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VIA E-MAIL & HAND DELIVERY

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room – MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**Re: FDA Docket # 2007N-0382
Ramipril Capsules and 180-Day Generic Drug Exclusivity**

Dear Mr. Buehler:

On behalf of Cobalt Pharmaceuticals, Inc. (“Cobalt”), we write in response to recently submitted letters from competitors asking the Food and Drug Administration (“FDA”) to strip Cobalt of its statutory right to a 180-day exclusivity period, an entitlement as the first to file an Abbreviated New Drug Application (“ANDA”) for Ramipril Capsules with a paragraph IV certification as to U.S. Patent No. 5,061,722 (“the ’722 patent”). Cobalt’s exclusivity period may be triggered upon the earlier of commercial launch of Cobalt’s capsules or a final decision (mandate) from the Federal Circuit, which recently held the ’722 patent invalid. Accordingly, this is not a case where exclusivity has been “parked” indefinitely as some competitors have argued. Cobalt’s late-filer competitors will have to wait only until the end of the 180-day exclusivity period that Cobalt earned by filing first and spending millions on protracted patent litigation.

The FDA does not have the authority to grant Cobalt’s competitors the extraordinary relief they are requesting. The FDA may not deprive Cobalt of a right bestowed by statute unless there is a statutory provision authorizing such a forfeiture, or an ambiguous statutory provision which may be reasonably interpreted to authorize such a forfeiture. The relevant pre-MMA statute did not contain any forfeiture provisions, and Congress expressly declined retroactively to apply the forfeiture provisions subsequently added by the MMA statute. **RECEIVED**

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does not extend to redrafting statutes. Further, Cobalt's competitors have failed to identify any statutory provision that is ambiguous.

In fact, the FDA already litigated this very same issue in *Mylan Pharmaceuticals, Inc. v. Thompson*, 207 F.Supp. 2d 476 (D.W.Va. 2001) and its position was rejected. As here, late-filing competitors in *Mylan* asked the FDA to strip the first-to-file of its statutory right to exclusivity. The Court concluded that the FDA had plainly exceeded its authority in granting the competitors' request. Specifically, the Court found that the FDA had acted without express or implicit statutory authority. No court in the country since has ruled to the contrary.

Finally, Cobalt suggests that even if FDA nevertheless believes it has authority to grant the relief requested, this is hardly an appropriate case in which to exercise that authority and devote substantial resources litigating the issue. This case is the last of — at most — a handful of cases governed by the pre-MMA version of the statute. There are not a significant number of similarly situated parties who might obtain meaningful guidance from a second judicial resolution of the issue which has since been rendered moot by an Act of Congress.

Factual Background

King Pharmaceuticals, Inc. ("King") is the new drug application ("NDA") holder and marketer of Altace® Capsules (Ramipril) 1.25mg, 2.5mg, 5mg, and 10mg. Aventis Pharma Deutschland GmbH ("Aventis") is the owner of the '722 patent, which is listed in the FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, (the "Orange Book"). Aventis has licensed the U.S. rights to the '722 patent to King.

On November 26, 2002, Cobalt was the first ANDA applicant to submit a substantially complete ANDA (ANDA # 76-549) containing a paragraph IV patent certification for the '722 patent. Cobalt thereby obtained the right to a 180-day exclusivity period, under the Federal Food, Drug, and Cosmetic Act ("FDCA") § 505(j)(5)(B)(iv); § 355(j)(5)(B)(iv) (2002).¹ Cobalt provided the requisite notice to King and Aventis, and was sued by both Aventis and King on March 13, 2003, for infringement of the '722 patent. See *Aventis Pharma Deutschland GmbH v. Cobalt Pharmaceuticals, Inc.*, Civil Action No. 03-10492 JLT (D. Mass.). The FDA approved Cobalt's ANDA on October 24, 2005, after the 30-month stay expired.

Cobalt's defenses to the '722 patent were that the patent was invalid in light of prior art, and unenforceable in light of inequitable conduct by the inventors before the PTO. In a stipulation to streamline the litigation, Cobalt agreed that its Ramipril Capsules product infringed

¹ Cobalt's ANDA was submitted for review prior to the passage of Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA"), Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003). Provisions in the MMA regarding 180-exclusivity were not applied retroactively. Therefore, for applications, such as Cobalt's, submitted prior to Dec. 8, 2003, the current MMA statutory provisions do not apply. All FDCA references in this letter are to the Pre-MMA version (2002) unless otherwise stated.

the claims, *but expressly reserved its invalidity and inequitable conduct defenses*. Indeed, Cobalt thereafter pursued those defenses through trial, which commenced in February 2006, and settled (at the strong urging of the Court) after two weeks of trial had been conducted.

On February 27, 2006, King, Aventis and 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. *See Attachment 1 at 5*. This dismissal was entered without any admission by Cobalt as the validity or enforceability of the '722 patent.

On September 11, 2007, in another ANDA Ramipril Capsules patent litigation case involving King, Aventis, and Lupin Pharmaceuticals, Inc. ("Lupin"), the U.S. Court of Appeals for the Federal Circuit reversed an earlier July 18, 2006, decision by the U.S. District Court for the Eastern District of Virginia and held the '722 patent invalid. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, Civil Action No. 06-1530 (RDG) (Fed. Cir. Sept. 11, 2007). We understand that King and Aventis jointly filed a Petition for Rehearing and Rehearing *En Banc* of this decision on September 25, 2007, and to our knowledge the Federal Circuit has not yet responded to this Petition or issued its mandate in this case.² *See Attachment 2*.

On September 25, 2007, Hyman, Phelps & McNamara, on behalf of an unnamed client, and Buc & Beardsley, on behalf Lupin, submitted letters ("HPM Letter" and "Lupin Letter," respectively) to FDA requesting that the Agency determine that Cobalt has forfeited its exclusivity and requesting final approval of the unnamed party's and Lupin's ANDAs respectively.³

Argument

I. The Statute Is Clear — No Subsequent ANDA May Be Approved Until the Expiration of Cobalt's 180-Day Exclusivity.

The statute provides in clear unambiguous language that the FDA may not approve a subsequent ANDA until after expiration of the 180 day exclusivity period — triggered either by the earlier of commercial marketing or a final decision of a court holding the patent not infringed or invalid.

² On October 2, 2007, an *Amicus Curiae* brief was submitted by the Pharmaceutical Research and Manufacturers of America ("PhRMA") in support of the combined petition of King and Aventis for rehearing and rehearing *en banc*.

³ We note that in legislation recently enacted by Congress, the Food and Drug Administration Amendments Act of 2007, parties submitting Citizen Petitions on behalf of third parties must identify on whose behalf they have "received or expect to receive [] payments from..." as well as make other certifications. *See FDCA § 505(q)(1)(H)*. Given that HPM has requested that FDA take action consistent with the scope and intent of a Citizen Petition, and FDA's initiation of a public docket for comment, one would have expected HPM to have complied with the spirit if not the letter of the law by identifying their client.

[I]f the application contains a [paragraph IV] certification . . . and is for a drug for which a previous application has been submitted . . . [containing] such a certification, the application shall be made effective not earlier than one hundred and eighty days after –

(I) -- the date [FDA] 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 . . . holding the patent which is the subject of the certification to be invalid or not infringed, whichever is earlier.⁴

21 U.S.C. § 355(j)(5)(B)(iv); FDCA § 505(j)(5)(B)(iv).

Even HPM and Lupin do not argue that this statutory language is ambiguous. Instead, they suggest that the FDA should “interpret” this language to mean that the FDA need not wait until 180 days before approving their later-filed ANDAs. HPM Letter at 11; Lupin at 4. That is, HPM and Lupin ask the FDA to “interpret” an unambiguous statute to mean precisely the opposite of what Congress wrote.

II. There Is No Statute, Regulation Or Case Law Under Which Cobalt May Be Found To Have Forfeited Its Statutory Right To 180 Days Of Exclusivity.

Next, HPM and Lupin ask the FDA to determine that Cobalt’s exclusivity period should somehow be forfeited. Here again, they fail to identify a statutory, regulatory or court decision that imbues the FDA with authority to do so. Instead they selectively quote from a stipulation in the litigation to suggest that Cobalt conceded its challenge to the patent.

HPM’s and Lupin’s selective quotation from this document is disingenuous at best. While they quote the stipulation that the Cobalt product would infringe the claims of the ‘722 patent, they conveniently omitted to mention that the very next sentence in the document states: *“This admission is without prejudice to Cobalt’s allegations that [various claims] of the ‘722 patent [are] invalid and unenforceable.”* Attachment 3 at 1. Indeed, from March 24, 2004, until after the entry of the stipulation on February 27, 2006, Cobalt, at the expense of millions of dollars, continued to pursue its challenge of the ‘722 patent. It was only in the midst of trial, and with the strong urging of the District Court, that Cobalt agreed to a settlement of the case. Although the Ramipril patent litigation was settled by voluntary dismissal of the parties, as part of the settlement, Cobalt did not admit to either the validity or enforceability of the ‘722 patent.

⁴ The MMA clarifies “decision of a court” to mean 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 § 1102(b)(3).

It speaks volumes that HPM's and Lupin's lead argument is based on the hope that the FDA would not notice that the very next sentence in a document preserved the invalidity and unenforceability challenges — and that the FDA would never learn how Cobalt pursued these defenses through the entire litigation process and in trial.

Finally, to the extent that HPM and Lupin are complaining that Cobalt is not today litigating the '722 patent that the Federal Circuit recently found invalidated, they have not pointed to any statutory provision or regulation that would require Cobalt to be engaged in such a futile enterprise.

III. The Only Court That Has Examined This Issue Found There Was No Statutory Basis For FDA To Administratively Convert A Paragraph IV To A Paragraph III Certification.

The only court to have considered the issue determined that the FDA does not have the authority to convert a paragraph IV certification to a paragraph III certification based upon anything other than the unambiguous statutory language. In *Mylan Pharmaceuticals, Inc. v. Thompson*, Teva made almost an identical argument with respect to Mylan's 180-day exclusivity involving Nifedipine. See *Mylan Pharmaceuticals, Inc. v. Thompson*, 207 F. Supp. 2d 476 (D. W.Va. 2001). In that case, Mylan and Pfizer had entered into a settlement agreement in which they stipulated to a dismissal of the patent litigation and subsequently Mylan launched an authorized generic version of Pfizer's Procardia® XL (nifedipine extended release). *Id.* at 481. Teva subsequently filed a Citizen Petition requesting that FDA determine that Mylan's ANDA was not eligible for or, alternatively, no longer eligible for the 180-day exclusivity. *Id.* at 482. Teva argued, like Lupin and HPM, that FDA should either require Mylan to amend its certification to a paragraph III, or that the FDA should otherwise administratively convert it to a paragraph III. See Teva Citizen Petition Docket 00P-1446, dated August 9, 2000 at 5. Teva argued in the alternative that Mylan's launch of an "authorized generic" should have triggered its exclusivity and that the exclusivity had already expired. *Id.* FDA granted Teva's Citizen Petition and Mylan brought suit shortly thereafter.⁵ See FDA Response to Teva, Docket 00P-1446.

⁵ FDA acknowledged in its Response to Teva that its regulations "regarding patent certification do not specifically address the circumstances here." FDA Response to Teva at 5. FDA noted that:

The regulations require an ANDA applicant to change its certification from a paragraph IV to a paragraph III when patent litigation determines the patent is infringed. The regulations also require an applicant to amend its certification if, before the ANDA is approved, the applicant learns that the certification is incorrect. The regulations say nothing about amending a patent certification that becomes inaccurate – other than with a finding of infringement – after an ANDA is approved.

Id. Thus, FDA has acknowledged that its regulations do not address this situation and FDA must regulate directly from the statute.

In an opinion addressing Mylan's motion for preliminary injunction, District Court Judge Stamp ruled against Mylan, finding that it had triggered its exclusivity when it began commercially marketing an authorized generic, and that the exclusivity had since expired. *See id.* at 487. However, the court plainly rejected FDA's position that it had the authority to administratively convert Mylan's paragraph IV certification to a paragraph III — exactly what Lupin and HPM argue FDA should do in this case. Because the court addressed the issue in great detail and analysis, though lengthy, we have included the full text of the relevant discussion:

The statute, while complex, is not in this Court's opinion, ambiguous. It is, however, silent on the question of Congress' intent to permit or require the agency change a "IV certification" to a "III certification," particularly where it is based upon a party's "presumed" conduct. Further, an agency in administering a program created by Congress, must be allowed to formulate policy and make rules to fill a "gap" which has been left, implicitly or explicitly, by Congress. There is an express delegation of authority to an agency to fill by regulation a gap explicitly left open by Congress. However, in this Court's opinion, there is no explicit gap in the statute on the subject of the change of a "IV certification" to a "III certification," particularly when one considers the somewhat severe results such a change by agency ruling can effect. Where there is a Congressional delegation to an agency that is implicit instead of explicit, a court still may not substitute its construction of a statutory provision for a "reasonable interpretation made by the administrator of an agency." *Chevron* at 467 U.S. 844.

While this Court fully recognizes the "considerable weight" that "should be accorded" to the FDA construction of the Hatch-Waxman Amendments, which it is entrusted to administer and the principle of deferral to administrative interpretations, *Chevron*, 467 U.S. at 844, this Court finds after a careful analysis of the FDA ruling of February 6, 2001 and the relevant statute, that the FDA's interpretation is an unreasonable one. First, there is no statutory provision which grants to the FDA, either expressly or implicitly, the authority to change a "IV certification" to a "III certification." Second, there is no FDA regulation that provides any basis for such a change. Third, the FDA ruling is based upon a presumption that is inadequately reached in this particular case. Finally, the sole precedent that the FDA relies upon, *Mylan v. Henney*, 94 F. Supp. 2d 36 (D.D.C. 2000), is clearly distinguishable because in that case Barr Laboratories, an ANDA applicant with a "IV certification" by its own actions changed its "IV certification" to a "III certification" as part of its settlement with the NDA holder. In this case, Mylan has not effected a change to its certification and there is no evidence that its settlement agreement with Pfizer requires it to make such a certification change. The FDA ruling, at least on this subject, is therefore unreasonable, even if it possesses a right to make a ruling on this subject on a "case-by-case" basis.

Id. at 487 (emphasis added). Although HPM attempts to dismiss this portion of the Court's opinion by stating that the District Court has "little experience" in these issues, the fact remains that this case, which is directly on point, remains the only case in which the Court has addressed this same precise issue. Other support cited for HPM's and Lupin's position involved only situations where the patent has already expired and the parties has not yet received final approval; thus, these cases are completely inapposite. See *Dr. Reddy's Labs., Inc. v. Thompson*, 302 F. Supp.2d 340 (D.N.J. 2003); *Ranbaxy Labs. v. FDA*, 307 F. Supp. 2d 15, (D.C. 2004), *aff'd*, 96 Fed. Appx. 1 (D.C. Cir. 2004); and *Mylan Laboratories, Inc. v. Thompson*, 332 F. Supp. 2d 106 (D.D.C. 2004), *aff'd*, 389 F. 3d 1272 (D.C. Cir. 2004). Cobalt does not dispute that where a patent has expired, it is no longer appropriate to maintain a paragraph IV certification. However, that is not the case here. In this situation, as noted by the *Mylan* Court, FDA simply does not have the statutory authority to convert Cobalt's paragraph IV certification to a paragraph III certification; and therefore should not and may not do so.

IV. Congress Expressly Declined Retroactively To Apply The Forfeiture Provisions Of The MMA To ANDA's Filed Before December 8, 2003.

HPM and Lupin essentially ask the FDA to apply the forfeiture provisions of the MMA retroactively to Cobalt specifically. The FDA should decline for two reasons.

First, Congress expressly made the decision as to whether the forfeiture provisions of the MMA would apply retroactively.⁶ Congress looked very carefully at the forfeiture provisions and whether they would be applied retroactively to applications such as Cobalt's which were submitted prior to enactment. Congress, in fact, did make one forfeiture provision retroactive: if either the Federal Trade Commission or the Attorney General files an antitrust complaint for which a final decision of a violation is upheld, "the applicant shall forfeit the 180-day exclusivity period ... without regard to when the first [paragraph IV] certification for the listed drug was made." See MMA § 1102(b)(2). Thus, it is clear that Congress carefully considered the issue of 180-day exclusivity forfeiture when they passed the MMA in 2003, and expressly decided not to enact changes which would have an impact on an application in Cobalt's situation.⁷ See *e.g.*, *Jones v. United States*, 376 F. Supp. 13, 15 (D. D.C. 1974) (describes a "classic example of the principle of *expressio unius est exclusio alterius* [the express mention of one thing excludes all others]" where "Congress dealt with the question of retroactivity in the private field when it felt that retroactive application of the 1972 amendments was necessary, i.e., those private sector Title

⁶ In the MMA, Congress provided that post-MMA applications eligible for exclusivity can forfeit exclusivity if a "forfeiture event" occurs and the applicant does not commercially launch its product within a specified period of time. See 21 U.S.C. § 355(j)(5)(D); FDCA §505(j)(5)(D) (2004).

⁷ Moreover, although HPM states authoritatively that "if this were a post-MMA case, Cobalt would almost certainly have forfeited its 180-day exclusivity," HPM Letter at 2, fn.1, this is actually incorrect. Even under the post-MMA rules, Cobalt's exclusivity would not yet have been triggered (since commercial marketing has not occurred) nor has a triggering event occurred, since there will be no final decision until the mandate issues in the *Lupin* case. See MMA § 1102(a)(1).

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VII cases pending before the EEOC on March 24, 1972, were given retroactive effect”). Therefore, arguments that FDA should interpret the statute to read in forfeiture provisions directly contradict express Congressional intent in this area.

Second, even if the FDA had the discretion to do so, it would be arbitrary and capricious for the FDA to apply the MMA forfeiture provisions retroactively to Cobalt alone, while the FDA has not applied those provisions retroactively to any other applicant under the pre-MMA version of the statute.

V. The Extraordinary Relief Sought Is Not Necessary To Avoid “Parking” Or “Blockage” Of Cobalt’s Exclusivity.

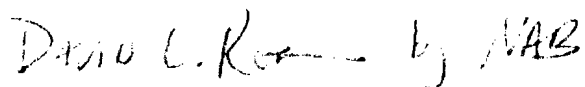
Although other applicants argue that FDA must take action to prevent the “blockage” or “parking” of its exclusivity that Cobalt has created, (Lupin Letter at 9; HPM Letter at 5), in reality this issue has already been mooted. With the Federal Circuit’s decision in the *Lupin* case, Cobalt’s exclusivity at the very latest will be triggered upon issuance of the Federal Circuit’s mandate. Therefore, this is not a situation where Cobalt’s exclusivity will continue indefinitely, rather the wheels have already been set in motion for its exclusivity to begin.

VI. Conclusion

For the foregoing reasons, FDA should take no action to grant final approval to any subsequent ANDA applicant for Ramipril Capsules until the expiration of Cobalt’s 180-day exclusivity, to be triggered by the final decision of a court or Cobalt’s commercial launch. Cobalt respectfully submits that its plans for launch are confidential business information, which Cobalt would be willing to discuss with the FDA on a confidential basis, if the FDA deems it necessary. Cobalt’s competitors, one of which was unwilling even to identify itself by name, however, should not be permitted to use a letter writing campaign to the FDA to force public disclosure of Cobalt’s confidential business plans.

Cobalt understands that an additional comment(s) has been filed to the docket, but that it is not yet publicly available at the time of this submission. Accordingly, Cobalt reserves its right to supplement this response.

Sincerely yours,



David L. Rosen, B.S. Pharm, J.D.
Nathan A. Beaver

Cc: Elizabeth Dickinson, Esq.