April 4, 2007

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

Dear Mr. Buehler:

Re: Comments of Mylan Pharmaceuticals Inc. Regarding Amlodipine Abbreviated New Drug Application Approvals; Docket No. 2007N-0123

Dear Mr. Buehler:

Mylan Pharmaceuticals Inc. ("Mylan") holds ANDA No. 76-418 for amlodipine besylate tablets. On behalf of Mylan, I am writing in response to your letter regarding the eligibility of amlodipine besylate ANDAs for final approval in light of: (i) the Federal Circuit's ruling in *Pfizer, Inc. v. Apotex, Inc.*, No. 2006-1261, 2007 U.S. App. LEXIS 6623 (Fed. Cir. March 22, 2007) holding certain claims of U.S. Patent No. 4,879,303 ("the '303 patent") invalid; (ii) Pfizer's claim to pediatric exclusivity; and (iii) Mylan's claim to 180 days of generic marketing exclusivity. Mylan is also submitting these comments to Docket No. 2007P-0116.

On May 22, 2002, Mylan was the first ANDA applicant to submit a substantially complete application containing a Paragraph IV certification to the patents listed in the Orange Book for the reference listed drug, Norvasc® (amlodipine besylate tablets). The FDA granted final approval to Mylan's Amlodipine ANDA on October 3, 2005, confirming in its final approval letter that because Mylan was the first applicant to file an ANDA with a Paragraph IV certification, "Mylan is eligible for 180 days of market exclusivity." October 3, 2005 letter from Gary J. Buehler to Mylan at 2 (attached as Exhibit A). The FDA's approval letter further states, consistent with the plain language of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 501, *et seq.* ("FDCA") and the FDA's own regulations, that Mylan's 180-day generic marketing exclusivity "will begin to run from the earlier of commercial marketing or court decision dates identified in [21 U.S.C.] section 355(j)(5)(B)(iv)." Mylan commenced commercial marketing of its generic Amlodipine products on March 23, 2007, and notified the FDA of this fact. *See* March 23, 2007 General Correspondence from Mylan to Gary J. Buehler and associated Form FDA 356h (attached as Exhibit B).

First and importantly, Mylan draws the FDA's attention to an incorrect factual premise which underlies all of the questions posed by the FDA: that the '303 patent was invalidated *in its entirety* by the Federal Circuit's decision. This is incorrect. The only claims before the Federal Circuit, and thus the only claims invalidated by the Federal Circuit's decision, were the first three claims. The remaining claims, claims 4-12, two of which were asserted by Pfizer against Mylan in its underlying patent litigation as covering Norvasc, were still presumed to be valid up until the time of the '303 patent's expiration. Mylan submits its specific comments and responses to the FDA's questions below.

1. What date controls FDA's giving effect to the decision in *Pfizer Inc. v. Apotex,* Inc., No. 2006-1261 (Fed. Cir. March 22, 2007) ("*Apotex* decision") holding that Pfizer's patent 4,879,303 ("the '303 patent") is invalid? Can FDA treat the '303 patent as invalid as of March 22, 2007, or must FDA await the issuance of the mandate? Is the answer the same for all purposes, that is, for determining the applicability of pediatric exclusivity, the triggering of 180-day exclusivity, and the eligibility of other ANDA applicants for final approval?

There can be no date assigned to the invalidity of the '303 patent because the Federal Circuit's decision did not hold "the '303 patent" to be invalid. The only claims before the Federal Circuit and invalidated by its decision were claims 1-3. *See Pfizer*, No. 2006-1261, 2007 U.S. App. LEXIS 6623 at *63. The Federal Circuit's decision did not affect the validity of the remaining claims, claims 4-12; therefore, the patent expired with presumptively valid claims irrespective of the date that the FDA gives effect to the decision. Moreover, for purposes of pediatric exclusivity, the FDA's long-standing pre-MMA rule and policy is to not give effect to a Federal Circuit decision reversing the trial court's finding of validity and/or infringement until the mandate is issued to the District Court. *See, e.g.*, FDA Guidance, *Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act*, ¶ IV.A (March 2000). Pfizer has publicly stated its intention to seek rehearing or reconsideration of the panel's decision. For the FDA to treat the Federal Circuit's decision as if it were a final decision, when it is not, would be contrary to law.

For purposes of triggering 180-day generic exclusivity under the pre-MMA provisions applicable to this case, 180-day exclusivity is triggered on the earlier of commercial marketing or "the date of a decision of a court" in an action brought under the Hatch-Waxman Act holding the patent which is the subject of the paragraph IV certification "to be invalid or not infringed." 21 U.S.C. § 355(j)(5)(B)(iv)(I)-(II) (2002). Mylan began commercial marketing of its amlodipine besylate products on March 23, 2007. Therefore, under any circumstances, Mylan's 180-day exclusivity period, at the latest, was triggered on that date. *See id.* at § 355(j)(5)(B)(iv)(I).

2. If FDA must await the issuance of the mandate, does pediatric exclusivity bar approval of all unapproved ANDAs in the meantime?

Yes, because the '303 patent was not invalidated, only claims 1-3. Further, under the FDA's pre-MMA rules, pediatric exclusivity would bar the approval of all unapproved ANDAs while awaiting the issuance of a mandate. Every amlodipine besylate ANDA that was tentatively approved as of midnight on March 25, 2007, is presently subject to Pfizer's pediatric exclusivity under the FDA's rules and regulations preceding this solicitation for comments. Unless the FDA were to arbitrarily depart from its existing precedents, Pfizer's awarded six-month period of pediatric exclusivity attaches to any ANDA that contained a paragraph II certification, paragraph III certification, or a paragraph IV certification for which the holder had tentative approval upon the expiration of the '303 patent, pursuant to 21 U.S.C. § 355a.

3. If and when the *Apotex* decision is implemented, what is the effect of the decision that the '303 patent is invalid on the obligation of an ANDA applicant to change its certification? Must Pfizer delist its patent, so that certifications can be withdrawn? Or can FDA treat an invalid patent as delisted as a matter of law, and presume the withdrawal of the certifications? Or must the ANDA applicants file paragraph II certifications stating that the '303 patent has expired?

As noted above, claims 4-12 of the '303 patent were not invalidated by the Federal Circuit's decision. Therefore, there is no obligation of an ANDA applicant to change its certification and the '303 patent does not need to be delisted.

The FDA does not have the authority to delist a patent, much less one with valid claims. *See* 21 C.F.R. § 314.53(f) (2006); *see also aaiPharma Inc. v. Thompson*, 296 F.3d 227, 233 (4th Cir. 2002) (stating that "[c]onsistent with its regulation," the FDA "would make no change to [a] listing unless [the patent holder] asked it to do so"), *cert. denied*, 538 U.S. 923 (2003). It is axiomatic, then, that a patent cannot be delisted so as to deprive the holder of 180 days of marketing exclusivity from reaping the reward of that exclusivity. *See Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120, 121 (D.C. Cir. 2006) (holding that "the FDA's requirement that a generic manufacturer's patent challenge give rise to litigation as a condition of retaining exclusivity when a patent is delisted is inconsistent with the Act, which provides that the first generic manufacturer to file an approved application is entitled to exclusivity when it either begins commercially to market its generic drug or is successful in patent litigation."). Here, delisting would not be appropriate at least until Mylan's 180-day exclusivity ends.

Additionally, any attempt by FDA to "presume" the validity or invalidity of a patent certification is against its long-standing rule not to interfere substantively with patent challenges and patent matters. *See Alphapharm Pty, Ltd. v. Thompson*, 330 F. Supp. 2d 1, 7-8 (D.D.C. 2004) ("This reading is consistent with FDA's claim, first announced shortly after the enactment of the Hatch-Waxman amendments, that it 'has no expertise in the field of patents,' and, therefore, 'no basis for determining whether a use patent covers the use sought by the generic applicant.'") (citations omitted); *see also aaiPharma*, 296 F.3d at 241 (noting that the "FDA has no expertise in making patent law judgments.").

4. If and when the *Apotex* decision is implemented and the patent is treated as invalid, does pediatric exclusivity attach to the '303 patent with respect to any unapproved ANDAs? Does it matter whether the ANDA applicant filed a paragraph III or IV certification before patent expiration?

Initially, Mylan notes that the '303 patent itself was not invalidated by the Federal Circuit's decision, but rather claims 1-3 of that patent were found invalid. Under the FDA's consistently-applied pre-MMA precedent, it should make no difference for purposes of pediatric exclusivity whether an applicant with tentative approval at the moment of patent expiration originally submitted a Paragraph III or a Paragraph IV certification, pediatric exclusivity attaches. *See Ranbaxy Labs v. FDA*, 307 F. Supp. 2d 15 (D.D.C. 2004), *aff'd*, 2004 U.S. App. LEXIS 8311 (D.C. Cir. 2004).

5. Does 180-day exclusivity triggered before a patent expires continue to bar approvals of other ANDAs after the patent expires, even if other ANDA applicants change their certifications to paragraph II or withdraw their certifications altogether?

Yes. Mylan's 180-day exclusivity period began on March 23, 2007, when Mylan began commercially marketing its generic amlodipine products prior to the '303 patent's expiration, and subsequent applicants are barred by that exclusivity period. The FDA should not interpret the FDCA to provide for the forfeiture of the 180-day exclusivity period upon patent expiration. Such an interpretation would violate the unambiguous language of the statute, as well as the structure, and purposes of several interrelated provisions of the FDCA.

A. THE PLAIN LANGUAGE OF THE HATCH-WAXMAN ACT PROHIBITS THE FDA FROM EXTINGUISHING MYLAN'S 180-DAY EXCLUSIVITY PERIOD

As it was first enacted by Congress in the 1984 Hatch-Waxman amendments to the FDCA, the 180-day exclusivity period for the first generic drug applicant to challenge a patent listed in the Orange Book was triggered upon the earlier of (1) the beginning of commercial marketing by the first applicant or (2) a judicial determination of patent invalidity or noninfringement. 21 U.S.C. § 355(j)(5)(B)(iv) (2002). Congress instructed that, once the exclusivity period had been triggered, any other approved ANDA "shall be made effective not earlier than one hundred and eighty days after" the beginning of the exclusivity period. *Id.* Congress said nothing about a potential forfeiture of this exclusivity period in the event that the underlying challenged patent expired during the period of exclusivity. The plain language of Hatch-Waxman authorized no such forfeiture, and it would be impermissible for the FDA to impose one here, even if the statute were otherwise silent on this issue. *See, e.g.*, *Ranbaxy Labs*, 469 F.3d at 125 (noting pattern of D.C. Circuit decisions "reject[ing] at *Chevron* step one the FDA's attempt to add to the statutory requirements for exclusivity").

Subsequent Congressional enactments reinforce the conclusion that the exclusivity period is not forfeited upon patent expiration. *See, e.g.*, *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000) ("[T]he meaning of one statute may be affected by other Acts, particularly where Congress has spoken subsequently and more specifically to the topic at hand."). Congress spoke to this precise issue in the *Medicare Prescription Drug, Improvement, and Modernization Act of 2003* ("MMA"), which amended the ANDA provisions of the FDCA in several important respects. Congress specifically provided in the MMA that patent expiration "shall" result in a "forfeiture" of the 180-day exclusivity period, but that this forfeiture provision "shall be effective *only* with respect to an [ANDA] filed ... *after* the date of the enactment of this Act [Dec. 8, 2003] for a listed drug for which no certification under [21 U.S.C. § 355(j)(2)(A)(vii)(IV)] was made before the date of the enactment of this Act [Dec. 8, 2003]." MMA, Pub. L. 108-173, Title XI, § 1102(b)(1), Dec. 8, 2003, 117 Stat. 2460 (emphasis added); *see* 21 U.S.C. § 355(j)(5)(D)(i)(VI); *id.* § 355(j)(5)(D)(ii). Congress in the MMA made other changes to the 180-day exclusivity provisions that expressly applied to ANDAs "filed *before, on, or after* the date of the enactment of this Act [Dec. 8, 2003]," but it instructed that forfeiture based on patent expiration would only apply to *prospective* ANDAs. Pub. L. 108-173, Title XI, § 1102(b)(3), Dec. 8, 2003, 117 Stat. 2460 (emphasis added).

If Congress had intended for the 180-day exclusivity period to be extinguished whenever the underlying patent expired, it would have provided that exclusivity would be forfeited upon patent expiration with respect to ANDAs filed "*before, on, or after*" December 8, 2003, as it did in other instances. Instead, Congress pointedly instructed that the exclusivity period would be forfeited due to patent expiration "*only*" with respect to ANDAs filed "*after*" that date. The first canon of statutory construction is that courts—and administrative agencies—"must presume that a legislature says in a statute what it means in a statute and means what it says there." *Conn. Nat'l Bank v. Germain*, 503 U.S. 249, 253-54 (1992). There is no way that "after" can be expanded to include "before." The plain language provides that patent expiration does indeed affect exclusivity rights, but only as to ANDAs filed "*after*" December 8, 2003. The only permissible reading is that, as to approved ANDAs filed *before* that date (like Mylan's ANDA here), patent expiration would *not* operate to forfeit exclusivity rights.[1]

This reading is reinforced by the interplay of the 180-day exclusivity provisions with those governing pediatric exclusivity. Under the FDCA, pediatric exclusivity by definition is triggered only when the underlying patent expires. *See* 21 U.S.C. § 355a. In the *Best Pharmaceuticals for Children Act* ("BPCA"), Pub. L. No. 107-109, 115 Stat. 1408 (2002), Congress clearly instructed that in cases of overlap, pediatric exclusivity would take place first, followed by the 180-day generic exclusivity period. This instruction, codified at 21 U.S.C. § 355a(k) (2002), provides in full:

> (k) Clarification of interaction of market exclusivity under this section and market exclusivity awarded to an applicant for approval of a drug under section 355(j) of this title.
>
> > If a 180-day period under section 355(j)(5)(B)(iv) of this title overlaps with a 6-month exclusivity period under this section, so that the applicant for approval of a drug under section 355(j) of this title 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 the overlap, if the 180-day period would, but

[1] To date, the FDA has not proposed any regulations regarding the MMA amendments to the Hatch-Waxman Act. As Mylan is successful under any interpretation of this statutory provision, such that one is not necessary for purposes of these Comments, Mylan reserves its right to comment upon any future regulations proposed by the FDA.

> for the 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 the application of this subsection, expire during the six-month exclusivity period.

This provision also compels the conclusion that the 180-day exclusivity period survives patent expiration. Any interpretation holding 180-day exclusivity rights to be extinguished simply as a result of patent expiration would ignore these statutory provisions and, indeed, render 21 U.S.C. § 355a(k) an absolute nullity. The FDA may not adopt such a construction. *See, e.g.*, *Brown & Williamson*, 529 U.S. at 133 (courts and agencies "must ... interpret the statute 'as a symmetrical and coherent regulatory scheme,' ... and 'fit, if possible, all parts into an harmonious whole'") (citations omitted); *TRW, Inc. v. Andrews*, 534 U.S. 19, 31 (2001) ("[i]t is a 'cardinal principle of statutory construction' that 'a statute ought, upon the whole, to be so construed that, if it can be prevented, no clause, sentence, or word shall be superfluous, void, or insignificant'") (citation omitted); *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 633-634 (1973) (rejecting proposed construction of the FDCA that would render one clause "superfluous" and without "operative effect").

B. STRIPPING MYLAN OF ITS 180-DAY EXCLUSIVITY WOULD ALSO VIOLATE THE CONGRESSIONAL PURPOSE AND INTENT OF THE HATCH-WAXMAN ACT

Imposing a forfeiture of Mylan's exclusivity rights would also violate the underlying Congressional purposes and policies of the statutory provisions in issue. One of the principal policy objectives of the Hatch-Waxman Act was to "[g]et safe and effective generic substitutes on the market as quickly as possible after the expiration of a patent." H.R. Rep. No. 98-857, pt. II (1984), *reprinted in* 1984 U.S.C.C.A.N. 2716-17. To do so, Congress created an incentive for generic manufacturers to bring early challenges of the validity and applicability of those patents.

The incentive was the right to market its generic products for 180 days without generic competition, and "[t]he purpose of [the 180-day exclusivity provision] of the act is to *reward* the first applicant to test the scope or validity of a patent…." 54 Fed. Reg. 28872, 28895 (July 10, 1989) (emphasis added).

The need for a "reward" is straightforward – the filing of a "paragraph IV" certification, informing the FDA that the applicant intended to challenge the patent or patents covering the brand drug, was made an act of infringement under 35 U.S.C. § 271(e)(2), also passed as part of the Hatch-Waxman Act. "Given this risk of patent infringement litigation, section 505(j)(5)(B)(iv) of the act provides an incentive for generic drug applicants to file paragraph IV certifications challenging patents that may be invalid, unenforceable, or not infringed by the product that is the subject of the ANDA." Proposed Rule, *180-Day Generic Drug Exclusivity for Abbreviated New Drug Applications*, 64 Fed. Reg. 42873, 42874 (Aug. 6, 1999), *withdrawn on other grounds by* 67 Fed. Reg. 212, 66593 (Nov. 1, 2002).[2] Indeed, it was Mylan that took the risk to first challenge the '303 patent – doing so more than a year before the next challenger, Apotex, even filed its ANDA. Mylan's challenge paved the way of subsequent filers' challenges to the '303 patent because those filers had the benefit of the fact and expert discovery developed in Mylan's case. This, combined with the retirement of the district court judge in Mylan's case, which caused a significant delay in its litigation, resulted in Apotex going to trial first and its appeal being decided before Mylan's appeal. Importantly, in the end, it was Mylan that first asserted the arguments that led to the Federal Circuit's decision and the ultimate downfall of claims 1-3 of the '303 patent.

[2] The 180-day exclusivity incentive has proved powerful and productive. According to an FTC report issued in 2002, generic patent challenges have succeeded in 73% of cases. *See* Federal Trade Commission, "Generic Drug Entry Prior to Patent Expiration" (July 2002), at 16.

Courts and industry alike recognize that the 180-day exclusivity period is a right conferred upon the first ANDA filer, against subsequent filers.[3] *See, e.g.*, *Purepac Pharm. Co. v. TorPharm, Inc.*, 354 F.3d 877, 879 (D.C. Cir. 2004) ("In order to encourage paragraph IV challenges, thereby increasing the availability of low-cost generic drugs, the FDCA provides that the first company to win FDA approval of an ANDA containing a paragraph IV certification has the right to sell its drug *without competition* for 180 days." (citing *Mead Johnson Pharm. Group v. Bowen*, 838 F.2d 1332, 1333 (D.C. Cir. 1988) (emphasis added); *see also Mylan Pharms. Inc. v. Henney*, 94 F. Supp. 2d 36, 40 (D.D.C. 2000) ("As an incentive to the first generic maker to expose himself to the risk of costly patent litigation, the Hatch-Waxman regime provides that the first to file a Paragraph IV certified ANDA ("the first filer") is eligible for a 180-day period of marketing protection, commonly known as the 180-day exclusivity period ("the Exclusivity Incentive"). By its terms, the Exclusivity Incentive affords the first filer protection from competition from subsequent generic makers for 180 days beginning from the earlier of a commercial marketing or court decision.") (internal citations omitted)).

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[3] This is especially so against those filers who did not contribute to clearing the way for generic drug competition and commercial marketing. *Cf. Mylan Pharms., Inc. v. Shalala*, 81 F. Supp. 2d 30, 33 (D.D.C. 2000) (The 180-day exclusivity period is intended to "encourage generic drug makers to incur the potentially substantial litigation costs associated with challenging pioneer drug makers' patents."). Unlike paragraph IV certifications whose accompanying ANDAs "shall" be approved "immediately," (21 U.S.C. § 355(j)(5)(B)(iii) (2002)), ANDAs accompanied with a paragraph II certification or paragraph III certification "may" be approved (21 U.S.C. § 355(j)(5)(B)(i)-(ii) (2002)). Thus, the statute does not prohibit the FDA from giving full force and effect to Congress' repeatedly expressed intention that first-filers are entitled to 180-day of marketing exclusivity. *Cf. Mylan Labs. Inc. v. Thompson*, 332 F. Supp. 2d 106, 120 (D.D.C.), *aff'd*, 389 F.3d 1272 (D.C. Cir. 2004) ("'[D]angerous consequences would flow' if an ANDA applicant has an unqualified right to become effective at a date in the future.") (quoting *Barr Labs. Inc. v. Thompson*, 238 F. Supp. 2d 236, 249 (D.D.C. 2002))). Of course, ANDAs submitted with a paragraph IV certification "shall" be approved but "not earlier than one hundred and eighty days after" the first-filer's triggering of its exclusivity period. 21 U.S.C. § 355(j)(5)(B)(iv) (2002).

But, even more important than the incentive, is the disincentive that stripping a manufacturer who first challenges a patent of its right to 180-day exclusivity would create. Such a policy would act to discourage generic companies from risking the financial investment to challenge patents that may be on the sunset of their patent life, *e.g.*, those patents like the Norvasc '303 patent, that have only 5-6 years left of patent life, because they would not have the opportunity to obtain any return on their investment. This would be flatly against Congress' clear purpose and intent in passing the 180-day exclusivity provision:

> This 6-month incentive is crucial to maintaining the balance between encouraging brand drug companies to make new drugs and encouraging generic drug companies to make existing drugs more affordable. Challenging a brand name drug's patent takes time, money, and involves absorbing a great deal of risk. Generic drug companies rely on the added revenue provided by the 180-day exclusivity period to recoup their costs, fund new patent challenges where appropriate, and ultimately pass savings onto consumers.

152 Cong. Rec. S2797 (daily ed. July 19, 2006) (statement by Sen. Rockefeller). In discussing the sanctity of the 180-day exclusivity provision, Senator Leahy has recently stated from the Senate floor:

> Under Hatch-Waxman law, the first generic company, called the first-filer, which successfully develops a generic versions of a patented drug and meets certain other requirements, can get a 180-day exclusivity period to be the only generic company to have permission to make and sell that generic drug.
>
> That was called an exclusivity period because that is what the Congress intended—that generic company would have the exclusive right for 180 days to make the generic version of the patented medicine.

152 Cong. Rec. S7928 (daily ed. July 19, 2006) (statement by Sen. Leahy). Congress has spoken clearly on the purpose of the 180-day exclusivity, and the FDA is required to give credence to that purpose. Any policy enacted by the FDA to strip a first-filer of its exclusivity – during the enjoyment of that exclusivity period – is unsupportable. *See MCI Telecomms. Corp. v. AT&T Co.*, 512 U.S. 218, 231 n.4 (1994) (stating that agencies "are bound, not only by the ultimate

purposes Congress has selected, but by the means it has deemed appropriate, and prescribed, for the pursuit of those purposes").

C. THIS IS A CASE OF FIRST IMPRESSION IN THE PRE-MMA CONTEXT

To the best of Mylan's knowledge – the FDA has never before been faced with a scenario in which a party has begun commercial marketing and triggered its 180-day exclusivity rights, and the patent subsequently expires during the 180-day exclusivity period. There have been cases in which the FDA or the courts have held that *potential eligibility* for 180-day exclusivity will not survive patent expiration in the case of an ANDA applicant that – at the time of patent expiration – had received only *tentative* approval, was only *potentially eligible* for 180-day exclusivity rights, and – crucially – had not yet triggered those rights through commercial marketing or an appellate court decision. *See, e.g., Dr. Reddy's Labs v. Thompson,* 302 F. Supp. 2d 340 (D.N.J. 2003); *Ranbaxy Labs.*, 307 F. Supp. 2d at 20. The FDA's prior administrative rulings in situations like cisplatin (August 6, 1999) or omeprazole (November 16, 2001), also involved ANDAs that were *tentatively approved* when a patent expired, and the FDA was deciding whether a first-filer retained *eligibility* for 180-day exclusivity.

While courts have upheld FDA's interpretation that *potential eligibility* for 180-day exclusivity does not survive patent expiration, no court has ever held that 180-day exclusivity rights are extinguished by patent expiration in the case of an ANDA applicant that has received final approval and has triggered its 180-day exclusivity period through commercial marketing or a court decision. In *Dr. Reddy's Labs*, the ANDA applicant ("Dr. Reddy's") had made numerous procedural missteps that precluded it from receiving FDA final approval to market with 180-day exclusivity. Dr. Reddy's, in other words, had received no more than tentative approval, as reflected in the quotation below.

> The FDA decided ...that neither Reddy nor Andrx was entitled to exclusivity before the '431 patent expired on October 5, 2001... [T]he patent expired before Reddy's ANDA was ready for final approval because: (1) Reddy did not notify the FDA that it was ready for final approval until October 25, 2001; (2) the FDA did not complete its review of a scientific challenge to generic omeprazole until November 16, 2001; and (3) not until after the patent expired did Reddy complete the "sprinkle study" for its omeprazole product, a study made necessary by a change to the labeling of the innovator drug.

Dr. Reddy's Labs, 302 F. Supp. 2d at 346-47. Once the patent expired, the FDA concluded that Dr. Reddy's – which had not yet received a *final effective* approval, let alone begun commercial marketing – should be required to change its paragraph IV certification in light of the FDA regulation requiring an ANDA applicant to amend a submitted certification if the applicants learns that the applicant is inaccurate "at any time before the effective date of the approval of the application." 21 C.F.R. § 314.94(a)(12)(viii)(c)(1). On these facts, where Dr. Reddy's ANDA still stood "*before the effective date* of the approval," the district court held that the FDA could reasonably require Dr. Reddy's to change its paragraph IV certification.

A similar result obtained in *Ranbaxy Labs,* 307 F. Supp. 2d at 20, where the ANDA applicant not only had failed to obtain final approval (and therefore had no more than tentative approval), but also had settled its patent infringement suit with the patentee, and therefore there was no prospect that the ANDA applicant would ever prevail in its patent infringement defenses on appeal. Accordingly, the court found that that "at that 'magic moment' [of] midnight [when the patent expired ..., Ranbaxy's] Paragraph IV certifications became invalid, and either converted as a matter of law to Paragraph II certifications or became inaccurate..." Mylan's case, however, is entirely different. Mylan received final approval and began commercial marketing.

Unlike the situations above, Mylan's ANDA was fully approved and the 180-day exclusivity period had been triggered before patent expiration. Mylan received FDA final approval with an effective date of October 3, 2005; and Mylan – having begun commercial marketing – currently enjoys its fully vested 180-day exclusivity rights. While claims 1-3 of Pfizer's '303 patent have been held invalid by the Federal Circuit, Pfizer has publicly stated that it will seek a rehearing *en banc* of that decision and Mylan will continue to challenge any attempts by Pfizer to overturn that invalidity finding. And, of course, as the Agency has previously concluded, Mylan's Paragraph IV certification did *not change* when the patent expired. *See* Letter from Gary Buehler dated June 22, 2004 (attached as Exhibit C) at 3 ("An application with full effective approval has no continuing obligation to update its patent certifications.").

In the almost twenty years leading up to the amendments of the Hatch-Waxman Act by MMA, the FDA has never before faced the situation here – where the patent expires shortly after an ANDA applicant with final approval triggers its 180-day exclusivity rights by beginning commercial marketing activities – and the FDA is likely not to be so faced again. In order to avoid adopting internally inconsistent and mutually contradictory positions, the FDA must not depart from its previously announced positions and must not seek to extinguish Mylan's 180-day exclusivity as a result of the expiration of Pfizer's patent. More to the point, the FDA must not nullify Mylan's 180-day exclusivity rights in the face of clear statutory mandates that protect 180-day exclusivity after such exclusivity has vested as a result of a triggering event (*e.g.*, commercial marketing) *even after* patent expiration.

Sincerely,

David J. Harth /SMB

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*Counsel for Mylan Laboratories Inc.
and Mylan Pharmaceuticals Inc.*

Exhibit A

Comments of Mylan Pharmaceuticals Inc.
Regarding Amlodipine Abbreviated New Drug Application Approvals
Docket No. 2007N-0123

DEPARTMENT OF HEALTH & HUMAN SERVICES

ANDA 76-418

Food and Drug Administration
Rockville MD 20857

OCT 2005
RECEIVED

OCT 3 2005

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 22, 2002, submitted pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act (Act), for Amlodipine Besylate Tablets, 2.5 mg (base), 5 mg (base) and 10 mg (base).

Reference is also made to your amendments dated October 2, 2002; and January 6, April 1, August 1, and August 4, 2005.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is approved. The Division of Bioequivalence has determined your Amlodipine Besylate Tablets 2.5 mg (base), 5 mg (base), and 10 mg (base), to be bioequivalent and therefore, therapeutically equivalent to the listed drug, Norvasc Tablets 2.5 mg (base), 5 mg (base), and 10 mg (base), respectively, of Pfizer, Inc. (Pfizer). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The listed drug product (RLD) referenced in your ANDA, Pfizer's Norvasc® Tablets, is subject to periods of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 4,572,909 (the '909 patent) and 4,879,303 (the '303 patent) are scheduled to expire (with pediatric exclusivity added) on January 31, 2007, and September 25, 2007, respectively.

Your ANDA contains patent certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that both these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Amlodipine Besylate Tablets, 2.5 mg (base), 5 mg (base) and 10 mg (base), under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Mylan Pharmaceuticals Inc. (Mylan) for infringement of either of the patents that were the subject of the paragraph IV certifications. This action must have been brought against Mylan prior to the expiration of 45 days from the date the notice you provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s). You have notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement of the '909 patent or the '303 patent was brought against Mylan within the statutory 45-day period, which action would have resulted in a 30-month stay under section 505(j)(5)(B)(iii).[1]

With respect to 180-day generic drug exclusivity, we note that Mylan was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification for Amlodipine Besylate Tablets, 2.5 mg (base), 5 mg (base) and 10 mg (base). Therefore, with this approval, Mylan is eligible for 180-days of market exclusivity. This exclusivity, which is provided for under section 505(j)(5)(8)(iv) of the Act,[2] will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv). Please submit correspondence to the ANDA informing the agency of the date the exclusivity begins to run.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

---

[1] Because information on the '909 and '303 patents was submitted before August 18, 2003, this reference to section 505(j)(5)(B)(iii) of the Act is to that section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) was enacted. See MMA § 1101(c)(3). The Agency is aware that Pfizer initiated patent litigation against Mylan shortly after expiration of the statutory 45-day period.

[2] Because your ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

Post-marketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler

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

Exhibit B

Comments of Mylan Pharmaceuticals Inc.
Regarding Amlodipine Abbreviated New Drug Application Approvals
Docket No. 2007N-0123

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

March 23, 2007

GENERAL CORRESPONDENCE

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: AMLODIPINE BESYLATE TABLETS, 2.5MG, 5MG AND 10MG
ANDA 76-418
Notification of Commencement of Commercial Marketing

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and to the Agency's letter dated October 3, 2005 notifying us that our application was approved. The October 3rd approval letter requested that Mylan submit correspondence stating the date our 180 days of market exclusivity begins to run since Mylan was the first ANDA applicant to submit a substantially complete ANDA containing a paragraph IV certification. A copy of the October 3, 2005 approval letter is provided in Attachment A for your reference.

The purpose of this correspondence is to provide FDA with notification that Mylan commenced commercial marketing of Amlodipine Beyslate Tablets, 2.5mg, 5mg and 10mg on March 23, 2007. We are also requesting that FDA's 'Orange Book' be updated accordingly.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Mr. Martin Shimer, Branch Chief
Regulatory Support

G:\Project\ANDA\AMLODIPINE BESYLATE\General Correspondence-03-23-07.doc

MYLAN PHARMACEUTICALS INC.

SIGNED FORM FDA 356h

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT **MYLAN PHARMACEUTICALS INC.**	DATE OF SUBMISSION **March 23, 2007**
TELEPHONE NO. *(Include Area Code)* **(304) 599-2595**	FACSIMILE *(FAX)* Number *(Include Area Code)* **(304) 285-6407**
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: **781 Chestnut Ridge Road** **P.O. Box 4310** **Morgantown, WV 26504-4310**	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE **N/A**

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **76-418**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* **Amlodipine Besylate Tablets**	PROPRIETARY NAME *(trade name)* IF ANY **N/A**	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* **(R.S.) 3-ethyl 5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro - 6-methyl-3,5-pyridinedicarboxylate benzenesulphonate**		CODE NAME *(If any)* **N/A**
DOSAGE FORM: **Tablets**	STRENGTHS: **2.5mg, 5mg and 10mg**	ROUTE OF ADMINISTRATION: **Oral**

(PROPOSED) INDICATION(S) FOR USE:

Indicated for the treatment of hypertension, chronic stable angina and the treatment of confirmed or suspected vasospastic angina.

APPLICATION DESCRIPTION

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug **Norvasc®** Holder of Approved Application **Pfizer**

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: ____________

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Notification of Commencement of Commercial Marketing

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED **1** THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* **Notification of Commencement of Commercial Marketing**

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
S. Wayne Talton	**S. Wayne Talton** **Vice President** **Regulatory Affairs**	**March 23, 2007**

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
781 Chestnut Ridge Road, P.O. Box 4310, Morgantown, WV 26504-4310	**(304) 599-2595**

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

AMLODIPINE BESYLATE TABLETS, 2.5MG, 5MG AND 10MG

ATTACHMENT A

APPROVAL LETTER DATED OCTOBER 3, 2005

DEPARTMENT OF HEALTH & HUMAN SERVICES

ANDA 76-418

Food and Drug Administration
Rockville MD 20857

OCT 2005
RECEIVED

OCT 3 2005

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 22, 2002, submitted pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act (Act), for Amlodipine Besylate Tablets, 2.5 mg (base), 5 mg (base) and 10 mg (base).

Reference is also made to your amendments dated October 2, 2002; and January 6, April 1, August 1, and August 4, 2005.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is approved. The Division of Bioequivalence has determined your Amlodipine Besylate Tablets 2.5 mg (base), 5 mg (base), and 10 mg (base), to be bioequivalent and therefore, therapeutically equivalent to the listed drug, Norvasc Tablets 2.5 mg (base), 5 mg (base), and 10 mg (base), respectively, of Pfizer, Inc. (Pfizer). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The listed drug product (RLD) referenced in your ANDA, Pfizer's Norvasc® Tablets, is subject to periods of patent protection. As noted in the agency's publication entitled <u>Approved Drug Products with Therapeutic Equivalence Evaluations</u> (the "Orange Book"), U.S. Patent Nos. 4,572,909 (the '909 patent) and 4,879,303 (the '303 patent) are scheduled to expire (with pediatric exclusivity added) on January 31, 2007, and September 25, 2007, respectively.

Your ANDA contains patent certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that both these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Amlodipine Besylate Tablets, 2.5 mg (base), 5 mg (base) and 10 mg (base), under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Mylan Pharmaceuticals Inc. (Mylan) for infringement of either of the patents that were the subject of the paragraph IV certifications. This action must have been brought against Mylan prior to the expiration of 45 days from the date the notice you provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s). You have notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement of the '909 patent or the '303 patent was brought against Mylan within the statutory 45-day period, which action would have resulted in a 30-month stay under section 505(j)(5)(B)(iii).[1]

With respect to 180-day generic drug exclusivity, we note that Mylan was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification for Amlodipine Besylate Tablets, 2.5 mg (base), 5 mg (base) and 10 mg (base). Therefore, with this approval, Mylan is eligible for 180-days of market exclusivity. This exclusivity, which is provided for under section 505(j)(5)(8)(iv) of the Act,[2] will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv). Please submit correspondence to the ANDA informing the agency of the date the exclusivity begins to run.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

[1] Because information on the '909 and '303 patents was submitted before August 18, 2003, this reference to section 505(j)(5)(B)(iii) of the Act is to that section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA)(Public Law 108-173) was enacted. See MMA § 1101(c)(3). The Agency is aware that Pfizer initiated patent litigation against Mylan shortly after expiration of the statutory 45-day period.

[2] Because your ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA)(Public Law 108-173) on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

Post-marketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler

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

Exhibit C

Comments of Mylan Pharmaceuticals Inc.
Regarding Amlodipine Abbreviated New Drug Application Approvals
Docket No. 2007N-0123

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 22 2004

NDA 19-813
ANDA 76-258

E. Anthony Figg
Rothwell, Figg, Ernst and Manbeck
1425 K Street, N.W. - Suite 800
Washington, D.C. 20005

Peter O. Safir
Covington & Burling
1201 Pennsylvania Avenue, N.W.
Washington, D.C. 20004-2401

Dear Messrs. Figg and Safir:

This letter responds to letters sent to the Food and Drug Administration (FDA) on behalf of Mylan Technologies, Inc. (Mylan) dated March 26, 2004, April 2, 2004, and April 12, 2004, as well as those sent on behalf of ALZA Corporation (ALZA) dated March 31, 2004 and April 8, 2004. In those letters, Mylan asks FDA to confirm that Mylan is not subject to ALZA's pediatric exclusivity for fentanyl. ALZA, on the other hand, asks FDA to confirm that pediatric exclusivity applies as to Mylan's generic fentanyl transdermal system. For the reasons described below, we find that effective approval of Mylan's ANDA will be subject to ALZA's pediatric exclusivity.

Background

ALZA obtained approval for its fentanyl transdermal system (trade name: Duragesic) on August 7, 1990. As required by section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (the Act), ALZA submitted with its new drug application (NDA) a list of any patents that claimed its drug and/or its approved uses. The last of these to expire was U.S. Patent Number 4,588,580 (the '580 patent), which is due to expire July 23, 2004. FDA listed these patents in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).[1]

On July 15, 1999, FDA issued a letter requesting pediatric studies (written request) to ALZA under section 505A of the Act, 21 U.S.C. 355a(c).[2] Specifically, the written request asked ALZA to evaluate the use of its fentanyl transdermal system in opioid-tolerant pediatric patients with chronic pain. ALZA submitted the requested studies on November 26, 2002. On January

[1] Two other patents listed for Duragesic have already expired - U.S. Patent No. 4,144,317 expired September 9, 1992 and U.S. Patent No. 4,060,084 expired June 29, 1994.
[2] The written request was subsequently amended on November 30, 1999 and on February 22, 2001.

29, 2003, FDA determined that ALZA's pediatric studies were timely submitted, fairly responded to the written request, were conducted in accordance with good scientific principles, and were reported in accordance with FDA's requirement for filing. Accordingly, FDA granted pediatric exclusivity to ALZA for fentanyl at that time. On May 20, 2003, FDA approved the labeling supplement that ALZA had submitted in response to the written request. Duragesic's labeling was amended to include important information about pediatric use.

Mylan submitted its abbreviated new drug application (ANDA) for fentanyl transdermal system on October 15, 2001. Mylan's ANDA contained a paragraph IV certification to the '580 patent. Mylan sent the required notice of this certification to ALZA. ALZA received that notice on December 10, 2001. ALZA filed suit for patent infringement against Mylan in the United States District Court for the District of Vermont (Vermont District Court) on January 25, 2002, one day after the end of the statutory 45-day period for suit.[3] Because suit was filed outside of the 45-day period prescribed in section 505(j)(5)(B)(iii), there was no 30-month stay of approval on Mylan's ANDA for fentanyl transdermal system. Thus, the pending patent litigation did not present a barrier to ANDA approval. FDA approved Mylan's ANDA on November 21, 2003.

Approximately four months after FDA approved Mylan's ANDA, on March 25, 2004, the Vermont District Court found the '580 patent to be valid and infringed by Mylan's generic fentanyl transdermal system. The court enjoined Mylan from "making, using, offering to sell, selling within the United States or importing into the United States" the fentanyl transdermal system described in its ANDA and ordered that, although Mylan had previously received a final, effective approval from FDA, "the effective date of any approval of Mylan's ANDA product shall be no earlier than the date of expiration" of the '580 patent. Thus, the question arises whether Mylan's previously approved but infringing product is subject to ALZA's pediatric exclusivity.

Statutory and Regulatory Framework

Under the Act, a pharmaceutical company seeking to market a "pioneer" or innovator drug must first obtain FDA approval of an NDA by filing "full reports" that demonstrate the safety and effectiveness of the proposed drug product under the conditions of use described in the label. 21 U.S.C. § 355(a), (b). An NDA applicant must also submit information on any patent that claims the drug or a method of using the drug, and for which a claim of patent infringement could reasonably be asserted against an unauthorized party. 21 U.S.C. 355(b)(1), (c)(2). FDA publishes the patent information it receives in the Orange Book. *Id.; see also* 21 C.F.R. § 314.53(e).

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments), codified at 21 U.S.C. 355, 360cc, and 35 U.S.C. § § 156, 271, 282, permits the submission of ANDAs for approval of generic versions of approved drug products. 21 U.S.C. § 355(j). The ANDA process shortens the time and reduces the quantity of information required for approval. If an ANDA applicant establishes that its proposed drug product has the same active ingredient, strength, dosage form, route of administration, labeling, and conditions of use

[3] The 45-day period begins on the day after notice is received. 21 U.S.C. 505(j)(5)(B)(iii).

as a drug described in an NDA (the listed drug), and that it is bioequivalent[4] to that drug, the applicant can rely on FDA's previous finding that the listed drug is safe and effective to obtain approval. 21 U.S.C. 355(j).

Tentative and Final ANDA Approval

Once FDA concludes that an ANDA has met the technical requirements for approval, FDA has two options: it can issue a full effective approval or it can issue a tentative approval. The rights and obligations that stem from each of these options differ. If FDA reviews an ANDA and concludes that the drug described in the ANDA is safe and effective under the conditions of use described in the labeling, and that there are no patent or exclusivity barriers to approval, the ANDA will get a full, effective approval. An applicant who gets a full effective approval will receive an approval letter that permits marketing. 21 C.F.R. 314.105(a). The approval of the application becomes effective on the date the approval letter is issued. *Id.* An application with full effective approval has no continuing obligation to update its patent certifications. See 21 C.F.R. 314.94(a)(12)(viii)(C) (obligation to amend certification applies before effective date of approval).

However, if FDA reviews an ANDA and concludes that the drug described in the ANDA is safe and effective for the conditions of use described in the labeling but patent protection or other marketing exclusivities prevent the approval from becoming effective immediately, FDA will issue a tentative approval. A tentative approval indicates that the technical requirements for approval have been met as of a particular date but that approval cannot be made effective (and marketing is not permitted) until after some future event (such as expiration of a 30-month stay, a patent, or a period of marketing exclusivity). *See* 21 C.F.R. 314.105(d). Under FDA's regulations and longstanding practice, an approval with a delayed effective date is a tentative approval and does not become final before the effective date. A new drug that has received an approval with a delayed effective date or tentative approval "may not be introduced or delivered for introduction into interstate commerce until approval of the [ANDA] is effective." 21 C.F.R. 314.105(a), (d). Moreover, a tentative approval cannot become effective without a final approval letter from the agency resulting in a final effective approval. 21 C.F.R. 314.107(b)(3)(v); *see also*, 59 Fed. Reg. 50338, 50352 (October 3, 1994) (a tentative approval becomes "final and, therefore, effective only when the agency sends an approval letter to the applicant"); *Barr Labs., Inc. v. Thompson,* 238 F. Supp. 2d 236, 245-50 (D.D.C. 2002) (affirming FDA's decision that an approval with a delayed effective date is tentative and does not give applicants the right to enter the market on a date certain without further action from FDA).

In contrast to the holder of a fully approved ANDA, the holder of a tentatively approved ANDA must amend its application to reflect any material changes in circumstances, such as expiration of the patent or withdrawal of a patent challenge. See 21 C.F.R. 314.94(a)(12)(viii)(C)(1). That regulation provides that "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." *Id. See also* 21 U.S.C. § 355(j)(4)(K) (barring approval of an application containing an untrue statement of material fact).

[4] Two drugs are considered bioequivalent if, in general, the rate and extent of absorption of the proposed drug is not significantly different from the rate and extent of absorption of the listed drug. 21 U.S.C. § 355(j)(8)(B).

Once all patent and exclusivity barriers to approval have been removed, a tentatively approved ANDA may be eligible for final approval. Before issuing a final approval letter to a tentatively approved application, FDA "will examine the application to determine whether there have been any changes in the conditions under which the application was tentatively approved." 59 Fed. Reg. 50338 at 50352. Even when an applicant has a tentative approval, final approval is neither inexorable nor automatic; the applicant with the tentative approval enjoys no vested right to market on a particular date. *See Barr Labs., Inc.*, 238 F. Supp. 2d at 245-50 (affirming FDA's decision that tentatively approved ANDAs do not have vested right to immediate approval upon patent expiry); *Ranbaxy Labs. Ltd. v. FDA*, 307 F. Supp. 2d. 15, 19, 21 (D.D.C. 2004) (upholding FDA's position that an applicant with a tentative approval has "no vested right to enter the market until the FDA gives its final formal approval.") *aff'd per curiam*, Civ. Action 04-5079 2004 U.S. App. LEXIS 8311 (D.C. Cir. Apr. 26, 2004). Instead, FDA must have time and the opportunity to reexamine an application to determine that the approval requirements continue to be met. Only after that examination has been completed will FDA issue a final approval letter. *Id.*

Patent Certifications and Timing of Approval

As noted above, the timing of an ANDA's approval depends in part on patent protections for the listed drug the ANDA references. A pending ANDA must contain one of four specified certifications for each patent that "claims the listed drug" or "a use for such drug for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(vii). The certification must state one of the following:

(I) that the required patent information relating to the patent has not been filed;
(II) that such patent has expired;
(III) that such patent will expire on a particular date; or
(IV) that such patent is invalid or will not be infringed by the drug for which approval is sought.

See id. If a certification is made under paragraphs I or II (indicating that patent information has not been filed or that the patent has expired), the patent, in itself, will not delay the approval of an ANDA.[5] 21 U.S.C. § 355(j)(5)(B)(i). A certification under paragraph III indicates that the ANDA applicant does not intend to market the drug until after the applicable patent has expired, and FDA will not issue a final effective approval for the ANDA until after patent expiration. 21 U.S.C. § 355(j)(5)(B)(ii).

If an ANDA applicant wishes to challenge the validity of a listed patent, or to claim that the patent will not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification. The applicant must provide notice of its paragraph IV certification to the NDA holder and the patent owner. The applicant must also describe the factual and legal basis for its opinion that the patent is invalid or is 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

[5] Of course approval may still be delayed due to other patents or marketing exclusivity or because the application is otherwise not ready for approval.

claimed in a patent" is an act of infringement. 35 U.S.C. 271(e)(2)(A). This provision enables the NDA holder to sue the ANDA applicant before the ANDA has been approved.

If the patent owner or NDA holder does not bring suit within 45 days after it has received notice of the paragraph IV certification, FDA may approve the ANDA despite the unexpired patent. FDA may do so as long as there are no other patent or exclusivity barriers to approval and the other conditions of approval are met. 21 U.S.C. 355(j)(5)(B)(iii); 21 C.F.R. 314.107(f)(2). FDA may also do so even if patent litigation was commenced outside the 45-day period and is ongoing as of the time the requirements for approval have been met.

If the patent owner or NDA holder brings a patent infringement suit against the ANDA applicant *within* 45 days, there will be an automatic stay of FDA approval for 30 months from the date that the patent owner or NDA holder received notice of the paragraph IV certification (30-month stay). (That is, unless a court decision has been reached earlier in the patent case or the patent court otherwise orders a longer or shorter stay period). 21 U.S.C. 355(j)(5)(B)(iii). If at the end of 30 months (or such shorter or longer period that the court orders) the litigation is ongoing, the 30-month stay will be lifted. If the ANDA is otherwise ready for approval, FDA will approve the ANDA in spite of the ongoing litigation and unexpired patent. Similarly, if the ANDA applicant were to win in the district court and the district court decision were appealed, the 30-month stay would be lifted after the district court decision. In these circumstances, if the ANDA is otherwise ready for approval, FDA can approve the ANDA in spite of the pending appeal -- unless the court otherwise imposes a stay of approval while the appeal is pending.

Delaying the Effective Date under 271(e)(4)

The Hatch-Waxman amendments also amended the patent code to specify the consequences that follow when the NDA holder or patent owner sues the ANDA applicant, and the court hearing the patent infringement litigation finds the patent valid and infringed. In these circumstances, 35 U.S.C. 271(e)(4)(A) 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). As the unqualified plain meaning of the statute reflects, this mandated delay of the effective date of approval takes place regardless of whether the ANDA remains pending or has obtained a final effective approval.[6]

The legislative history explicitly recognized that this requirement would affect previously approved as well as unapproved applications:

> If the infringing party has not begun commercial marketing of the drug, injunctive relief may be granted to prevent any

[6] As noted above, if an applicant meets the requirements for final approval, final effective approval may be issued while patent litigation is ongoing under 3 different circumstances: (1) the ANDA applicant was sued outside of the 45 days so no 30-month stay of approval was imposed; (2) the applicant was sued within the 45 days but the 30-month stay expired while the litigation was ongoing; or (3) the ANDA applicant was sued within the 45 days, won at the lower court level, and the decision lifted the 30-month stay and permitted approval, but that decision was appealed.

> commercial activity with the drug and FDA would be mandated to make the effective date 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 effective date.**

H.R. Rep. No. 98-857, pt. 1, at 46 (1984) (emphasis added).

The language of the provision regarding a delay in the effective date under 271(e)(4)(A) parallels the language of the provisions regarding 30-month stays, 5-year exclusivity, 3-year exclusivity and 180-day exclusivity that were enacted at the same time as part of the Hatch-Waxman amendments. Section 271(e)(4)(A), like the provisions regarding 30-month stays, 5-year exclusivity, 3-year exclusivity, and 180-day exclusivity, speaks not in terms of delays in FDA approvals but in terms of delays in the dates such approvals can be made effective. See 21 U.S.C. 505(j)(5)(B)(iii) ("approval shall be made effective upon the expiration of the thirty month period"); 21 U.S.C. 505(j)(5)(B)(iv) ("application shall be made effective not earlier than one hundred eighty days after . . ."); 21 U.S.C. 505(j)(5)(D)(ii) ("approval of such an application shall be made effective in accordance with subsection (b)"); 21 U.S.C. 505(j)(5)(D)(iii) ("Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years . . . .").

If an ANDA has met the technical requirements for approval and a delay in effective dates is required due to a 30-month stay, 5-year exclusivity, 3-year exclusivity or 180-day exclusivity, FDA issues a tentative approval. 21 C.F.R. 314.105, 314.107. ANDA applicants with tentative approvals that are subject to delays due to 30-month stays, 5-year, 3-year or 180-day exclusivity are not entitled to go to market immediately when the barrier to approval expires; after the applicable stay or exclusivity expires, applicants must still wait until FDA issues an approval letter. FDA will not issue a letter to make the approval of the tentatively approved application effective until after FDA has reexamined the application to determine whether the requirements for approval continue to be met.

Similarly, where patent litigation between an ANDA applicant and NDA holder or patent owner results in a court order under 271(e)(4)(A) stating that the effective date of ANDA approval shall be no earlier than the date the patent expires, FDA will not issue a final effective approval until after the date in the order has passed. If, in the interim between the court's order and the date the approval can be made effective, FDA determines that the applicant meets the technical requirements for approval, a tentative approval will be issued. FDA will not issue a letter to make the approval of the tentatively approved application effective until after the period stated in the court order has run and FDA has reexamined the application to determine whether the requirements for approval continue to be met.

The same result obtains where an ANDA has already received a full effective approval and a court finding patent validity and infringement issues an order under 271(e)(4)(A) stating that the approval of the ANDA not be made effective until after the date the patent expires -- that is, the ANDA reverts to tentative approval status. As the legislative history of the Hatch-Waxman amendments confirms, Congress contemplated that, in these circumstances, the approval would no longer remain effective and the date of effective approval should be delayed to a date in the future. See H.R. Rep. No. 98-857, pt. 1, at 46 (1984) ("In the case where an ANDA had been approved, the order would mandate a change in effective date"). Like other applications with approvals with delayed effective dates, such an approval is tentative and does not give the applicant a vested right to go to market on a date certain. Applicants with tentative approvals cannot go to market until they have received an approval letter. As noted above, FDA will not issue an approval letter until after the barrier to approval has expired (i.e., the period stated in the court order has run) and FDA has reexamined the application to determine whether the requirements for approval continue to be met.

Pediatric Exclusivity

In 1997, as part of the Food and Drug Administration Modernization Act ("FDAMA"), Congress amended the Act to provide an economic incentive for drug manufacturers to invest the resources necessary to conduct and submit studies of the safety and effectiveness of drugs in pediatric populations. Recognizing that pediatric populations are "therapeutic orphans," and that pediatric studies "pose ethical and moral issues," carry the risk of product liability, and are hard to attract patients for and conduct, Congress created the pediatric exclusivity incentive to ensure that more drugs were studied and adequately labeled for the pediatric patients who use them. S. Rep. No. 105-43 at 51 (1997). Under these provisions, codified at 21 U.S.C. 355a[7], FDA can issue a written request to ask a sponsor to conduct and submit studies on the use of a drug in the pediatric population. If FDA issues a written request for pediatric studies, and the company submits pediatric studies that "fairly respond" to the written request in accordance with FDA's requirements for filing, and conducts the studies in accordance with good scientific principles and protocols, the company is entitled to six months of additional exclusivity (pediatric exclusivity) that attaches to existing patent and exclusivity protection for the moiety. This exclusivity results in an additional six-month delay of approval for ANDAs that are blocked from approval by existing patent or exclusivity rights. By giving NDA sponsors an additional six-month period without generic competition, Congress elevated the goal of obtaining pediatric labeling information over the goal of approving generic copies of brand name drugs at the earliest possible time.[8]

In fact, even if an ANDA is on the verge of being given an effective approval, the submission of pediatric studies in response to a written request allows FDA to delay the effective date while FDA determines whether the studies qualify for a pediatric exclusivity award. 21 U.S.C. § 355a(e) ("if the approval of an [ANDA] . . . may occur after submission of reports of pediatric studies . . . but before the Secretary has determined whether the requirements of subsection (d)

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[7] Congress reauthorized and amended the pediatric exclusivity provisions in the Best Pharmaceuticals for Children Act, Pub. L. No. 107-109 (2001) and made additional amendments in the Pediatric Research Equity Act of 2003, Pub. L. No. 108-155 (2003).

[8] *See, e.g.* 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 generics 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.").

have been satisfied, the Secretary shall delay the . . . approval . . . until the determination under subsection (d) is made, but any such delay shall not exceed 90 days").

The prospect of an additional six months of delay in ANDA approvals has been a valuable incentive for NDA holders. Whereas previous attempts to obtain pediatric information from sponsors had largely failed, the pediatric exclusivity provision has proven highly effective. *See* The Pediatric Exclusivity Provision, January 2001 Status Report to Congress, at 3-5, 12 ("In general, the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date")(available at http://www.fda.gov/cder/pediatric/reportcong01.pdf). Since the pediatric exclusivity provisions took effect in November 1997, FDA has issued 288 requests for pediatric studies, has made 108 pediatric exclusivity determinations, and has granted pediatric exclusivity for 98 drugs for indications ranging from hypertension to HIV. *See* http://www.fda.gov/cder/pediatric/exgrant.htm.

The statute governing which ANDAs are blocked by pediatric exclusivity provides in relevant part:

> (c) MARKET EXCLUSIVITY FOR ALREADY MARKETED DRUGS. If the Secretary determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population and makes a request to the holder of the approved [NDA] for pediatric studies (which shall include a timeframe for completing such studies), the holder agrees to the request, the studies are completed within any such timeframe, and the reports are submitted in accordance with subsection (d)(2) of this section or accepted in accordance with subsection (d)(3) of this section -
>
> * * *
>
> (2)(A) if the drug is the subject of–
>
> (i) a listed patent for which a [paragraph II] certification has been submitted . . . and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or
>
> (ii) a listed patent for which a [paragraph III] certification has been submitted . . . ,
>
> 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 (including any patent extensions); or

> (B) if the drug is the subject of a listed patent for which a [paragraph IV] certification has been submitted under subsection . . . (j)(2)(A)(vii)(IV) of section 505, 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 ANDA may not be approved under . . . section 505(j)(5)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

21 U.S.C. 355a(c).

Here, there is no dispute that ALZA conducted pediatric studies fairly responding to a written request issued by FDA. ALZA conducted the studies in accordance with good scientific principles and protocols, and submitted them in a supplement appropriate for filing. At issue in this dispute are which statutory provisions govern whether ALZA's pediatric exclusivity delays the approval of Mylan's ANDA beyond the date the '580 patent expires, as well as how those provisions apply to the facts presented.

Mylan's Argument

Mylan contends that it is not subject to ALZA's pediatric exclusivity. Mylan argues that because its application was submitted with a paragraph IV certification, section 355a(c)(2)(B) (relating to paragraph IV certifications) determines whether pediatric exclusivity will attach.[9] Under 355a(c)(2)(B), if the NDA holder satisfies the prerequisites for pediatric exclusivity by completing the requested studies in the requested timeframe, and in the lawsuit resulting from the paragraph IV certification the patent is found valid and infringed, "the period during which an ANDA may not be approved under . . . section [505(j)(5)(B)] shall be extended by six months after the date the patent expires." Mylan notes that the statute's provisions regarding paragraph IV certifications at 355a(c)(2)(B) provide for an extension of the "period in which an application may not be approved under 505(j)(5)(B)." Mylan argues that the only period during which an application may not be approved under 505(j)(5)(B) is the 30-month stay provided for in that section. Because Mylan was sued outside of the 45-day period, it contends that no 30-month stay attached, there is no "period" to extend, and the terms of 355a(c)(2)(B) do not require a delay of Mylan's approval.

Moreover, although the court reset the effective date of Mylan's ANDA under 271(e)(4)(A) to a date that is not earlier than the date the '580 patent expires, in Mylan's view, the court order did not create a "period during which [Mylan's ANDA] may not be approved." Mylan maintains that its application remains approved and such approval can only be withdrawn in accordance with the withdrawal provisions of section 505(e) of the Act, 21 U.S.C. 355(e), which require, among other things, notice and opportunity for hearing before withdrawal can occur. Similarly, in Mylan's view, the court's order does not and cannot convert (or require FDA to convert) its final approval to a tentative approval.

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[9] Mylan argues that because it has appealed the district court order of validity and infringement, in the interim, its paragraph IV certification (indicating it is challenging the validity or infringement of the patent) remains valid.

On the contrary, Mylan argues that although a tentatively approved application is subject to further FDA review before an approval letter will issue and the approval becomes effective, Mylan's application has a different status that does not necessitate such review. In Mylan's view, the court's order does not require FDA to act on Mylan's application before Mylan can begin marketing under it. The court order merely creates a new date certain when the approval will be made effective by operation of law (i.e., the date the patent expires). Under this theory, when the patent expires on July 23, 2004, Mylan's ANDA will once again have a final effective approval without any further action by Mylan or FDA.

Under Mylan's theory, even if new patents have been listed, or ALZA supplements its NDA with a material change in formulation or labeling, or Mylan's application otherwise falls out of compliance with applicable statutes and regulations before July 23, 2004, the approval of Mylan's ANDA would nevertheless "become effective" -- and it may begin marketing -- the moment the patent expires. Moreover, because its application will regain a final effective approval at the moment the patent expires, and because applications with final effective approval have no further obligation to update their patent certifications post approval, Mylan argues that it will not be required to amend its application to change to a paragraph II certification when the patent expires. Mylan thus argues that 355a(c)(2)(A)(i) (which prohibits FDA's approval of ANDAs with paragraph II certifications for six months after the patent expires) will never apply to delay approval of Mylan's ANDA.

ALZA's Argument

ALZA, on the other hand, argues that its pediatric exclusivity delays final effective approval of Mylan's fentanyl transdermal system ANDA until no earlier than 6 months after the date the '580 patent expires. ALZA argues that where an application has been approved and a court subsequently holds the patent valid and infringed, FDA properly responds to a court order delaying the effective date of approval by converting the full approval to a tentative approval. ALZA notes that, under FDA's regulations, where FDA issues an approval with a delayed effective date, that approval is tentative and does not become final until (1) patent and exclusivity barriers to approval expire, (2) FDA determines that the approval requirements continue to be met, and (3) FDA issues an approval letter. ALZA contends that, under *Barr Labs. Inc. v. Thompson,* when FDA issues an approval with a delayed effective date, the ANDA applicant has no vested right to obtain a final effective approval on a particular date. ALZA argues that the same result necessarily applies when the delay in effective date has been ordered by the court under 271(e)(4)(A). Although in this case the patent is due to expire shortly after the court order resetting the ANDA effective date, ALZA notes that, under Mylan's theory, the same result would apply even if the patent were due to expire 10 or more years in the future.

Moreover, ALZA argues that, once Mylan's effective approval has been converted to a tentative approval, the statutory language, regulations, and policy underlying pediatric exclusivity, require that Mylan be subject to ALZA's pediatric exclusivity. ALZA argues that, under FDA's regulations at 21 C.F.R. 314.94(a)(12)(i)(C), Mylan should have converted its certification to a paragraph III certification after it lost its patent suit. However, ALZA notes that, regardless of whether Mylan's ANDA should now contain a paragraph III or a paragraph IV certification, upon patent expiration, Mylan's ANDA must contain a paragraph II certification to be accurate.

ALZA notes that, under the rule of *Ranbaxy*, the only relevant certification for determining pediatric exclusivity is the one in place at the time of final approval. *Ranbaxy Labs. Ltd.*, 307 F. Supp. 2d at 19, 21. Accordingly, because Mylan cannot receive final effective approval until after the patent has expired and patent expiration will require Mylan to submit a paragraph II certification, ALZA argues that 355a(c)(2)(A)(i) (relating to paragraph II certifications), not 355(c)(2)(B) (relating to paragraph IV certifications) determines whether pediatric exclusivity will attach. Under 355(a)(c)(2)(A)(i), pediatric studies were submitted before expiration of the patent so the period during which Mylan's ANDA cannot be approved is "extended six months after the date the patent expires."

FDA's Determination

FDA finds that ALZA's pediatric exclusivity for fentanyl will attach, and thus delay effective approval of Mylan's ANDA. Unless Mylan were to win its patent case on appeal, Mylan's ANDA would be eligible for final effective approval no earlier than six months after the '580 patent expires on July 23, 2004.

The Vermont District Court found that Mylan infringed ALZA's valid patent. As noted above, pursuant to 35 U.S.C. 271(e)(4)(A), the district court hearing the patent infringement case enjoined Mylan from "making, using, offering to sell [and] selling within the United States or importing into the United States" its fentanyl transdermal system and ordered that the effective date of Mylan's ANDA "shall be no earlier than the date of expiration of U.S. Patent No. 4,588,480."

Under the FDA's regulations, as upheld in *Barr Labs. Inc. v. Thompson* , an approval with a delayed effective date is a tentative approval that cannot be made effective until FDA issues a letter granting final effective approval. 21 C.F.R. 314.107(b)(3)(v); see also *Barr Labs*, 238 F.Supp at 245-50. This is the case regardless of whether approval has been blocked by a 30-month stay, 5-year exclusivity, 3-year exclusivity, 180-day exclusivity or, as in this case, because the court has issued an order prohibiting approval from being made effective until after the patent expires. In each of these cases, the Hatch-Waxman amendments bar FDA's issuance of a final effective approval. See 21 U.S.C. 505(j)(5)(B)(iii); 21 U.S.C. 505(j)(5)(B)(iv); 21 U.S.C. 505(j)(5)(D)(ii); 21 U.S.C. 505(j)(5)(D)(iii); 35 U.S.C. 271(e)(4)(A).

Just as applicants barred from final approval due to 5-year or other Hatch-Waxman exclusivity need FDA to act to issue an approval letter before they are permitted to have a final effective approval, so too, does the Vermont District Court's order require FDA to act before Mylan's effective approval can be restored. Under the court's order, approval of Mylan's ANDA cannot be made effective until after the '580 patent has expired. An approval with a delayed effective date (including a previously effective approval that has had its effective date delayed by court order) is tentative.[10] It does not give Mylan an unqualified right to obtain final effective approval without further action by Mylan or FDA on the date the patent expires. Although tentatively approved status embodies FDA's determination that the requirements for approval have been met as of a particular date, FDA must review a tentatively approved application to determine whether the standards for approval continue to be met before it will issue a final approval letter. Among other requirements, Mylan's ANDA, like all applications with tentative approvals, must maintain accurate patent certifications. 21 C.F.R. 314.94(a)(12)(viii)(C)(i).

Once the patent expires, Mylan's paragraph IV certification (indicating that the patent is invalid or not infringed) will no longer remain accurate. See *Ranbaxy*, 307 F. Supp. 2d at 19, 21. A change in certification (in this case to a paragraph II certification indicating that the patent has expired) is required when an applicant whose application does not have final, effective approval learns that its existing certification is no longer proper. See 21 C.F.R. 314.94(a)(12)(viii)(C)(i) ("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."); see also 21 U.S.C. 355(j)(4)(K) (an ANDA that contains an untrue statement of material fact cannot be approved). If Mylan refuses to amend its application to change its certification after the patent expires, FDA can treat that certification as automatically amended to contain a paragraph II certification (because there is no other proper certification upon patent expiry). See *Ranbaxy*, 307 F. Supp. 2d at 19, 21. Alternatively, FDA can refuse to issue a final approval letter on the ground that the application contains an untrue statement of material fact. In either case, Mylan cannot obtain final approval until its application actually contains or is deemed to contain a paragraph II certification. See *id.*

Once Mylan's certification has changed - *de facto* or *de jure* - to a paragraph II certification, pediatric exclusivity attaches under 355a(c)(2)(A)(i). See *Ranbaxy*, 307 F. Supp. 2d at 20, 21. Under 355a(c)(2)(A)(i), if an application contains a paragraph II certification and the pediatric studies qualifying for exclusivity were submitted before the patent expires, "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." This provision gives ALZA pediatric exclusivity as to Mylan and further delays the effective date of Mylan's approval for 6 months after the patent expires. If, at the end of this additional 6 months, FDA were to determine that Mylan's ANDA continues to meet the approval requirements and there are no remaining patent or exclusivity barrier to approval, FDA will issue a new letter granting Mylan a final effective approval.

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[10] Although, in essence, the court's order withdraws Mylan's full effective approval, contrary to Mylan's arguments FDA was not required to comply with the withdrawal provisions of 505(e). Under 505(e), FDA can withdraw approval of an approved application after notice and opportunity for hearing under certain narrowly defined circumstances. However, 505(e) does not state the only circumstances in which withdrawal of effective approval is possible. Instead, 35 U.S.C. 271(e)(4)(A) speaks more specifically to the circumstances at issue. This provision mandates a withdrawal of effective approval where, as here, an ANDA applicant has received a final effective approval and subsequently loses its patent lawsuit with a finding that the patent is valid and infringed. Once that effective approval is withdrawn, the status of Mylan's ANDA is the same as that of other ANDAs blocked from final approval by patent or exclusivity rights - tentatively approved.

This approach properly rewards ALZA for conducting and submitting its pediatric studies and preserves the necessary incentive to conduct such studies.[11] It is consistent with *Barr* and *Ranbaxy* as well as with the structure and purpose of 21 U.S.C. 355a. For all of these reasons, FDA concludes that effective approval of Mylan's ANDA for fentanyl transdermal systems will be subject to ALZA's pediatric exclusivity.

Sincerely,

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

[11] Although Mylan argues that its approach (which prevents ANDAs from being subject to pediatric exclusivity if they obtain approval and the effective date of approval is reset by a court) properly punishes NDA holders for failing to sue within the statutory 45-day period, the logic of Mylan's argument applies to any application that has a final effective approval that is reset after a finding of validity and infringement; it is not limited to applications that received approval because the NDA holder or patent owner missed the deadline for suit. Specifically, Mylan's argument would also apply where the NDA holder sued the ANDA applicant within the 45-day period and the ANDA was approved after 30 months while the litigation was ongoing. In that case, if the court subsequently found the patent valid and infringed and reset the effective date of approval, under Mylan's theory this approval would become effective on the date of patent expiry regardless of whether the NDA holder had earned pediatric exclusivity because there is no remaining "period" under 505(j)(5)(B) to extend. Similarly, if the ANDA applicant won its patent litigation at the district court level, obtained final, effective approval after that victory, and subsequently lost on appeal with an order resetting the ANDA approval effective date, approval of that application would also become effective on the date of patent expiration, regardless of whether the NDA holder had earned pediatric exclusivity. This outcome makes little sense, and would substantially diminish the incentives for innovator firms to undertake the studies requested by FDA to earn a pediatric exclusivity which was so tenuous and easily evaded.