and any pediatric exclusivity that attached to the patent will no longer serve as a barrier to ANDA approval. If, on the other hand, one or more of the remaining claims claims the approved drug substance, approved drug product, or approved method of use, the patent can remain properly listed until the expiration of pediatric exclusivity. In such a case, the patent should remain in the Orange Book and the remaining unapproved ANDAs are potentially subject to Pfizer's pediatric exclusivity.

It is not clear to FDA, based on the current record, whether the remaining claims of the '303 patent would provide a valid basis to list the patent if claims 1-3 are invalid. Moreover, FDA has long maintained that its has neither the expertise nor the resources to resolve patent issues and does not make independent determinations of the merits or applicability of patent claims. 59 Fed. Reg. 50338, 50342-43, 50345, 50349, 50352 (1994). FDA's ministerial role in the listing process has been upheld. *Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1348-49 (Fed. Cir. 2003); *aaiPharma, Inc. v. Thompson*, 296 F.3d 227, 243 (4th Cir. 2002), *cert. denied*, 538 U.S. 923 (2003); *Alphapharm Pty Ltd. v. Thompson*, 330 F. Supp 2d 1, 7-8 (D.D.C. 2004).

Because FDA lacks both relevant information and expertise to resolve this issue based on the information before it, in the absence of further judicial or other action clarifying the status of the patent, FDA will assume the '303 patent remains validly listed. If one or more of the remaining claims qualified the patent for listing as of the time the patent expired, all of the remaining ANDAs who had paragraph III and paragraph IV certifications at the time of patent expiry are required to maintain their paragraph II certifications. As such, those ANDAs will be blocked by Pfizer's pediatric exclusivity.

4. Mylan's Eligibility for 180-day Exclusivity Does Not Extend Beyond the Expiration of the Patent.

Mylan asserts that regardless of the applicability of pediatric exclusivity, all of the remaining ANDAs are subject to Mylan's 180-day exclusivity, which, if viable, would expire on September 19, 2007. Most commenters assert that it is well settled that 180-day exclusivity does not extend beyond the expiration of the patent. See, e.g., Apotex Comments at 8; Teva Comments at 6-7. Although Mylan acknowledges FDA's longstanding position that 180-day exclusivity expires with the patent, Mylan urges FDA to change that position, at least in the circumstances here, where the 180-day exclusivity has been triggered and begun to run before the patent expires.

By the terms of the statute, when a listed patent expires, a paragraph IV certification is no longer accurate. In these circumstances, the statute and FDA's regulations require ANDA applicants to change from a paragraph IV certification stating that the patent "is invalid or will not be infringed" to a paragraph II certification stating "that such patent has expired." 21 U.S.C. § 355(j)(2)(A)(vii)(II),(IV); 21 C.F.R. § 314.94(a)(12)(viii)(C) ("an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate"). In cases where an applicant neglects to amend its certification to a paragraph II certification after a patent expires, FDA will treat it as having done so. This approach was upheld in *Dr. Reddy's Laboratories, Inc.* v. *Thompson*, 302 F. Supp. 2d 340 (D.N.J. 2003) and *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).

As noted above, applications with paragraph II certifications are eligible for immediate effective approval; the patent ceases to be a barrier to that approval upon its expiration. 21 U.S.C. § 355(j)(2)(A)(ii); 21 U.S.C. § 355(j)(5)(B)(i)(where an applicant files a paragraph II certification, approval of the applicant's ANDA "may be made effective immediately"); 21 C.F.R. § 314.94(a)(12)(viii). Thus, consistent with the statutory language and purpose of 180-day exclusivity, FDA has consistently construed the statute to award 180-day exclusivity based upon paragraph IV certifications only to unexpired patents. See 59 Fed. Reg. 50338, 50348 (stating "a patent is deemed to be relevant [for exclusivity purposes] until the end of the term of the patent or applicable 180-day period, whichever occurs first"). Because only subsequent applicants with valid paragraph IV certifications are blocked by 180-day exclusivity, and

because paragraph IV certifications cease to be accurate once the patent expires, the patent and 180-day exclusivity based on a paragraph IV certification to that patent cease to prevent approval of subsequent ANDAs once the patent expires.[7] See *Ranbaxy Labs., Ltd.* v. *Leavitt*, 469 F.3d 120, 126 (D.C. Cir. 2006)("[T]he first generic applicant may no longer retain exclusivity when the patent has expired.").

This plain language reading of the statute effectuates the statutory goals. The 180-day exclusivity provisions were drafted to give ANDA applicants an incentive to be first to challenge a listed patent and remove that patent as a barrier to approval. Once a listed patent expires and is no longer a barrier to ANDA approval, there is no longer a need to provide an incentive to challenge it in court. Thus, an expired patent does not serve as the basis for a 180-day exclusivity award and 180-day exclusivity does not extend beyond the life of the patent.

Mylan has argued that 21 U.S.C. § 355a(k) compels the conclusion that 180-day exclusivity extends beyond the date the patent expires. See Mylan comments at 7-8. That section provides that:

> If [180-day exclusivity period] overlaps with a 6-month [pediatric exclusivity] period . . ., so that the applicant for approval of a drug under section 505(j) entitled to the 180-day period under that section loses a portion of the 180-day period to which the applicant is entitled for the drug, the 180-day period shall be extended from
>
> (1) the date on which the 180-day period would have expired by the number of days of overlap, if the 180-day period would, but for application of this subsection, expire after the 6-month exclusivity period; or
>
> (2) the date on which the 6-month exclusivity period expires, by the number of days of the overlap if the 180-day period would, but for application of this subsection, expire during the six-month exclusivity period.

21 U.S.C. § 355a(k). On its face, this section is inapplicable here because Mylan is approved and is not subject to Pfizer's pediatric exclusivity and, thus, there is no 180-day exclusivity to restore. No commenters appear to contend otherwise.

Instead, Mylan argues that, by providing, in circumstances not applicable here, that 180-day exclusivity will follow pediatric exclusivity, Congress must have been assuming that 180-day exclusivity survives patent expiration. See Mylan comments at 7-8. If Mylan were correct, then section 355a(k) would conflict with FDA's longstanding understanding of the Hatch-Waxman statutory provisions governing 180-day exclusivity, as discussed above, which FDA believes to be compelled by the plain language of the statute. Thus, Mylan is essentially arguing that section 355a(k) repealed part of the Hatch-Waxman 180-day exclusivity provisions.

For one federal statute to repeal another:

---

[7] We note that if Mylan were correct and 180-day exclusivity continued to block approvals of ANDAs with paragraph IV certifications after the patent expired (essentially ignoring the automatic switch of the certifications to paragraph II), 180-day exclusivity would block ANDAs containing paragraph IV certification but not those containing paragraph III certifications under the plain language of 21 U.S.C § 355(j)(5)(B)(iv). This would have the perverse effect of punishing applicants who took the risk of challenging a patent with a paragraph IV certification in order to remove a barrier to approval and to reward those applicants who sat back and waited for the patent to expire. This result is clearly inconsistent with the intent and logic of Hatch-Waxman. Thus, the fact that section 355(j)(5)(B)(iv) by its terms blocks only ANDAs containing paragraph IV certifications -- the only ANDA that can be approved before the expiration of an applicable patent -- indicates that Congress did not intend exclusivity to extend beyond patent expiration.

> [T]he intention of the legislature to repeal must be clear and manifest. . . . In practical terms, this "cardinal rule" means that in the absence of some affirmative showing of an intention to repeal, the only permissible justification for a repeal by implication is when the earlier and later statutes are irreconcilable.

Tennessee Valley Auth. v. Hill, 437 U.S. 153, 189 (1978) (citations omitted). The "irreconcilable conflict" required is a conflict

> in the sense that there is a positive repugnancy between [the two statutes] or that they cannot mutually coexist. It is not enough to show that the two statutes produce differing results when applied to the same factual situation, for that no more than states the problem.

Radzanower v. Touche Ross & Co., 426 U.S. 148, 155 (1976) (emphasis added). Here, there is no evidence that Congress ever affirmatively indicated that it intended to repeal or change the operation of the 180-day exclusivity provision in enacting section 355a(k).

Nor can Mylan show that the 180-day provisions in Hatch-Waxman and section 355a(k) are irreconcilable because it is possible to construe them in a way that they can mutually coexist. By its terms, section 355a(k) only addresses the curtailment of exclusivity to which the applicant is otherwise "entitled." As explained above, under Hatch-Waxman, the applicant is not entitled to exclusivity after the patent expires. That means, in reconciling the statutes, that the application of section 355a(k) is limited to the situation where there is more than one patent and the two exclusivity periods are each attached to different patents. Thus, one patent may expire, and pediatric exclusivity would start to run, but the ANDA applicant could still be eligible for 180-day exclusivity on a later patent that had not yet expired. If that 180-day exclusivity period were triggered by a court decision on the later patent, it would be running at the same time the ANDA was blocked from approval by the pediatric exclusivity on the earlier patent.

Indeed, the legislative history demonstrates that Congress intended to address this narrow situation by adding 21 U.S.C. § 355a(k) to restore the exclusivity to which the ANDA applicant was entitled but which otherwise would have been lost because the pediatric exclusivity on another patent blocked final effective approval:

> The amendment gives the filer of an [ANDA] who challenges a patent no more and no less time to market his drug exclusively before subsequent [ANDAs] for the drug may be approved then it would have received but for the intervening period of pediatric exclusivity.
> For example, the committee understands that there may be instances in which 2 patents on a drug are challenged in an [ANDA], and that, in subsequent litigation, a court holds the first patent to expire to be valid and infringed, and the second patent to expire to be invalid. If the section [355(b)(1), 21 U.S.C.] drug is granted a period of pediatric exclusivity with respect to the first patent, and if the court decision, which triggers the beginning of ANDA exclusivity, falls 60 days before that period of pediatric exclusivity begins (that is, 60 days before the first patent will expire), the ANDA exclusivity will overlap with the pediatric exclusivity for 120 days. In the absence of the pediatric exclusivity, the holder of the [ANDA] would enjoy at most 120 days to market its drug before a subsequent [ANDA] for the drug could be approved. But for the amendment, because of pediatric exclusivity, the holder of the [ANDA] would enjoy no ANDA exclusivity, because

> the first 120 days of the pediatric exclusivity period would run over the last 120 days of its ANDA exclusivity period.

S. Rep. No. 107-79, at 6-7 (2001); see also *id.* at 14 ("[Section 9 of BPCA] specifies that, when the pediatric exclusivity period for a drug overlaps with a period of ANDA exclusivity for the drug, the period of ANDA exclusivity is extended by an amount necessary to ensure that the holder of ANDA exclusivity enjoys the same possibility of exclusive commercial marketing as that the holder would have enjoyed in the absence of pediatric exclusivity, no more and no less."). This language confirms both that Congress intended only the limited application of section 355a(k) and that this section can be construed consistently with the Hatch-Waxman exclusivity provisions. Thus, "[b]ecause the statutes are not irreconcilable and there is no convincing evidence that the later act was intended as a substitute, ... a repeal by implication did not occur." *United States v. Williams*, 216 F.3d 1099, 1102 (D.C. Cir. 2000).

Furthermore, the statute also does not distinguish, as Mylan proposes, between situations in which 180-day exclusivity has been awarded and triggered at the time of patent expiry and cases in which it has not. See Mylan Comments at 12-14. Although Mylan correctly notes that the obligation to update a patent certification only applies before the effective date of approval, *id.* at 14; Mylan's Petition for Stay at 3, and thus approved applications (such as Mylan's) have no continuing obligation to update their patent certifications, this does not mean that 180-day exclusivity for an approved application extends beyond the date the patent expires. On the contrary, if all of the remaining unapproved applications change to a paragraph II certification when the patent expires, as they are required to do, they will no longer be applications containing paragraph IV certifications that are blocked by the previous application containing a paragraph IV certification. This is the case regardless of whether Mylan's application, which has been approved, is also required to change its certification. As a result, because all unapproved applications must change to a paragraph II certification when the patent expires, and applications with paragraph II certifications are not blocked by 180-day exclusivity, for all intents and purposes, Mylan's 180-day exclusivity will terminate with the expiration of the patent regardless of the fact that Mylan itself is no longer obligated to change its certification upon patent expiry.

Conclusion

In sum, FDA has concluded:

- All of the unapproved ANDAs are currently blocked by Pfizer's pediatric exclusivity.
- If and when the mandate effectuating the panel's March 22 decision issues in the *Apotex* case, Apotex's ANDA will not be blocked by Pfizer's pediatric exclusivity.
- FDA cannot determine on the current record whether other ANDAs will continue to be blocked by pediatric exclusivity at that time.
- Mylan's 180-day marketing exclusivity terminated when the patent expired.

If you have any questions regarding this letter please contact Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs at 240-276-9319

Sincerely,

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

cc: Pfizer Inc.