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September 25, 2007

BY E-MAIL/CONFIRMATION COPY BY MAIL

Gary J. Buehler, R.Ph.
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room E150
Rockville, MD 20855-2773

Re: Ramipril Oral Capsules, 1.25mg, 2.5mg, 5mg, and 10mg

Dear Mr. Buehler:

We are writing on behalf of a company with a tentatively approved Abbreviated New Drug Application ("ANDA") for generic versions of the above-referenced drug products to request that the Food and Drug Administration ("FDA") immediately resolve an issue that could unduly delay the final approval of that company's (and other companies') tentatively approved ANDAs. As discussed below, Cobalt Pharmaceuticals, Inc. ("Cobalt") was the first ANDA applicant to submit a substantially complete application (ANDA #76-549) containing a paragraph IV patent certification to a patent listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") for the Reference Listed Drug ("RLD"), King Pharmaceuticals, Inc.'s ("King's") ALTACE Capsules, 1.25mg, 2.5mg, 5mg, and 10mg (NDA #19-901). As such, Cobalt was eligible for 180-day exclusivity under the Federal Food, Drug, and Cosmetic Act ("FDC Act") § 505(j)(5)(B)(iv).[1] Certain events have occurred, however, that should cause FDA to determine that Cobalt lost its eligibility for 180-day exclusivity.

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[1] ANDA #76-549 was submitted to FDA prior to the enactment of Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA"),

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Cobalt submitted ANDA #76-549 on November 26, 2002. The ANDA contained a paragraph IV certification to U.S. patent #5,061,722 ("the '722 patent"), a composition of matter patent that is scheduled to expire on October 29, 2008.[2] FDA approved ANDA #76-549 on October 24, 2005. FDA took this action after: (1) Cobalt notified the Agency that the company complied with the requirements of FDC Act § 505(j)(2)(B) concerning paragraph IV certification notice; (2) Cobalt notified FDA that a patent infringement action was initiated against Cobalt by the NDA holder (i.e., King) and patent owner (i.e., Aventis Pharma Deutschland GmbH ("Aventis"), now known as Sanofi-Aventis Deutschland GmbH) in the U.S. District Court for the District of Massachusetts within the 45-day statutory period (i.e., on March 14, 2003); and (3) the statutory 30-month stay of approval (FDC Act § 505(j)(B)(iii)) expired on August 10, 2005. See FDA Approval Letter, ANDA #76-549, (Oct. 24, 2005) at 2.

In March 2004, prior to the expiration of the 30-month stay of approval on ANDA #76-549, Cobalt entered into a stipulation with Aventis and King in the Massachusetts patent infringement litigation in which Cobalt admitted that Cobalt's "making, using, offering to sell, importing, or selling" Ramipril Capsules (or the active ingredient, ramipril) in the U.S. "would infringe" certain claims of the '722 patent. Aventis Pharma Deutschland GmbH v. Cobalt Pharma., Inc., Civil Action No. 03-10492 (JLT) (D. Mass.), Document 98 (Attachment #1). Cobalt's admission was made without prejudice that such claims are invalid and unenforceable. See id.

In February 2006, Aventis, King, and Cobalt entered into a dismissal agreement, which provided that the three companies would jointly file a stipulation of dismissal to voluntarily dismiss the Massachusetts patent litigation, as well as a generic distribution agreement, which provides the terms under which Cobalt will market an authorized generic

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Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003). As such, 180-day exclusivity is governed by FDC Act § 505(j)(5)(B)(iv)(I)-(II) (2002). All FDC Act references in this letter are to the pre-MMA version of the statute unless otherwise stated. It is noteworthy that if this were a post-MMA case, Cobalt would almost certainly have forfeited its 180-day exclusivity.

2 ANDA #76-549 also contained a "section viii statement" to U.S. patent #5,403,856 ("the '856 patent"), which is a method-of-use patent that does not claim a use for which Cobalt was seeking approval.

version of ALTACE Capsules.[3] The terms of the Dismissal Agreement state, in relevant part, that "[t]he Parties agree that the lawsuit record, including without limitation all rulings by the [U.S. District Court for the District of Massachusetts], shall be binding, subject to any rights of appeal, on the Parties in the event any of King's or Aventis's claims are reasserted by any Party hereto." Dismissal Agreement at § 2.1. In other words, Cobalt's March 2004 stipulation that the company's Ramipril Capsules drug products "would infringe" the '722 patent remains in effect. On April 4, 2006, the Massachusetts patent infringement litigation was "voluntarily dismissed in its entirety without prejudice" pursuant to the Dismissal Agreement entered into between Aventis, King, and Cobalt. Aventis Pharma Deutschland GmbH v. Cobalt Pharma., Inc., Civil Action No. 03-10492 (JLT) (D. Mass.), Document 291 (Attachment #3).[4]

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[3] Copies of the dismissal agreement and the generic distribution agreement were included as exhibits in King's May 10, 2006 Form 10-Q filing with the U.S. Securities and Exchange Commission ("SEC"). A copy of the dismissal agreement (hereinafter "Dismissal Agreement") is *available at* http://www.sec.gov/Archives/edgar/data/1047699/000095014406004699/g00994exv10w5.txt and is attached as Attachment #2. A copy of the generic distribution agreement is *available at* http://www.sec.gov/Archives/edgar/data/1047699/000095014406004699/g00994exv10w1.txt.

[4] According to a recent Form 10-Q King filed with the SEC:

> [t]he Company has received a civil investigative demand ("CID") for information from the U.S. Federal Trade Commission ("FTC"). The CID requires the Company to provide information related to the Company's . . . dismissal without prejudice of the Company's patent infringement litigation against Cobalt under the Hatch-Waxman Act of 1984 and other information. The Company is cooperating with the FTC in this investigation.

King, Form 10-Q, (Aug. 7, 2007) at 18, *available at* http://www.sec.gov/Archives/edgar/data/1047699/000095014407007396/g08394e10vq.htm (Attachment #4).

If there is a decision that the agreement between Aventis, King, and Cobalt violates the antitrust laws, then any 180-day exclusivity period to which Cobalt might be entitled would be forfeited. See FDC Act § 505(j)(5)(D)(i)(V) (2007). Although this provision was added to the FDC Act by the MMA, it applies to pre-MMA ANDAs as well.

On September 11, 2007, in separate Ramipril Capsules patent litigation between Aventis, King, and Lupin Pharmaceuticals, Inc. ("Lupin") (which is one of several generic applicants with a pending Ramipril Capsules ANDA), the U.S. Court of Appeals for the Federal Circuit reversed a July 18, 2006 decision by the U.S. District Court for the Eastern District of Virginia and found the '722 patent invalid. See Aventis Pharma Deutschland GmbH v. Lupin, Ltd., Civil Action No. 06-1530 (RGD) (Fed. Cir. 2007) (Attachment #5). The Federal Circuit has not yet (to our knowledge) issued its mandate.

Because Cobalt was the first ANDA applicant to submit a substantially complete application containing a paragraph IV patent certification claiming that the '722 patent is invalid and/or not infringed, the company was eligible for a 180-day exclusivity period under FDC Act § 505(j)(5)(B)(iv). This exclusivity period means that, generally, FDA cannot approve subsequent ANDAs with a paragraph IV certification to the '722 patent until 180 days after the exclusivity period is triggered —the earlier of either: (1) the first commercial marketing of Cobalt's approved Ramipril Capsules drug product; or (2) a court decision finding that the '722 patent is invalid and/or not infringed. See FDC Act § 505(j)(5)(B)(iv)(I)-(II). However, we believe that Cobalt is no longer eligible for 180-day exclusivity. As such, there is no generic exclusivity preventing FDA from approving the tentatively approved Ramipril Capsules ANDAs.

Although FDA approved Cobalt's ANDA almost two years ago, Cobalt has not, to our knowledge, amended its '722 patent certification from a paragraph IV to a paragraph III (i.e., the date of patent expiry), even though the patent infringement litigation upon which Cobalt's 180-day exclusivity eligibility is based was dismissed in its entirety after Cobalt stipulated that the company's products "would infringe" the '722 patent. Cobalt also has not, to our knowledge, provided FDA notice that the company has commercially marketed the Ramipril Capsules drug product approved in its application. Indeed, as of today, Cobalt's ANDA is listed in FDA's Orange Book as "discontinued." Thus, Cobalt's 180-day exclusivity (if it still exists, which we do not believe to be the case) is "parked" to the detriment of subsequent ANDA applicants with tentative approval (unless and until a court decision triggers such exclusivity).

As explained below, FDA should determine that ANDA #76-549 no longer contains a paragraph IV patent certification to the '722 patent, but rather, a paragraph III patent certification (the appropriate patent certification for an ANDA applicant that has abandoned patent infringement litigation and admitted infringement), and that Cobalt is therefore no longer eligible for 180-day exclusivity. Once the Federal Circuit issues its mandate in the

Lupin litigation, FDA should remove the '722 patent from the Orange Book and promptly grant final approval to tentatively approved Ramipril Capsules ANDAs.

I. COBALT IS NO LONGER ELIGIBLE FOR 180-DAY EXCLUSIVITY

Cobalt's March 2004 stipulation with Aventis and King that Cobalt's Ramipril Capsules drug products "would infringe" the '722 patent, and the February 2006 Dismissal Agreement (which incorporates the March 2004 stipulation) and the April 2006 dismissal of the litigation effectively changed Cobalt's patent certification from a paragraph IV to a paragraph III, because Cobalt is no longer challenging the '722 patent and has conceded that the company's Ramipril Capsules drug products "would infringe" the '722 patent. Thus, Cobalt is not eligible for 180-day exclusivity, and FDA can (and should) fully approve tentatively approved Ramipril Capsules ANDAs once the '722 patent is removed from the Orange Book (i.e., once the Federal Circuit issues its mandate in the Lupin '722 patent litigation). Absent such a determination from FDA, Cobalt's continued eligibility for 180-day exclusivity would mean that the company could continue to "park" that exclusivity and, once such exclusivity is triggered by the Federal Circuit's issuance of the mandate in the Lupin case, unfairly delay the introduction of other generic versions of ALTACE Capsules. This is not in the interest of the public, and is contrary to Congress' intent in creating the 180-day exclusivity period.

Neither the FDC Act nor FDA's ANDA regulations address the issue of generic applicants losing eligibility for 180-day exclusivity as a result of agreements between NDA and ANDA sponsors terminating patent infringement litigation, and that could result in "parked" exclusivity.[5] Instead, FDA has stated that in such cases the Agency "will regulate

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[5] The MMA amended the FDC Act to add certain 180-day forfeiture provisions that prevent a "first applicant" submitting an ANDA with a paragraph IV certification from indefinitely "parking" its 180-day exclusivity. See FDC Act § 505(j)(5)(D)(i)(I). Congress made these changes based, in part, on an FTC report expressing concern about "parked" 180-day exclusivity. See FTC, Generic Drug Entry Prior to Patent Expiration, (July 2002) at viii, 34, 58, 63, *available at* http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf. Congress did not, however, make most of these changes retroactive. Nevertheless, FDA can carry out Congress' intent in creating FDC Act § 505(j)(5)(D)(i)(I) in pre-MMA cases involving "parked" exclusivity by regulating directly from the statute and converting Cobalt's '722 patent certification from a paragraph IV to a paragraph III.

directly from the statute, and will make decisions on 180-day generic drug exclusivity on a case-by-case basis." FDA, Guidance for Industry - 180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act, (June 1998) at 4.[6] In fact, in a case similar to the one here, FDA concluded that a

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Although the case with Cobalt's ANDA no longer involves a scenario in which 180-day exclusivity is indefinitely "parked," as the Federal Circuit's September 11, 2007 decision and issuance of the mandate in the Lupin case will soon trigger any 180-day exclusivity period, such a distinction is not important here. The relevant issue is whether Cobalt's ANDA still contains a paragraph IV certification to the '722 patent given the company's abandonment of patent infringement litigation. The Federal Circuit's decision is important, however, insofar as it means that FDA must quickly determine that Cobalt is not eligible for 180-day exclusivity once the mandate issues.

6 FDA announced that the Agency would "regulate directly from the statute" when making exclusivity decisions on a case-by-case basis in the wake of the decisions in Mova Pharmaceutical Corp. v. Shalala, 140 F.3d 1060 (D.C. Cir. 1998), and Granutec, Inc. v. Shalala, 139 F.3d 889 (4th Cir. 1998). Under the pre-Mova regulations, Cobalt would not have been entitled to exclusivity because the company did not "successfully defend" the patent lawsuit brought by Aventis and King. In 1999, FDA issued proposed regulations that it believed responded to some of the issues created as a result of the aforementioned court decisions. See FDA, Proposed Rule, 180-Day Generic Drug Exclusivity for ANDAs, 64 Fed. Reg. 42,873, 42,874 (Aug. 6, 1999) (FDA stated that the proposal would "continue to provide an incentive for challenging a listed patent, while at the same time preventing prolonged or indefinite delays in the availability of generic drug products.") (proposal withdrawn for other reasons, see 67 Fed. Reg. 66,593 (Nov. 1, 2002)). In addressing NDA and ANDA sponsor commercial arrangements involving 180-day exclusivity, FDA noted the potentially negative effects of such arrangements. See id. at 42,882-83 ("The result [of a commercial arrangement between a generic and an innovator company] may be that, notwithstanding the intent of the Hatch-Waxman Amendments, rewards are directed to generic companies for hindering rather than speeding generic competition."). To help remedy this situation, FDA proposed a 180-day exclusivity "triggering" approach with the "requirement that, within 180 days of the first tentative approval of a subsequent ANDA, the first ANDA applicant begin commercially marketing its own product or obtain a favorable court decision." Id. at 42,880 (proposed 21 C.F.R. § 314.107(c)(5)). Although these regulations were never made final, FDA clearly has long been concerned about the potential negative implications of commercial arrangements when 180-day exclusivity

settlement agreement terminating paragraph IV patent certification litigation effectively changed an ANDA applicant's patent certification from a paragraph IV to a paragraph III, thereby eliminating the applicant's eligibility for 180-day exclusivity. It is our understanding that FDA still takes this position, but has not recently been challenged on the issue, perhaps because of a dwindling number of pre-MMA cases involving 180-day exclusivity in which this issue might arise.

In February 2001, FDA responded to a citizen petition submitted by Teva Pharmaceuticals USA, Inc. ("Teva"), in which the company requested that FDA determine that an ANDA with a paragraph IV patent certification submitted by Mylan Pharmaceuticals, Inc. ("Mylan") for Nifedipine Extended-Release Tablets, 30mg, is not eligible for 180-day exclusivity. See FDA Response, Docket No. 2000P-1446, (Feb. 6, 2001). Mylan submitted the first ANDA with a paragraph IV patent certification, was sued by the NDA holder (Pfizer) and patent owner (Bayer), and subsequently entered into settlement and licensing agreements with these parties. Instead of commercially marketing its generic drug product, Mylan "parked" its 180-day exclusivity for more than a year without amending its patent certification, and proceeded to market an "authorized generic" version of the RLD. Teva, a subsequent ANDA applicant blocked by Mylan's 180-day exclusivity, argued in a citizen petition, among other things, that Mylan's settlement agreement with Pfizer rendered Mylan ineligible for 180-day exclusivity. FDA agreed.[7] Specifically, FDA stated:

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is involved. Because FDA's regulations do not cover the matter here, FDA can, and must, regulate directly from the statute to resolve this unintended situation.

[7] FDA also determined, on an alternative and independent basis, that Mylan's marketing of an authorized generic version of Pfizer's PROCARDIA XL Tablets, 30 mg, constituted "first commercial marketing" that had triggered Mylan's 180-day exclusivity. See FDA Response, Docket No. 2000P-1446, at 7-8. The MMA codified this decision. See FDC Act § 505(j)(5)(B)(iv)(I). Presumably Cobalt has not yet launched an authorized generic version of ALTACE Capsules pursuant to company's February 2007 generic distribution agreement with Aventis and King, which would have triggered any 180-day exclusivity to which Cobalt might have been eligible. Nevertheless, we request that FDA immediately contact Cobalt to inquire about such a possibility. Clearly, if any such authorized generic was marketed that meets FDA's definition of the term "first commercial marketing," then Cobalt's 180-day exclusivity would have been triggered. See FDA, Letter to All NDA and ANDA Holders and Applicants, (July 28, 1988) at 3 (defining the term "first commercial marketing" to

> [The] facts lead FDA to presume that Mylan believes the product described in its ANDA may infringe the listed patent and is therefore waiting until patent expiry before marketing its own product. The appropriate certification for a company that has chosen to wait until a listed patent expired before marketing is a paragraph III certification stating the date of patent expiration. Because FDA considers Mylan's actions in settling the litigation and marketing Pfizer's nifedipine product to have effectively changed Mylan's certification from a paragraph IV to a paragraph III, and because applicants who change from a paragraph IV to a paragraph III are no longer eligible for 180-day exclusivity, Mylan has lost its eligibility for exclusivity. This interpretation is consistent with the principles articulated by the [court in Mylan Pharm., Inc. v. Henney, 94 F. Supp. 2d 36 (D.D.C. 2000)]: it avoids perpetuating the first generic and innovator parties' "anti-competitive hold" over the drug and allows market access to other generic manufacturers.

FDA Response, Docket No. 2000P-1446, at 6-7.

Mylan challenged FDA's determination in the U.S. District Court for the Northern District of West Virginia. See Mylan Pharm., Inc. v. Thompson, 207 F. Supp. 2d 476 (N.D. W.Va. 2001). In ruling on Mylan's motion for preliminary injunction, the court held that while FDA's treatment of Mylan's marketing of an authorized generic as triggering 180-day exclusivity was reasonable, FDA's deemed conversion of Mylan's patent certification from a paragraph IV to a paragraph III was unreasonable. See id. at 486-88. This rejection of FDA's position was not final. In fact, the court stated only that "there is, at least at this point, some likelihood of success by plaintiff Mylan on this feature of the FDA ruling." Id. at 487-88.

Mylan appealed the District Court's decision to the U.S. Court of Appeals for the Fourth Circuit. FDA vigorously defended the argument in its February 2001 citizen petition response that Mylan had effectively abandoned its paragraph IV patent certification, thereby transforming it into a paragraph III patent certification, and was no longer eligible for 180-day exclusivity. In FDA's brief, the Agency stated that the District

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> mean, in relevant part, "the first date of introduction or delivery for introduction into interstate commerce outside the control of the manufacturer, except for investigational use under 21 CFR Part 312.").

Court "failed to recognize the 'gap' in the statutory scheme," "erred in construing the [FDC Act] too rigidly," and "may have misinterpreted what FDA intended to convey in its citizen petition response." Mylan Pharm., Inc. v. Thompson, No. 01-1554 (4th Cir.), Brief of Federal Defendants-Appellees, (July 25, 2001) at 44-55. Specifically, "FDA was not presuming that Mylan wanted to give up the exclusivity reward behind a paragraph IV certification; instead, FDA deemed that Mylan's conduct was no longer consistent with a paragraph IV certification so it should be treated as if it had changed its certification." Id. at 51. FDA argued that such a conclusion was well within its discretion, and was not only consistent with the intent of the law, but with its ANDA patent certification regulations at 21 C.F.R. § 314.94(a)(12)(viii)(A) requiring a patent certification change from a paragraph IV to a paragraph III after a finding of infringement. Id. at 50.

Although the appeal was dismissed upon Mylan's request, FDA has not, to our knowledge, retreated from the position it took in its February 2001 petition response and in its July 2001 brief to the U.S. Court of Appeals for the Fourth Circuit. Indeed, in a subsequent case, in 2005, FDA discussed its "deemed patent certification conversion" ruling without giving any indication that the Agency had abandoned this position.[8] Moreover, the court's ruling in Mylan was made only in the context of a motion for a preliminary injunction and is not a final ruling on the merits of FDA's argument. And because the U.S. District Court for the Northern District of West Virginia has little experience on 180-day exclusivity matters compared to, for example, the U.S. District

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[8] For example, in a brief submitted by FDA in March 2005 in a case concerning an "authorized generic" of NEURONTIN (gabapentin) marketed during an ANDA sponsor's 180-day exclusivity period, FDA described the Mylan decision as follows:

> [FDA concluded] that Mylan's marketing of Pfizer's product was "commercial marketing of the drug" that triggered the exclusivity period. Alternatively, FDA determined that Mylan was no longer eligible for exclusivity because it had effectively changed its paragraph IV certification to a paragraph III certification . . . in that Mylan had apparently chosen to wait until Pfizer's patent expired before marketing its own version of the drug. The district court affirmed FDA's determination on the "commercial marketing trigger" issue, agreeing with the agency that Mylan's marketing of Pfizer's product under those circumstances triggered the exclusivity period.

FDA Brief in Teva Pharma. v. Crawford, 410 F.3d 51 (D.C. Cir. 2005), (Mar. 15, 2005) at 30, note 17 (citations omitted).

Court for the District of Columbia, little, if any, weight should be given to its decision on this issue.

It is also noteworthy that FDA has, under different circumstances, effectively converted paragraph IV patent certifications without an ANDA amendment when the circumstances supported such a change. For example, in Ranbaxy Labs. v. FDA, 307 F. Supp. 2d 15 (D.D.C. 2004), aff'd, 96 Fed. Appx. 1 (D.C. Cir. 2004), in Mylan Labs., Inc. v. Thompson, 389 F.3d 1272 (D.C. Cir. 2004), and in Dr. Reddy's Labs., Inc. v. Thompson, 302 F. Supp 2d 340 (D.N.J. 2004), the courts upheld FDA's decisions to convert the generic applicants' patent certifications from paragraph IVs to paragraph IIs (patent has expired) as a reasonable interpretation of the law and FDA's ANDA regulations.[9] Similarly, a deemed patent certification conversion from a paragraph IV to a paragraph III to remedy a situation in which 180-day exclusivity is "parked" and where the company eligible for such exclusivity has abandoned patent litigation is a reasonable interpretation of the FDC Act and FDA's ANDA regulations.

The circumstances in this case strongly support such a remedy. Cobalt abandoned patent infringement litigation and entered into a stipulation acknowledging that the company's products "would infringe" the '722 patent. The dismissal of the Massachusetts litigation did not change this admission. In fact, the terms of the February 2006 Dismissal Agreement between Aventis, King, and Cobalt clearly incorporate this admission with respect to any future litigation between the parties: "The Parties agree that the lawsuit record, including without limitation all rulings by the [U.S. District Court for the District of Massachusetts], shall be binding, subject to any rights of appeal, on the Parties in the event any of King's or Aventis's claims are reasserted by any Party hereto." Dismissal Agreement § 2.1 (emphasis added). Without a determination by FDA that Cobalt is no longer eligible for 180-day exclusivity, the full approval of those tentatively approved Ramipril Capsules ANDAs will be unfairly delayed once the Federal Circuit issues its mandate.

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[9] Indeed, FDA relied on these court decisions to support the Agency's recent administrative decision concerning 180-day and pediatric exclusivity issues for amlodipine besylate. See Letter from Gary Buehler, Director, Office of Generic Drugs, FDA, to Amlodipine Besylate Tablets ANDA Applicants/Holders, at 8, 10 (Apr. 18, 2007).

Consistent with FDA's "deemed patent certification conversion" argument in Mylan (Nifedipine Extended-Release Tablets, 30mg), the Agency should consider Cobalt's March 2004 stipulation with Aventis and King that Cobalt's Ramipril Capsules drug products "would infringe" the '722 patent, and the February 2006 Dismissal Agreement (which incorporates the March 2004 stipulation) and April 2006 dismissal of the litigation to have converted Cobalt's patent certification from a paragraph IV to a paragraph III so that Cobalt is no longer eligible for 180-day exclusivity. Clearly, Cobalt is no longer challenging the '722 patent and is therefore "no longer participating in litigation intended to prove that its product will not infringe the listed patent." FDA Response, Docket No. 2000P-1446, at 6. That Cobalt entered into a generic distribution agreement with Aventis and King to market an authorized generic version of ALTACE Capsules is further evidence that Cobalt believes its Ramipril Capsules drug products infringe the '722 patent. The proper patent certification under such circumstances is a paragraph III.

Cobalt's dubious claim to 180-day exclusivity would delay the final approval and availability of generic Ramipril Capsules drug products once the Federal Circuit issues its mandate in the Lupin case. Such an outcome is precisely the opposite of what Congress intended when it created the 180-day exclusivity period. Such exclusivity is intended as an incentive and reward for certain generic applicants who are willing to expose themselves to the potential liabilities of patent litigation for their non-infringing drug products. Although Cobalt admits that its Ramipril Capsules drug products "would infringe" the '722 patent (and has engaged in other activities consistent with this admission), the company still believes it is eligible for 180-day exclusivity, as it has not changed its paragraph IV to a paragraph III certification. Cobalt cannot have its cake and eat it too. As such, consistent with Congress' intent, and FDA's decision in the Mylan nifedipine case, FDA should interpret the FDC Act and its ANDA regulations to eliminate Cobalt's 180-day exclusivity eligibility by deeming the company's patent certification changed from a paragraph IV to a paragraph III.

II. FDA SHOULD FULLY APPROVE ALL TENTATIVELY APPROVED RAMIPRIL CAPSULES ANDAs ONCE THE '722 PATENT IS REMOVED FROM THE ORANGE BOOK

Because Cobalt's ANDA should properly be deemed to contain a paragraph III instead of a paragraph IV patent certification to the '722 patent, once the Federal Circuit issues its mandate in the Lupin Ramipril Capsules litigation that the '722 patent is invalid, there should be no bar to FDA from removing the patent from the Orange Book and fully

approving all tentatively approved Ramipril Capsules ANDAs containing a certification to such patent (and a "section viii" statement to the '856 patent). Such "delisting" of the '722 patent is consistent with FDA's regulations implementing the FDC Act.

An FDA regulation provides that in certain limited circumstances a patent may be removed from the Orange Book. Specifically, the regulation states:

> If a patent is removed from the [Orange Book], any applicant with a pending [ANDA] (including a tentatively approved application with a delayed effective date) who has made a certification with respect to such patent shall amend its certification. The applicant shall certify under paragraph (a)(12)(ii) of this section that no patents described in paragraph (a)(12)(i) of this section claim the drug or, if other relevant patents claim the drug, shall amend the certification to refer only to those relevant patents. . . . A patent that is the subject of a lawsuit under Sec. 314.107(c) shall not be removed from the [Orange Book] until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended. An applicant shall submit an amended certification. Once an amendment or letter for the change has been submitted, the application will no longer be considered to be one containing a [paragraph IV patent] certification . . . .

21 C.F.R. § 314.94(a)(12)(viii)(B) (emphasis added).

The limited exception to "delisting" an Orange Book-listed patent in the above regulation is not applicable here because Cobalt is no longer eligible for 180-day exclusivity, as explained in Section I of this letter. The reason for the limited exception is to avoid an unjust result that would occur if an ANDA applicant who is eligible for exclusivity prevails in the patent litigation but lost exclusivity if the NDA holder decided to remove the patent from the Orange Book. See FDA, Final Rule, ANDA Regulations, Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,348 (Oct. 3, 1994) ("If a patent were removed from the [Orange Book] immediately upon a court decision that the patent is invalid or unenforceable, an applicant with a subsequently filed [ANDA] might seek to certify that there is no relevant patent and seek an immediately effective approval."). Because Cobalt is no longer eligible for 180-day exclusivity, there is "no delay in effective dates of approval," and the '722 patent should be removed from the Orange Book (once the

mandate is issued) and tentatively approved Ramipril Capsules ANDAs should be fully approved.

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Timely resolution of the status of any 180-day exclusivity period to which Cobalt might be entitled is of critical importance to those generic applicants with tentatively approved Ramipril Capsules ANDAs. As such, we request that FDA respond to this letter within one week so that our client can consider what additional action might be necessary, including the need to litigate the issue given the possibility that the Federal Circuit could issue its mandate at any time. We look forward to your prompt reply. Please contact me at 202.737.4282, or my colleague, Kurt Karst at 202.737.7544, if you would like to further discuss this issue.

Very truly yours,

Robert A. Dormer

Kurt R. Karst

cc: Elizabeth H. Dickinson, Esq.
Office of Chief Counsel, FDA