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October 17, 2007

BY OVERNIGHT COURIER

Division of Dockets Management
Food and Drug Administration
Room 1061 (HFA-305)
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. 2007N-0382 (180-Day Exclusivity For Ramipril Capsules)

Dear Food and Drug Administration:

Sandoz, Inc. ("Sandoz") respectfully responds to the Food and Drug Administration's ("FDA") solicitation of comments regarding 180-day exclusivity for generic ramipril capsules. Sandoz holds tentatively approved abbreviated new drug application ("ANDA") 77-514 for ramipril capsules.

For the reasons discussed below, the sponsor that was once entitled to 180-day exclusivity for this drug product is no longer eligible for that exclusivity. Thus, as soon as the U.S. Court of Appeals for the Federal Circuit issues the mandate on its September 11, 2007 decision that invalidated the '722 patent that serves as the basis for that 180-day exclusivity period, FDA should de-list that patent from the *Orange Book*. Thereafter, FDA should issue final ANDA approval to Sandoz (and any other eligible ANDA sponsor).

I. Neither Cobalt Nor Any ANDA Sponsor Is Entitled To 180-Day Exclusivity.

FDA approved Cobalt Pharmaceuticals, Inc.'s ("Cobalt") ANDA 76-549 for generic ramipril capsules on October 24, 2005. FDA's approval letter (available at www.fda.gov/cder/foi/appletter/2005/076549ltr.pdf) discloses that Cobalt was then

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eligible for 180-day exclusivity because Cobalt had submitted the first Paragraph IV certification as to U.S. Patent No. 5,061,722 (“the ’722 patent”). The approval letter further notes that Cobalt was then engaged in patent infringement litigation with regard to the ’722 patent. *Aventis Pharma Deutschland GmbH and King Pharmaceuticals, Inc. v. Cobalt Pharmaceuticals, Inc.*, Civil Action No. 03-10492 (JLT) (D. Mass.).

In that patent litigation, in March 2004, Cobalt had entered into a Stipulation (available from the federal courts’ PACER system) with the patent owner and licensee that Cobalt’s activities and product “would infringe” the ’722 patent. In April 2006, the parties to the patent litigation entered into a Stipulation of Dismissal (available from the federal courts’ PACER system), voluntarily dismissing the case without prejudice. As part of the settlement of the patent case, Cobalt entered into a Generic Distribution Agreement (available at www.sec.gov/Archives/edgar/data/1047699/000095014406004699/g00994exv10w1.txt), under which it acquired the right to market an “authorized generic” version of the innovator’s ramipril capsules at some undisclosed time in the future.

Cobalt’s ramipril ANDA is listed in the “discontinued” section of FDA’s *Orange Book*. When that “discontinued” status is coupled with Cobalt’s agreement to distribute an “authorized generic,” it is plain that Cobalt has no intentions of marketing a generic product under its ANDA in the foreseeable future. Despite that reality, Cobalt has apparently maintained its Paragraph IV certification. Cobalt has “parked” its 180-day exclusivity, thereby blocking the entire market for generic ramipril capsules, to the

detriment of consumers, federal and state governments, third party payors, and firms like Sandoz.

Under very similar circumstances, FDA determined in 2001 that an ANDA sponsor situated like Cobalt had lost its eligibility for 180-day exclusivity. FDA should follow the same reasoning here, as the similarities between the two situations are striking.

In that 2001 matter, Mylan Pharmaceuticals, Inc. ("Mylan") had been the first to file an ANDA for nifedipine extended release tablets with a Paragraph IV certification. The patent holder sued Mylan for infringement. To settle the patent infringement litigation, Mylan entered into an "authorized generic" licensing and distribution agreement with the innovator sponsor, just like Cobalt. Mylan did not change its Paragraph IV certification to a Paragraph III certification, despite having abandoned its patent challenge, again, just like Cobalt. Mylan had not marketed its generic product for over one year, despite having received final approval. In comparison, Cobalt's situation is even more egregious, as Cobalt has not marketed its generic product in the almost two years since it received final approval on October 24, 2005. The bottom line is that Mylan effectively blocked the generic market by "parking" its 180-day exclusivity, just as Cobalt has done and is doing here with regard to ramipril capsules.

In response to a citizen petition, FDA concluded that Mylan's settlement of patent litigation had "effectively changed" its Paragraph IV certification to a Paragraph III certification, leading to Mylan's loss of eligibility for 180-day exclusivity. *See Mylan Pharmaceuticals, Inc. v. Thompson*, 207 F. Supp. 2d 476 (N. D. W. Va. 2001). To the

best of our knowledge, FDA has never renounced this sound position, and thus should – if not must – follow it, to conclude that Cobalt lost its 180-day exclusivity.¹

Mylan challenged FDA’s decision that its Paragraph IV certification for extended release nifedipine tablets had been “effectively changed” to a Paragraph III certification. 207 F. Supp.2d 476. Although the West Virginia district court rejected FDA’s decision, *see* 207 F. Supp. at 486-88, Sandoz does not believe that the district court’s decision should be viewed as “controlling” for several sound reasons.

As a threshold matter, the West Virginia court’s decision was not a final decision on the merits; rather, it was reached only in the context of Mylan’s motion for a preliminary injunction. 207 F. Supp. 2d at 487-88 (court stating that “there is, *at least at this point*, some likelihood of success by plaintiff Mylan on this feature of the FDA ruling” (emphasis added)).

The West Virginia district court articulated several separate reasons for its conclusion that FDA’s interpretation was unreasonable. 207 F. Supp. 2d at 487. The first and second reasons were that there was no statutory provision and no FDA regulation that provide a basis for FDA’s authority to change a certification. That was 2001. Since then, the courts have had several occasions to consider – and uphold – FDA’s actions in closely related contexts where FDA has deemed patent certifications to have been changed by operation of law, despite the failure of the ANDA sponsors to take

¹ While an agency may change its position, it must be able to present an adequate basis and explanation for doing so. *Motor Vehicle Manufacturers Association of the United States v. State Farm Mutual Automobile Insurance Company*, 463 U.S. 29, 57 (1983). Here, we are not aware of any basis that has ever been articulated by FDA to support a change in agency position.

action. Twice, the U.S. Court of Appeals for the District of Columbia Circuit – the appellate court with by far the most experience with generic drug exclusivity issues – has upheld FDA’s authority to convert a Paragraph IV certification to a Paragraph II certification. *Mylan Laboratories, Inc. v. Thompson*, 389 F. 3d 1272 (D. C. Cir. 2004) (involving fentanyl patch); *Ranbaxy Laboratories, Inc. v. Food and Drug Administration*, 307 F. Supp. 2d 15 (D.D.C. 2004), *affirmed*, 96 Fed. Appx. 1 (D.C. Cir. 2004) (involving fluconazole). A New Jersey federal district court reached a similar conclusion. *Dr. Reddy’s Laboratories, Inc. v. Thompson*, 302 F. Supp. 2d 340 (D.N.J. 2004) (involving omeprazole). These courts upheld FDA’s decisions even though there was neither an express statutory provision nor a directly on-point FDA regulation on the change in patent certification.

The third basis for the West Virginia district court’s decision stemmed from the fact that FDA had “*presume[d]* that Mylan believes that the product described in its ANDA may infringe the listed patent.” 207 F. Supp. 2d at 486 (emphasis in original). The court concluded that “the FDA ruling is based upon a presumption that is inadequately reached in this particular case.” 207 F. Supp. 2d at 487. With regard to ramipril capsules, no presumption by FDA is needed, since (as noted above) Cobalt has already admitted infringement.

For these reasons, the reasoning of the West Virginia district court in the *Mylan* nifedipine litigation is easily distinguished. The *Mylan* nifedipine decision does not require FDA to abandon its 2001 interpretation that an ANDA sponsor who settles patent litigation and enters into an “authorized generic” agreement has effectively converted its

Paragraph IV certification to a Paragraph III certification and thereby loses its eligibility for 180-day exclusivity.² FDA's nifedipine rationale should apply here, leading to the conclusion that Cobalt's patent certification has been converted to a Paragraph III. Without a valid Paragraph IV certification to the '722 patent, it follows that Cobalt cannot be entitled to any 180-day exclusivity that would delay the final approval of any subsequent ANDA sponsors (such as Sandoz).

II. FDA Should De-List the '722 Patent From The *Orange Book* And Issue Final Approvals To All Tentatively Approved ANDAs As Soon As The Federal Circuit Issues The Mandate On Its Decision That The '722 Patent Is Invalid.

The discussion in this section is based on the assumption that, for the reasons discussed in Section I, Cobalt has lost its eligibility for 180-day exclusivity.

In separate Paragraph IV litigation involving the '722 patent and another ANDA sponsor, Lupin Pharmaceuticals, Inc. ("Lupin"), the district court had held that the '722 patent was valid. Lupin appealed. On September 11, 2007, the U.S. Court of Appeals for the Federal Circuit reversed the district court and held that all asserted claims of the '722 patent were invalid; the court did not remand for any further proceedings consistent with its decision. *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, ___ F.3d ___, 2007 WL 2593791 (Fed. Cir. 2007). As of the date of this letter, the Federal Circuit had not yet issued its mandate.

It is FDA's longstanding interpretation that the agency will give effect to a Federal Circuit decision of invalidity, where the Federal Circuit reversed a district court

² The West Virginia district court ruled for FDA on alternative grounds, so FDA had no reason to appeal. Mylan appealed to the Fourth Circuit, but subsequently dismissed its appeal.

decision upholding the patent, when the Federal Circuit issues its mandate.³ FDA's views on this topic are set forth in its *Guidance for Industry, Court Decisions, ANDA Approvals and 180-Day Exclusivity under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act* ("Guidance") (March 2000) (availability announced in 65 Fed. Reg. 16,922 (March 30, 2000)), where the agency stated:

If the district court finds the patent is infringed, but that decision is reversed on appeal, the Agency may approve the ANDA on the date the district court issues a decision that the patent is invalid, unenforceable, or not infringed pursuant to a mandate issued by a court of appeals.

Guidance at 4.⁴

Although the quoted language from FDA's March 2000 *Guidance* turns on the date of the district court's judgment following issuance of the Federal Circuit's mandate, waiting until the district court issues judgment would not serve a meaningful purpose in this case. Here, as noted, the Federal Circuit reversed, and did not remand for further proceedings consistent with its opinion. As a result, the only action left for the district court following issuance of the mandate is the ministerial act of closing its case file. *See* 28 U.S.C. § 2106. In the recent amlodipine

³ This is also the approach that FDA recently followed in its April 18, 2007 decision with regard to amlodipine besylate tablets ANDAs in a closely related context. *See* FDA amlodipine letter (available at www.fda.gov/ohrms/dockets/dockets/07n0123/07n-0123-let0002-vol1.pdf) at 8-9.

⁴ The *Guidance* was issued before 21 U.S.C. § 355(j)(5)(B)(iii) was amended in 2003 by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA"), Pub. L. No. 108-173. In relevant part, the MMA merely codified the agency interpretation that the March 2000 *Guidance* was intended to help implement, namely, the agency's acquiescence in the interpretation that a *district* court decision of patent non-infringement or invalidity would end the 30-month delay of final approval period under section 355(j)(5)(B)(iii) as it then existed. Current section 355(j)(5)(B)(iii), as amended by the MMA, explicitly continues that approach. Under these circumstances, there was no reason for the agency to change its interpretation, as set forth in the March 2000 *Guidance*, after enactment of the MMA and FDA did not do so.

matter, where the Federal Circuit also reversed the district court and held all asserted claims of the patent invalid without remanding for further proceedings consistent with its opinion, FDA gave effect to the Federal Circuit decision when the mandate issued. *See* FDA amlodipine letter at 8-9. FDA should follow the same approach here.

Therefore, immediately upon issuance of the Federal Circuit's mandate, FDA should deem the '722 patent to be de-listed from the *Orange Book* by operation of law. FDA should not wait until the innovator drug sponsor formally requests that the '722 patent be removed from the *Orange Book*. Waiting for such a request would be elevating form over substance and be contrary to the Hatch-Waxman goal of providing lower cost generic drugs to the marketplace as quickly as possible. The innovator sponsor could refuse to request de-listing of its patent, possibly on the basis that there is no express statutory provision or regulation that compels such action. At a minimum, that sponsor's de-listing request might have to be subject to its own detailed review process, a potentially time-consuming step.

Moreover, FDA has repeatedly stated that the agency does not possess any expertise in patent listing, and that its role in patent listings is only ministerial. This view has been accepted by the courts. *See, e.g., aaiPharma Incorporated v. Thompson*, 296 F.3d 227, 237-41 (4th Cir. 2002). De-listing of the '722 patent in this instance would be fully consistent with FDA's ministerial role since, as noted, the Federal Circuit held all asserted claims of the patent to be invalid.

We note that 21 C.F.R. § 314.94(a)(12)(viii)(B) presents no obstacle to de-listing the '722 patent. This regulation provides that a patent that is the subject of a Paragraph IV certification lawsuit "shall not be removed from the [*Orange Book*] until FDA *determines* either

that no delay in effective dates of approval is required under [21 C.F.R. § 314.107(c)] as a result of the lawsuit, that the patent expired, or that any such period of delay in effective dates of approval has ended.” (Emphasis added.) Here, as discussed in section I above, Cobalt is not entitled to any 180-day exclusivity and there is, therefore, no basis for delaying final approval of tentatively-approved ramipril ANDAs.

Sandoz’s ANDA includes a Paragraph III certification to the ’722 patent. Once the ’722 patent is de-listed from the *Orange Book*, Sandoz can remove the Paragraph III certification from its ANDA and receive final ANDA approval.

III. No ANDA Sponsor Is Entitled To A “Head Start.”

Lupin’s comment in this docket contends that Lupin, as the ANDA sponsor that succeeded in invalidating the ’722 patent, is entitled to immediate final approval and a “head start” over other ANDA sponsors. Lupin’s arguments are without merit and contrary to longstanding FDA interpretations of the relevant statutory language.

As a threshold matter, we note that Lupin has not received tentative approval of its ramipril ANDA, and Lupin does not represent in its comment that it has met all substantive ANDA approval requirements (*e.g.*, bioequivalency, chemistry, manufacturing, labeling). On that basis alone, Lupin’s request for immediate final approval should fail.

Lupin asserts that it should be entitled *at this time* to change its Paragraph IV certification to the ’722 patent to a “no relevant patents” statement, as authorized by 21 C.F.R. § 314.107(a)(12)(ii) where appropriate. That argument is easily dismissed. So long as the ’722 patent is in the *Orange Book*, Lupin must address it by means of an appropriate patent

certification.⁵ See 21 U.S.C. § 355(j)(2)(A)(vii) and 21 C.F.R. § 314.94(a)(12)(i). A “no relevant patents” statement with regard to the ’722 patent while it remains in the *Orange Book* would be “an untrue statement of material fact” that would be a basis for FDA to refuse to approve the ANDA. See 21 U.S.C. § 355(j)(4)(K) and 21 C.F.R. § 314.125(b)(7).

Lupin’s request for immediate final approval also ignores the fact that it is currently subject to a 30-month delay of final approval under section 355(j)(5)(B)(iii) that (according to the facts set forth in Lupin’s comment) does not expire until December 8, 2007. Lupin completely ignores longstanding agency practice in situations such as this, where the district court upheld the patent but the Federal Circuit reversed and held the patent to be invalid and/or not infringed. Specifically, the date of the Federal Circuit’s mandate is controlling. As discussed in Section II, this is the same date FDA applies to giving effect to a court decision invalidating an *Orange Book* patent for purposes of de-listing the patent from the *Orange Book*. In fact, FDA’s March 2000 *Guidance* states that it is expressly applicable to decisions regarding the 30-month delay of final ANDA approval under 21 U.S.C. § 355(j)(5)(B)(iii). *Guidance* at 4. Thus, even assuming Lupin is otherwise entitled to final approval at all, there is no basis for approving Lupin before any other ANDA sponsors.

Lupin raises a number of “fairness” arguments in support of its contention that it is entitled to special treatment, but it articulates no statutory or regulatory basis for that purported distinction. Lupin cites FDA’s recent amlodipine decision as a basis for special treatment, but in fact amlodipine cuts against Lupin. In the amlodipine matter, Apotex Inc. (“Apotex”) was the subsequent ANDA sponsor that was the first to prevail in patent litigation. As noted, FDA gave

⁵ Since the ’722 patent is not a method of use patent, a “(viii) statement” is not an option.

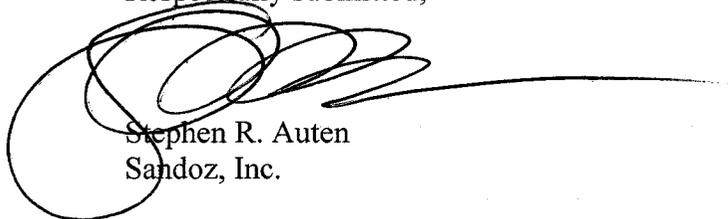
effect to Apotex's Federal Circuit victory on the date of the Federal Circuit's mandate and issued final approval to Apotex on the basis of that mandate. Although FDA did not issue final approvals to other amlodipine ANDA sponsors based on the Federal Circuit mandate, the agency's decision was based on the peculiar workings of the pediatric exclusivity statutory provisions involved. *See* FDA amlodipine letter at 9-10. Those provisions and FDA's reasoning are of no applicability to ramipril. Finally, FDA's amlodipine decision was in no way based on equity or fairness grounds. Thus, the amlodipine matter does not help Lupin at all.

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For the reasons stated, Sandoz urges FDA to conclude that Cobalt is not entitled to any 180-day exclusivity for generic ramipril capsules. As soon as the Federal Circuit issues the mandate on its September 11, 2007 decision holding the '722 patent invalid, FDA should deem the patent to be de-listed from the *Orange Book* by operation of law. Thereafter, Sandoz (and any other otherwise eligible ANDA sponsor) should receive final approval. No ANDA sponsor is entitled to a "head start."

Sandoz appreciates the agency's attention to this important matter.

Respectfully submitted,



Stephen R. Auten
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