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October 24, 2007

Dockets Management Branch
Room 1061, Mail Stop HFA-305
5630 Fishers Lane
Rockville, Maryland 20852

Re: Docket 07N-0382 – Ramipril Capsules and 180-Day Exclusivity

Dear Sir or Madam:

The Food and Drug Administration ("FDA") has invited comment regarding 180-day exclusivity for Ramipril Capsules.[1] Simply put, FDA must honor the applicable statutory "trigger" provisions when approving abbreviated new drug applications ("ANDAs") for Ramipril Capsules. For these ANDA products subject to pre-Medicare Modernization Act ("MMA") law, there remain two – and only two – events that may trigger running of a 180-day exclusivity period to which the first Paragraph IV filer is entitled. They are:

1. Notification to FDA by the first Paragraph IV ANDA filer that commercial marketing has commenced under the first filer's ANDA; or

2. A decision of a court in ANDA-related patent infringement litigation, holding a patent subject to a Paragraph IV certification to be invalid or not infringed.[2]

Former 21 U.S.C. § 355(j)(5)(B)(iv) (prior to Dec. 8, 2003). Neither triggering event appears to have occurred in this case, although the second may be reasonably close at hand. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, Civil Action No. 06-1530 (RGD) (Fed. Cir. 2007). Until such a statutorily sanctioned triggering event occurs, there is no basis to approve a subsequently filed ANDA for Ramipril Capsules.

[1] The facts surrounding this issue are described in detail in comments previously filed to this docket. Hence, we do not repeat them, but simply note that Cobalt Pharmaceuticals, Inc. appears to have been the first applicant to submit a substantially complete ANDA containing a Paragraph IV patent certification. Cobalt's product has been approved, but has not been commercially marketed. Lupin Pharmaceuticals, Inc. appears to have filed a subsequent Paragraph IV-containing ANDA.

[2] The MMA clarified that "decision of a court" in relevant context means "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." Pub. L. 108-173, § 1101(c) (Dec. 8, 2003).

2007N-0382 C4

FDA and the courts determined years ago that a 180-day triggering court decision may arise in litigation involving *either* a first Paragraph IV ANDA filer *or a subsequent* Paragraph IV filer. *See Granutec, Inc. v. Shalala*, 1998 U.S. App. LEXIS 6685, Nos. 97-1873, 97-1874, slip op. at 14-18 (4th Cir., April 3, 1998) (unpublished opinion). Thus, a second Paragraph IV filer can cause running of the first filer's 180-day period through a successful patent challenge. Lupin, the second filer with respect to Ramipril Capsules, has taken the steps necessary to trigger the exclusivity of Cobalt by challenging the validity of the ramipril patent and, if the mandate issues, will have successfully done so.

The law and facts interact in straightforward manner in this case. Cobalt was the first applicant to file an ANDA containing a Paragraph IV certification and is entitled to 180-day exclusivity. Former 21 U.S.C. § 355(j)(5)(B)(iv). Lupin filed a subsequent ANDA containing a Paragraph IV certification; challenged the Orange Book-listed patent (U.S. Patent No. 5,061,722) that is delaying its final approval; and, on September 11, 2007, invalidated the patent at the U.S. Court of Appeals for the Federal Circuit. This decision currently is the subject of a petition for rehearing and rehearing *en banc*, and thus is not yet a final decision of the Court of Appeals. Should the decision finally issue in favor in Lupin, it will trigger running of Cobalt's 180-day exclusivity, and *after that period expires*, subsequent ANDA filers (including Lupin) may receive final FDA approval (assuming they are otherwise eligible).

Other comments submitted to the docket highlight creative legal arguments that ignore the text of the applicable Hatch-Waxman statute in an effort to correct a perceived abuse of the system. These comments would allow FDA to potentially curtail a first Paragraph IV filer's 180-day exclusivity (but presumably only after exhaustive and highly specific, case-by-case analysis of facts and circumstances). FDA should reject these arguments as not supported by law, because they appear nowhere in the statute or existing regulations. *See Mylan Pharmaceuticals, Inc. v. Thompson*, 207 F. Supp. 2d 476, 487 (N.D. W.Va. 2001) ("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.").[3]

[3] Although the court in *Mylan* found FDA's interpretation of the "commercial marketing" trigger potentially reasonable, it does not appear that Cobalt has marketed any Ramipril Capsules following approval of its ANDA. The commercial marketing trigger has not been pulled.

The original Hatch-Waxman provisions have never have been judged to be perfect, but they are legally binding.[4] FDA does not have the authority to cure any perceived defects in this case. Any correction is properly done only through means other than the FDA, such as legislative change or enforcement of other statutes like antitrust or unfair competition laws. In fact, Congress has already addressed the perceived problem in this case by modifying the statute to adopt numerous forfeiture events when it passed the MMA. The exclusivity rules applicable to pre-MMA ANDAs, however, allow only two statutory triggers: first commercial marketing and a court decision of patent invalidity or non-infringement. Until one of the events occurs, the agency has no lawful basis to regard Cobalt's 180-day period applicable to Ramipril Capsules as eliminated.[5]

Sincerely,

E. Brendan Magrab
Executive Vice President of Commercial Operations &
General Counsel

EBM/ph
cc: Gary Buehler, R.Ph., Director
Cecelia Parise, Regulatory Policy Advisor
Office of Generic Drugs, CDER, FDA

[4] *E.g.*, Granutec slip op. at 17, n. 3 ("[T]his problem, like many others, arises from the manner in which Congress drafted the exclusivity mechanism, and, as such, the remedy lies with Congress.")

[5] This approach also is most consistent with a recent FDA policy statement concerning application of the 180-day "court decision" trigger. The agency determined to: "adhere[ ] closely to the language of the statute, and ... provide a bright line that is more easily administrable by FDA and that will enable industry to make appropriate business planning decisions." *See* Letter from Gary Buehler, Director, Office of Generic Drugs, FDA to Pravastatin ANDA Applicants (April 11, 2006 (available at http://www.fda.gov/cder/ogd/announce/Pravastatin-180Day-amend.pdf)).