DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 18 2007

Jeffrey B. Chasnow
Kelly A. Falconer
Pfizer Inc.
235 E. 42nd Street
New York, NY 10017

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Re: Docket Nos. 2007P-0110/CP1 and 2007P-0111/PSA1

Dear Mr. Chasnow and Ms. Falconer:

This letter responds to your citizen petition (the Petition) and petition for stay of action (PSA) received on March 22, 2007. In the Petition, you request that the Food and Drug Administration (FDA or Agency) (1) deem Novartis Pharmaceutical Corporation's (Novartis) Lotrel new drug application (NDA) a section 505(b)(2) application subject to Pfizer's pediatric exclusivity, (2) rescind final approval of the Lotrel NDA and reclassify the approval as tentative, and (3) withhold final approval of any supplemental NDA (sNDA) for Lotrel because such supplement would be subject to Pfizer's pediatric exclusivity for amlodipine. The PSA requests that FDA stay the approval of any supplements to the Lotrel NDA concerning the active ingredient amlodipine until after September 25, 2007, when Pfizer's pediatric exclusivity will expire. We have carefully considered the Petition and PSA, as well as the comments filed in the docket. For the reasons stated in this response, the Petition and PSA are denied.

I. BACKGROUND

The drug at the center of this dispute is Lotrel, a fixed combination drug product containing the active ingredients amlodipine besylate and benazapril hydrochloride. The Agency approved NDA 20-364 for Lotrel 12 years ago, in March 1995. The Lotrel NDA was submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) (21 U.S.C. 355(b)(1)), as a "stand alone" NDA, in that the sponsor either had conducted all of the studies essential to approval of the application or had obtained a right of reference to the studies. Ciba Geigy Corporation, the sponsor of the Lotrel NDA at that time, had obtained from Pfizer a right of reference to Pfizer's approved NDA 19-787 for Norvasc, an approved product containing amlodipine besylate, one of the two active ingredients in Lotrel. In section 505(b)(2) of the Act (21 U.S.C. 355(b)(2)), a "right of reference" is recognized as a means for one applicant to rely on another sponsor's safety and/or effectiveness data to obtain approval of an NDA (see also 21 CFR 314.3(b) (a "*[r]ight of reference or use* means the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application"). The right of reference provided by Pfizer permitted FDA to refer to the safety and effectiveness data in the Norvasc NDA during the Agency's review of the Lotrel NDA and to rely on that information to approve Lotrel.

The Petition states that on March 21, 2007, Pfizer notified FDA that because Pfizer and Novartis were in a dispute over the terms of the agreement under which the right of reference was provided, Pfizer was revoking its right of reference, "as of midnight March 25, 2007" (Petition at 3 and Attachment A). Pfizer also asserts that, absent other data from another source to support

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the approval, "as of midnight March 25, 2007," Novartis could not continue to market Lotrel (Petition at 3). As described above, Pfizer's Petition, also dated March 21, 2007, specifically requests that the Agency rescind the Lotrel approval, reclassify the Lotrel NDA as tentatively approved, "[d]eem the Lotrel NDA a section 505(b)(2) application subject to Pfizer's pediatric exclusivity for amlodipine," and withhold approval of the Lotrel 505(b)(2) application until the pediatric exclusivity for Norvasc expires on September 25, 2007 (Petition at 1-2).[1] The PSA asks that we not approve any sNDAs for Lotrel until after September 25, 2007.

Novartis has filed an opposition to the Pfizer petitions, asserting that the approval of the Lotrel NDA and any related sNDAs remain valid and that the Agency has no basis for becoming embroiled in what is a purely private commercial dispute.

II. ANALYSIS

A. Citizen Petition

The threshold issue in this matter is whether the termination of a right of reference to data that was necessary for approval of an NDA requires that the Agency withdraw approval of the NDA. The plain language of the FDCA does not address this question. Provisions of the FDCA contemplate that a sponsor may obtain a right of reference to data from another party and rely on data so referenced for approval (see section 505(b)(2) (describing a type of application relying on data to which the sponsor has not obtained a right of reference and related patent certification requirements) and 505(c)(3)(E)(ii), (iii) and (iv) of the Act (describing exclusivity periods that will delay submission or approval of applications of the type described in section 505(b)(2)). The FDCA does not further address rights of reference.

You have asserted no basis on which the Agency may withdraw approval of the Lotrel NDA. The FDCA describes certain grounds for withdrawing approval of an NDA at section 505(e). None of the enumerated grounds in this provision is applicable here; indeed, you do not assert that the Agency has any grounds under section 505(e) to withdraw approval of Lotrel. Instead, the Petition asserts that the Agency "need not invoke the procedures of section 505(e)" but may convert the status of the Lotrel NDA from approved to tentatively approved for the same reasons the Agency changed the status of an abbreviated new drug application (ANDA) for a fentanyl transdermal patch from approved to tentatively approved in the matter that was the subject of litigation in *Mylan Labs. v. Thompson,* 389 F.3d 1272 (D.C. Cir. 2004). This argument is not persuasive.

[1] Both Pfizer and Novartis include in submissions to the dockets information regarding the nature of the dispute between the parties over the terms of the Licensing Agreement under which the right of reference was granted. Although the merits of this dispute fall well outside FDA's purview, we note that one focus of the disagreement is the effect of Pfizer's pediatric exclusivity for Norvasc on Novartis' obligations under the Licensing Agreement. The scope and effect of Pfizer's pediatric exclusivity for amlodipine on other applications referencing Norvasc has already been the subject of considerable regulatory activity and litigation, particularly in light of a Federal Circuit opinion finding certain claims of the only remaining patent listed for Norvasc invalid (see *Mylan Labs. v. Leavitt,* No. 07-579 (D.D.C. April 30, 2007); FDA Docket 2007N-0123).

The Agency's conversion of the status of the Mylan fentanyl ANDA from approved to tentatively approved does not serve as a precedent for withdrawing approval of the Lotrel NDA.[2] As noted in its June 22, 2004, letter to E. Anthony Figg and Peter O. Safir at p. 12, n. 10 (attached), the Agency converted the Mylan approval to tentative pursuant to a court's order under 35 U.S.C. 271(e)(4)(A), which mandates the withdrawal of effective approval where there is a finding that the patent is valid and infringed. Thus, the Agency acted on the basis of an express statutory provision that authorizes withdrawal of final approval of an application in precisely the circumstances presented by the Mylan ANDA (see *Mylan Labs,* 389 F.3d at 1281-82 (FDA was bound under the district court's order pursuant to 35 U.S.C. 271(e)(4)(A) to treat the Mylan ANDA as it would other ANDAs blocked from final approval by patent rights or exclusivity)). In contrast, you have identified no statutory or other regulatory basis that necessitates withdrawal of approval of the Lotrel NDA on the grounds that Pfizer has revoked its right of reference. In the absence of such authority, the Agency will not withdraw the Lotrel approval. We also find that you have not provided a basis for the Agency to convert the Lotrel NDA from an approved 505(b)(1) application to a tentatively approved 505(b)(2) application. Because we are not withdrawing the final approval of the Lotrel NDA, as either a 505(b)(1) application or a 505(b)(2) application, we do not need to address the issue of whether the Lotrel NDA is subject to Pfizer's pediatric exclusivity for amlodipine.[3]

Although the Agency will not withdraw the approval of the Lotrel NDA, Pfizer's revocation of the right of reference to the Norvasc NDA may have implications for the review of supplements to the Lotrel NDA. As of March 25, 2007, the date identified in Pfizer's March 21, 2007, letter as the date upon which the right of reference to Norvasc was to be revoked, FDA may not rely on data and information contained in the Norvasc NDA to approve supplements to the Lotrel application. Therefore, the approval of any section 505(b)(1) supplement to the Lotrel NDA must be based on data owned by Novartis, or to which Novartis has a right of reference. A section 505(b)(2) supplement would require appropriate patent and exclusivity certifications, and approval of such supplement could be delayed by patent or exclusivity protections.

B. Petition for Stay of Action

You request that FDA stay approval of any supplements to Novartis' NDA for Lotrel (NDA 20-362) concerning the amlodipine ingredient until after Pfizer's pediatric exclusivity for amlodipine has expired on September 25, 2007, because Pfizer was revoking Novartis' right of reference effective midnight March 25, 2007 (PSA at 1-2). You also assert that Pfizer faces irreparable injury in the absence of a stay because unless the stay is granted, Novartis will be

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[2] The Petition also cites *A.L. Labs., Inc. v. Phillips Roxane, Inc.*, 803 F.2d 383 (8th Cir. 1986), a case involving animal drugs, for the proposition that it is FDA's view that if a right of reference is invalidated, it would void a drug approval based on data obtained through the right of reference. The Agency was not a party to the cited case, and we have not identified any evidence that this has ever been the Agency's position or that the Agency has ever withdrawn an approval on this basis.

[3] We note that pediatric exclusivity, as with other exclusivity periods applicable to drug products approved under section 505, provides only for a delay in the approval of certain applications; it has no effect on the approval status of approved drug products and is not a basis for withdrawing approval. For example, section 505A(c)(2)(A) provides that if pediatric exclusivity is applicable, "the period during which an application *may not be approved* .... shall be extended by a period of six months" (emphasis added).

able to continue selling Lotrel during the period of pediatric exclusivity, and you will lose your pediatric exclusivity rights as against Novartis and the associated monetary reward (PSA at 2). You further assert that your case is not frivolous and is being pursued in good faith and that you have raised legal and policy reasons in support of your request for stay (PSA at 2-3). You also claim that you have demonstrated sound public policy grounds supporting the stay and that the delay resulting from the stay is not outweighed by public health or other public interests (PSA at 3). You request that if FDA determines that a mandatory stay is not warranted, that it grant a stay under its discretionary authority (PSA at 3). We have carefully considered all of the arguments raised and information provided in the Petition and PSA. Based on our analysis, the PSA is denied.

FDA's regulation at 21 CFR 10.35(e) sets out the standard for review of a petition for stay of action as follows:

> The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action as is warranted by the petition. The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:
>
> (1) The petitioner will otherwise suffer irreparable injury.
> (2) The petitioner's case is not frivolous and is being pursued in good faith.
> (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
> (4) The delay resulting from the stay is not outweighed by public health or other public interests.

The Commissioner shall grant a stay if all four of these criteria apply.

We need not address your irreparable harm argument[4] or whether your request is not frivolous and is being pursued in good faith because we find that you have failed to demonstrate public policy grounds for the stay, and we have determined that the delay would be outweighed by public health or other public interests.

You have not demonstrated that sound public policy grounds exist in support of the stay. You assert that you responded to the statutory incentive of pediatric exclusivity by conducting studies of amlodipine on the effects of the drug on children (PSA at 3). You assert that FDA should not permit Novartis to circumvent your pediatric exclusivity because it would undermine the incentive to conduct pediatric research (PSA at 3).

As discussed in section II.A of this response, the threshold issue in this matter is whether the termination of a right of reference to data that was necessary for approval of an NDA requires that the Agency withdraw approval of the NDA. You identified no statutory or other regulatory basis that necessitates withdrawal of approval of the Lotrel NDA on the grounds that Pfizer

[4] We note, however, that you have not demonstrated that you would suffer irreparable harm. You assert that you would lose the monetary reward associated with pediatric exclusivity in the absence of a stay, but economic loss is insufficient to demonstrate irreparable injury.

revoked its right of reference. Because the approval of Lotrel remains in effect, Pfizer's pediatric exclusivity for Norvasc has no effect on the Lotrel NDA. Because the merits of your challenge are unpersuasive, we do not believe there are any legitimate public policy grounds that would warrant staying the approval of any supplements for Lotrel.

You also have not demonstrated that the delay resulting from the stay is not outweighed by public health or other public interests. You assert that the public interest is best served by effectuating your pediatric exclusivity and the temporary unavailability of Lotrel will cause no harm to either the public health or interests (PSA at 3). You further assert that both amlodipine besylate and benazepril hydrocholoride are available as monotherapies and, at worst, grant of a stay could result in a temporary inconvenience (PSA at 3). As stated above, you have failed to identify any statutory or other regulatory basis that necessitates withdrawal of approval of the Lotrel NDA, conversion of the Lotrel NDA to a tentatively approved section 505(b)(2) application, or delay of approval of any supplements associated with that NDA. We find that a delay resulting from a stay would be outweighed by the public interest in the continued availability of Lotrel, which has been on the market for a number of years and for which there is no basis to withdraw approval. For the reasons described above, FDA denies your request for a stay.

You further request that even if the criteria for a mandatory stay (the four criteria discussed above) have not been satisfied, a stay should nonetheless be granted under FDA's discretionary authority to stay an action in the public interest and in the interest of justice (21 CFR 10.35(e)) (PSA at 3). For the reasons discussed above, we do not believe a stay would be in the public interest or in the interest of justice. Therefore, we decline to exercise our discretionary authority to grant your request.

However, with respect to supplements to the Lotrel NDA, beginning March 25, 2007, the date upon which you state the right of reference to Norvasc was to be revoked, FDA will not rely on data and information contained in the Norvasc NDA to approve supplements to the Lotrel application, and the approval of any 505(b)(1) supplement to the Lotrel NDA must be based on data owned by Novartis, or to which Novartis has a right of reference.

III. CONCLUSION

For the reasons discussed in this response, the Petition and PSA are denied.

Sincerely,

Randall W. Lutter, Ph.D.
Associate Commissioner for Policy
and Planning

Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 22 2004

NDA 19-813
ANDA 76-258

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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)

[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.

[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.

[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.