DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

Carmen M. Shepard, Esq.
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919 18th Street, NW
Washington, DC 20006-5503

RE: Docket No. 2007N-0382
Ramipril Capsules

Dear Ms. Shepard and Ms. Beardsley:

This is in response to your letter dated September 25, 2007 (Lupin Letter), in which you request immediate approval of abbreviated new drug application (ANDA) 77-626 for ramipril capsules, submitted by your client Lupin Pharmaceuticals, Inc. (Lupin). Your letter also asserts that Cobalt Pharmaceuticals, Inc. (Cobalt) should not be entitled to 180-day generic drug exclusivity under section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act) for its ramipril capsule product.

On the same day you submitted your letter, the law firm of Hyman, Phelps & McNamara (HPM) submitted a letter on the same issue. Docket No. 2007N-0382/Let1 (HPM Letter). This was submitted on behalf of an unnamed client with a tentatively approved ANDA for ramipril capsules. Although offering slightly different arguments, the Lupin Letter and HPM Letter are in fundamental agreement that Cobalt is not eligible for 180-day exclusivity.

We established a public docket in which both letters were placed. We have received comments from various interested parties, which take differing positions on the issues raised in your letter. The agency has carefully considered the views of all of the comments submitted to the docket.

We have concluded that Cobalt is entitled to 180-day generic drug exclusivity, which was triggered on December 10, 2007, with issuance by the Federal Circuit of the mandate in *Aventis Pharma Deutschland Gmbh v. Lupin Ltd.*, Civil Action No. 06-1530 (RDG)(Fed. Cir. December 10, 2007). As explained in this letter, Cobalt's 180-day exclusivity is currently a barrier to approval of other ANDAs for ramipril capsules, including Lupin's ANDA 77-626. Your request, therefore, is denied.[1]

[1]It is FDA's practice to make decisions on eligibility for 180-day exclusivity only in the context of specific ANDAs that are otherwise eligible for approval. This approach is based on the multiple factors that may influence eligibility for exclusivity or forfeiture up to the time an application is ready for approval (e.g., patent expiration, patent delisting, failure to obtain a tentative approval within 30 months, withdrawal of ANDA) and could thus render a premature eligibility determination incorrect. When the agency must make an approval decision for an ANDA, it will inform the applicant that it is either 1) a first applicant and entitled to exclusivity, 2) a first applicant that has forfeited its exclusivity, or 3) eligible only for a tentative approval because one or more first applicants are eligible for 180-day exclusivity. It is possible that an ANDA applicant could be informed upon approval that it is a "first applicant" eligible for 180-day exclusivity pursuant to section 505(j)(5)(B)(iv), but later forfeit that exclusivity

I. FACTUAL BACKGROUND

The reference listed drug (RLD) for the ramipril ANDAs at issue is Altace Capsules. Altace is marketed pursuant to new drug application (NDA) 19-901, held by King Pharmaceuticals, Inc. (King). Two patents are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) as claiming the drug. On November 26, 2002, FDA received Cobalt's ANDA 76-549, which used Altace Capsules as its RLD. The ANDA contained a paragraph IV certification to U.S. Patent No. 5,061,722 (the '722 patent). The other listed patent is a method-of-use patent and is not at issue here. Cobalt provided notice as required to the NDA holder and patent owner. Cobalt's paragraph IV certification to the '722 patent made Cobalt eligible for 180-day exclusivity for ramipril capsules.

The owner of the '722 patent brought an infringement suit against Cobalt in U.S. District Court for the District of Massachusetts within 45 days of receiving Cobalt's notice letter. That suit triggered an automatic 30-month stay of approval which expired on August 10, 2005. FDA approved ANDA 76-549 on October 24, 2005. Cobalt has notified FDA that it began commercial marketing of its ramipril capsules on December 26, 2007.

According to documentation submitted by Cobalt, in March 2004, as part of the patent litigation, Cobalt stipulated that its ramipril product would infringe certain claims of the '722 patent, but reserved its invalidity and unenforceability defenses, which it continued to pursue.[2] On February 27, 2006, Cobalt entered into a dismissal agreement, which provided that the parties would jointly file a stipulation of dismissal to voluntarily dismiss the patent litigation against Cobalt without prejudice. As required by law, the settlement agreement was submitted to the Federal Trade Commission (FTC) for review. To date, the FTC has issued no opinion with respect to the settlement agreement.

On March 18, 2005, Lupin submitted ANDA 77-626, which, like Cobalt's earlier ANDA, also referenced King's Altace Capsules, and contained the same patent certification. Lupin was sued by King in July 2005 in the U.S. District Court for the Eastern District of Virginia. In July 2006, the court (a different court from the one hearing the Cobalt litigation) entered a judgment against Lupin on infringement and invalidity. Lupin, however, prevailed on appeal. In a decision issued on September 11, 2007, the U.S. Court of Appeals for the Federal Circuit found the two claims at issue to be invalid. *Aventis Pharma Deutschland, GmbH and King Pharmaceuticals, Inc. v. Lupin*, 499 F.3d 1293 (Fed. Cir. 2007). Your letter to FDA demanding immediate approval of Lupin's ANDA was submitted two weeks after this decision. The Federal Circuit's mandate issued on December 10, 2007.

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under section 505(j)(5)(D). FDA will consider whether there has been a forfeiture of 180-day exclusivity when approval of a subsequent ANDA may be blocked by a first applicant's exclusivity. In the present case, Cobalt was informed in its October 24, 2005 approval letter that it was eligible for exclusivity. Had subsequent events resulted in forfeiture of that exclusivity, thus permitting approval of other ANDAs referencing Altace, the agency would have notified Cobalt of the forfeiture.

[2] 2007N-0382/C3, Foley & Lardner comment dated October 19, 2007, submitted on behalf of Cobalt (Cobalt Comment).

II. STATUTORY AND REGULATORY BACKGROUND

Under the 1984 Hatch-Waxman Amendments to the Act, an NDA applicant must submit information for each patent that claims the drug or method of using the drug that is the subject of the NDA and for which "a claim of patent infringement could reasonably be asserted if a person not licensed by the patent owner engaged in the manufacture, use, or sale of the drug." Sections 505(b)(1) and (c)(2) of the Act. FDA publishes this patent information in the Orange Book. With respect to each listed patent, an ANDA must provide a certification:

> (I) that such patent information has not been filed [a paragraph I certification],
> (II) that such patent has expired [a paragraph II certification],
> (III) of the date on which such patent will expire [a paragraph III certification], or
> (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted [a paragraph IV certification]; ....

Section 505(j)(2)(A)(vii).[3] See also 21 CFR 314.94(a)(12)(i)(A).

An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and the patent owner with notice of its patent certification, including a description of the legal and factual basis for its assertion that the patent is invalid or not infringed. Section 505(j)(2)(B). Should the NDA holder or patent owner initiate a patent infringement action against the ANDA applicant within 45 days of receiving the required notice, approval of the ANDA will be stayed for 30 months from the date of the notice. Section 505(j)(5)(B)(iii).

The 180-day exclusivity provisions of the Act give the first ANDA applicant to submit a paragraph IV certification challenging a patent - and thus undertake the risk of litigation - an incentive in the form of the opportunity to be the only generic drug manufacturer to compete with the innovator for a 180-day period.[4] The 180-day exclusivity period delays FDA approval of competing generic products until 180 days after the earlier of two so-called "triggering" events:

> (iv) If the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under

[3] The Act provides only one circumstance in which an ANDA applicant need not certify to a listed patent: "if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection," the applicant can submit "a statement that the method of use patent does not claim such a use" (a section viii statement). Section 505(j)(2)(A)(viii); see also 21 CFR 314.94(a)(12)(iv). Cobalt and Lupin each submitted a section viii statement with respect to the second listed patent for Altace.

[4] Because Cobalt, the first applicant to submit an ANDA referencing Altace, submitted its paragraph IV certification before the date of enactment of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) (Pub. L. No. 108-173) on December 8, 2003, unless otherwise noted, reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA section 1102(b)(1).

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

Section 505(j)(5)(B)(iv)(2002). The MMA revised the trigger under section 505(j)(5)(B)(iv)(II) for ANDAs, such as those for ramipril capsules, for which there had been no commercial marketing or court decision trigger before December 8, 2003; for those applications, the trigger would be a final decision of a court from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken. See MMA Sec. 1102(b)(3). Thus, the start of the 180-day exclusivity period can be triggered by either of two events: (1) commercial marketing by the first applicant to file a paragraph IV certification (the commercial marketing trigger) or (2) a final, unappealable court decision that the patent is invalid or not infringed (the court decision trigger), whichever is earlier. The court decision triggering the beginning of exclusivity can arise in litigation involving either the applicant eligible for 180-day exclusivity or a subsequent applicant. *Teva Pharms. USA, Inc. v. FDA*, 182 F.3d 1003 (D.C. Cir. 1999), *on remand*, 1999 WL 1042743 (D.D.C. 1999), *aff'd*, 2000 WL 1838303 (D.C. Cir. 2000) (unpublished opinion).

With passage of the MMA in 2003, Congress made significant revisions to the Hatch-Waxman Amendments. One issue Congress addressed directly for the first time is the effect on 180-day exclusivity when the first applicant to file a paragraph IV certification (the first applicant) enters into a settlement agreement with the NDA holder and/or owner of the patents listed on the listed drug. Congress enacted in the MMA a forfeiture provision under which a first applicant loses its exclusivity if there is an unappealable order finding that the agreement violates the antitrust laws:

> (i) DEFINITION OF FORFEITURE EVENT.-In this subparagraph, the term "forfeiture event", with respect to an application under this subsection, means the occurrence of any of the following:
> …
> (V) AGREEMENT WITH ANOTHER APPLICANT, THE LISTED DRUG APPLICATION HOLDER, OR A PATENT OWNER- The first applicant enters into an agreement with another applicant under this subsection for the drug, the holder of the application for the listed drug, or an owner of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV), the Federal Trade Commission or the Attorney General files a complaint, and there is a final decision of the Federal Trade Commission or the court with regard to the complaint from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the agreement has violated the antitrust laws (as defined in section 12 of Title 15, except that the term includes section 45 of Title 15 to the extent that that section applies to unfair methods of competition).

Section 505(j)(5)(D)(i)(V)(2004). This forfeiture event sometimes is referred to as the "collusive agreement" forfeiture event.

The MMA created a number of forfeiture events, by which a first applicant previously eligible for 180-day exclusivity could lose that eligibility. See Section 505(j)(5)(D)(i)(2004). Most of the forfeiture events apply solely to ANDAs referencing a listed drug for which the first paragraph IV certification was filed after December 8, 2003. See MMA Sec. 1102(b)(1).[5] The collusive agreement forfeiture event is the only one that applies to all pending ANDAs, regardless of when the first paragraph IV ANDA was filed. See MMA Sec. 1102(b)(2).[6]

III. DISCUSSION

The arguments in the submissions focus both on Cobalt's continued eligibility for exclusivity as a result of its paragraph IV certification to the '722 patent and on subsequent applicants' eligibility for immediate approval notwithstanding Cobalt's paragraph IV certification. Lupin and others claim that, because of its settlement, Cobalt is no longer entitled to 180-day exclusivity. Alternatively, Lupin claims it should be excused from any patent certification requirements for the '722 patent, and thus not be blocked by any exclusivity to which Cobalt is entitled. We disagree with both views.

A. Cobalt has not forfeited 180-day exclusivity as a result of its settlement.

Lupin's argument is that the Cobalt settlement rendered its paragraph IV certification inaccurate, as Cobalt had effectively stopped asserting that the '722 patent is invalid. Similarly, Lupin asserts that Cobalt was unwilling to stand behind its initial opinion that the patent is invalid and unenforceable because Cobalt failed to market its approved generic ramipril product. In short, Lupin argues, "Cobalt has long since given up its challenge to the '772 patent, and its ANDA no longer contains a valid paragraph IV certification." Lupin Letter at 5.

In enacting what is now section 505(j)(5)(D)(i)(V), Congress provided that the first applicant forfeits its exclusivity by virtue of entering into a settlement agreement when there is a final, unappealable order finding that the terms of the agreement violate the federal antitrust laws. Congress did not provide for such a forfeiture as the result of any other type of settlement for ANDAs otherwise governed by the pre-MMA 180-day exclusivity provisions. Where "the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron, USA., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842-43 (1984). Because the Act addresses directly the question of forfeiture as a result of a settlement, the agency does not have the discretion to determine that settlements not otherwise meeting the statutory requirements also will result in forfeiture.

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[5] Section 1102(b)(1) of the MMA provides that, except as provided in section 1102(b)(2), the forfeiture events "shall be effective only with respect to an application filed under [section 505(j) of the Act] after the date of the enactment of this Act for a listed drug for which no certification under section 505(j)(2)(A)(vii)(IV) of that Act was made before the date of the enactment of this Act."

[6] Section 1102(b)(2) of the MMA provides. "(2) COLLUSIVE AGREEMENTS.-If a forfeiture event described in section 5050)(5)(D)(i)(V) of that Act occurs in the case of an applicant, the applicant shall forfeit the 180-day period under section 505(j)(5)(B)(iv) of that Act without regard to when the first certification under section 505(j)(2)(A)(vii)(IV) of that Act for the listed drug was made."

In this case, there is no final, unappealable order finding that the King/Cobalt agreement violates antitrust laws. Consequently, despite the fact that the settlement agreement, and the circumstances surrounding it, may be objectionable to Lupin and others, there is no legal basis for the Agency to find that Cobalt has forfeited its exclusivity.

B. Cobalt's paragraph IV certification to the '722 patent is appropriate.

The HPM Letter asserts that the proper patent certification for Cobalt under the circumstances of this case is a paragraph III certification, and that FDA should remove the '722 patent from the Orange Book once the Federal Circuit issues its mandate in the Lupin case and fully approve all tentatively approved ANDAs for ramipril capsules.

The Act requires an ANDA applicant to address each Orange Book patent for the reference listed drug. See section 505(j)(2)(A)(vii). It further specifies the type of certification an ANDA applicant must make when it seeks to market its generic product prior to the expiration of a listed patent; such an application must contain a paragraph IV certification stating that the listed patent "will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." Section 505(j)(2)(A)(vii)(IV).

Cobalt's paragraph IV certification remains appropriate. Because the NDA holder submitted information on the `722 patent, a paragraph I certification to this patent, asserting that patent information has not been submitted, would be incorrect. Section 505(j)(2)(A)(vii)(I). The '722 patent has not expired, and will not expire until October 29, 2008), which would make a paragraph II certification that the patent has expired improper. Section 505(j)(2)(A)(vii)(II). Cobalt sought and obtained approval to market its ramipril capsule products prior to the expiration of the '722 patent, making a paragraph III certification to this patent improper, as a paragraph III certification permits approval only when the patent expires. Section 505(j)(5)(B)(ii).[7] Notwithstanding Cobalt's ultimate settlement of its litigation with King, it appears from the material before us that Cobalt pursued its claims of invalidity and unenforceability until it settled the case "at the strong urging of the court."[8] Cobalt Comment at p. 3. Therefore, a paragraph IV certification is an appropriate patent certification for Cobalt to make to the '722 patent.

There is likewise no persuasive argument that FDA's regulations require that Cobalt amend its certification to the '722 patent. These regulations mirror the statutory requirements. The regulation at 21 CFR 314.94(a)(12)(viii) provides three circumstances under which a patent certification should be amended, none of which apply here. Subclause (A) of this regulation

[7] HPM asserts that in the response to the Teva nifedipine citizen petition (Docket No. 2000P-1446) and ensuing court challenge by Mylan, *Mylan Pharm., Inc. v. Thompson*, 207 F. Supp. 2d 476 (N.D. W.Va. 2001), FDA considered a paragraph IV certification as effectively amended to a paragraph III certification as a result of a settlement agreement. The court rejected this attempt. An essential fact in the nifedipine case was that Mylan commenced marketing an authorized generic of the brand name drug. The court agreed with FDA's opinion that this act triggered the 180-day exclusivity period. In this case, there has been no evidence that Cobalt has marketed an authorized generic of Altace Capsules. Moreover, the nifedipine case occurred prior to passage of the MMA, which, as discussed above, establishes the effect of settlement agreements on 180-day exclusivity.

[8] We note that there is no evidence that at any point Cobalt conceded the '733 patent as valid, enforceable, and infringed by the product described in its ANDA.

addresses amendments when "a final judgment in the [infringement] action against the applicant is entered finding the patent to be infringed." 21 CFR 314.94(a)(12)(viii)(A). This regulation is not relevant to the circumstances here because no final judgment has been entered against Cobalt finding its ramipril capsule products to infringe any claim of the `722 patent. Under subclause (B), "[i]f a patent is removed from the list, any applicant with a pending application ... who has made a certification with respect to such patent shall amend its certification." 21 CFR 314.94(a)(12)(viii)(B). The `722 patent remains listed in the Orange Book, rendering this provision inapplicable. Subclause (C) of this regulation states 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." 21 CFR 314.94(a)(12)(viii)(C)(1). Cobalt's paragraph IV certification was accurate when submitted and remains accurate. Moreover, we note that Cobalt's ANDA has already been - and remains - approved.[9] Therefore, Cobalt is not required under FDA regulations to amend its existing paragraph IV certification to the '722 patent.

Cobalt's continued paragraph IV certification to the `722 patent is appropriate, therefore Cobalt is eligible for 180-day exclusivity. Because Cobalt is eligible for 180-day exclusivity as to the '722 patent, FDA cannot remove the patent from the Orange Book until that exclusivity expires. *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120 (D.C. Cir. 2006).

C. Lupin cannot certify that there are no relevant patents.

Lupin argues that the Act and FDA's regulations provide for changes in certification when circumstances change. "In this case, the circumstances have changed and Lupin should be permitted to amend its certification so that its approval is not affected by Cobalt's exclusivity." Lupin Letter at 6. This argument also is not persuasive. As discussed above, the Act and regulations require that all ANDA applicants, including Lupin, certify to each listed patent. The regulations also preclude the withdrawal of a paragraph IV certification until expiration of 180-day exclusivity:

> … an applicant who has submitted a paragraph IV patent certification may not change it to a paragraph III certification if a patent infringement suit has been filed against another paragraph IV applicant unless the agency has determined that no applicant is entitled to 180-day exclusivity or the patent expires before the lawsuit is resolved or expires after the suit is resolved but before the end of the 180-day exclusivity period.

[9] In two of the cases that HPM cites to require Cobalt to change its certification, FDA amended, or required an applicant to amend, paragraph IV certifications to paragraph II certifications when the listed patents expired before the final approval of the ANDAs at issue. *Ranbaxy Labs. Ltd. v. FDA*, 307 F. Supp. 2d 15, 21 (D.D.C.), *aff'd*, 96 Fed. Appx. I (D.C. Cir. 2004); *Dr. Reddy's Labs. v. Thompson*, 302 F. Supp. 2d 340, 351 (D.N.J. 2003). These cases do not apply here, as Cobalt's ANDA is approved, and was approved before the expiration of the '722 patent. In another cited case, *Mylan Labs. v. Thompson*, 389 F.3d 1272 (D.C. Cir. 2004), Mylan filed a paragraph IV certification, obtained final approval, but later lost its patent infringement case and the status of the ANDA was changed to tentatively approved. The issue in this *Mylan* case was the effect of statutory provisions at section 505A governing pediatric exclusivity that are not applicable here. FDA finds none of these cases to be on point or persuasive.

21 CFR 314.94(a)(12)(viii). As discussed in the preamble to the final rule:

> [T]he protection offered by 180-day exclusivity should not be undermined by changes from paragraph IV certification … [T]he agency has required that a patent remain on the list after being declared invalid or unenforceable until the end of any applicable 180-day exclusivity period. This means that a patent is deemed to be relevant under Sec. 314.94(a)(12)(ii) until the end of the term of the patent or applicable 180-day exclusivity period, whichever occurs first. Thus, where there is a patent that has been challenged by a paragraph IV applicant, **a subsequent applicant will not be able to file a certification that there is no relevant patent or seek an immediately effective approval until either the patent or the 180-day exclusivity period expires.**

59 FR 50338, 50348 (Oct. 3, 1994)(emphasis added). The regulation refers specifically to a change from a paragraph IV certification to a paragraph III certification because both the Act and the regulations require that, if an unexpired patent is listed in the Orange Book, the only alternative under these circumstances to a paragraph IV certification would be a paragraph III certification. Further, a subsequent applicant such as Lupin may not make an end run around the continued listing of an invalid patent - and the related 180-day exclusivity - merely by changing its certification. The fact that Lupin, not Cobalt, was successful in obtaining a judgment that the '722 patent is invalid does not alter this conclusion.

D. The clear language of the Act did not entitle Lupin to immediate approval.

You argue that Lupin was entitled to final approval as of the date of the Federal Circuit decision finding the '722 patent invalid. You claim that "[w]hen a district court judgment in favor of the patent holder is overturned on appeal (and no 180-day exclusivity delays the approval), the clear statutory language directs FDA to approve the ANDA on 'the date on which the court of appeals decides that the patent is invalid or not infringed. (citation omitted)." Lupin Letter at 9-10. That date, you assert, should have been the date of the *decision* of the Court of Appeals, not the date of the *mandate*. Because, as explained above, Cobalt is entitled to 180-day exclusivity, neither the Lupin ANDA, nor any other ANDA referencing Altace, will be eligible for final approval until the expiration of Cobalt's 180-day exclusivity on June 7, 2008.

IV. CONCLUSION

For the reasons discussed above, we have determined that Cobalt's paragraph IV certification in ANDA 76-549 is appropriate, and that Cobalt is entitled to 180-day generic drug exclusivity as the first applicant to file an ANDA for ramipril capsules with a paragraph IV certification to the '722 patent. Therefore, no other ANDA referencing Altace can be approved until June 7, 2008, the date upon which the 180-day exclusivity period will expire.

If you have any questions regarding this correspondence, please contact Cecelia M. Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 240-276-9310.

Sincerely yours,

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

cc: ANDA 77-626 - Lupin Pharmaceuticals, Inc.
ANDA 76-549 - Cobalt Pharmaceuticals, Inc.

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/s/

Gary Buehler

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