

OCT 19 2010

Food and Drug Administration
Rockville MD 20857

Gerald F. Masoudi
Covington & Burling LLP
1201 Pennsylvania Avenue, NW
Washington, DC 20004-2401

Re: Docket No. FDA-2010-P-0223

Dear Mr. Masoudi:

This letter responds to your citizen petition submitted on behalf of Genzyme Corporation (Genzyme), which was received by the Food and Drug Administration (FDA or Agency) on April 27, 2010 (Petition). Your petition requests that FDA confirm that it will stay approval of abbreviated new drug application (ANDA) 90-040 for doxercalciferol injection, absent another specified event under 21 U.S. C. 355(j)(5)(B)(iii) (section 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act (FFDC Act or the Act)), for 30 months from November 24, 2009, the date Genzyme received a notice of a paragraph IV certification from Cobrek Pharmaceuticals, Inc. (Cobrek) regarding U.S. Patent No. 5,602,116 (the '116 patent).

Specifically, you request that FDA confirm that the Act requires a "second" 30-month stay,¹ despite there having been a prior 30-month stay of approval of Cobrek's ANDA based on a prior paragraph IV certification and patent infringement lawsuit regarding the '116 patent. You assert that this request should be granted because section 505(j)(5)(B)(iii) of the Act requires a separate 30-month stay analysis for each paragraph IV certification to a listed patent. You claim that under this analysis, all of the statutory requirements for a 30-month stay with respect to this paragraph IV certification have been met: (1) Genzyme filed information regarding the '116 patent for listing in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) before the date on which Cobrek's ANDA was submitted; (2) Cobrek made a paragraph IV certification to the '116 patent; and (3) Genzyme filed a patent infringement lawsuit within 45 days of receiving notice for infringement of the '116 patent.²

¹ The Petition refers to this as a "second" 30-month stay. It might, however, be more appropriately referred to as a superseding stay. The first stay was related to a formulation covered by the ANDA as initially submitted. As discussed in the text, however, that formulation was subsequently abandoned and the stay at issue here relates to the revised formulation.

² The FDA regulation at 21 CFR 314.430(b) provides that "FDA will not publicly disclose the existence of an application or abbreviated application before an approval letter is sent to the applicant under 314.105 or tentative approval letter is sent to the applicant under 314.107, unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged." In analyzing and responding to your petition, the Agency has relied generally on the description of the facts provided in submissions to the dockets by you and in comments submitted in response to your petition at Docket. FDA-2010-P-0223. Existence of any pending abbreviated new drug application at issue in this petition has been disclosed or acknowledged by virtue of notice of paragraph IV certifications.

You ask that FDA grant this request regardless of whether the 2003 amendments to the FDCA brought about by the Medicare Prescription Drug, Improvement, and Modernization Act (MMA)³ apply to this case. Specifically, you believe that the MMA's prohibitions against some successive 30-month stays — those arising from certifications to patents listed after an ANDA is filed — are inapplicable in this instance because the '116 patent was listed by Genzyme before the MMA was enacted. However, you also assert that should the MMA be found to apply in this instance, the additional criterion for a 30-month stay would be satisfied because the '116 patent was listed in 1999, prior to the submission of Cobrek's ANDA.

We have carefully considered your petition as well as comments to your petition submitted by Cobrek on May 20, 2010 (Cobrek's Comments). For the reasons described below, your petition is granted.

I. BACKGROUND

A. Genzyme's NDA for Hectorol

Genzyme's new drug application (NDA) 21-027 for Hectorol (doxercalciferol injection, 2 micrograms/milliliter (mcg/mL), aseptically formulated in ampules) was first approved on April 6, 2000, as a treatment for secondary hyperparathyroidism in patients with end stage renal disease. Genzyme submitted the '116 patent titled "Method for Treating and Preventing Secondary Hyperparathyroidism" for listing in the Orange Book on February 1, 1999, certifying that the '116 patent claims one or more methods of use for which approval of the NDA was sought. The '116 patent expires on February 11, 2014.

On December 8, 2008, FDA approved Genzyme's supplemental new drug application (sNDA or supplement) for a new injectable formulation and packaging configuration for Hectorol (PAS-015, a terminally sterilized formulation in amber glass, stoppered vials).⁴ Within 30 days of the approval of the supplement, Genzyme submitted patent listing information for the '116 patent as well as U.S. Patent No. 7,148,211 (the '211 patent) titled "Formulation for Lipophilic Agents," which you assert claims the vial formulation of Hectorol. The '211 patent issued on December 12, 2006, and expires on September 14, 2023.

Following FDA approval of the Hectorol vial product, Genzyme states that it intends to withdraw the Hectorol ampule product from sale (Petition at 5).⁵

³ Pub. L. No. 108-173.

⁴ The new formulation was developed to produce a formulation that could be terminally sterilized rather than aseptically processed (Letter from FDA to Lachman Consultant Services, Inc., July 29, 2010, at 1 (Docket No. FDA-2009-P-0088)).

⁵ Genzyme has indicated that the original ampule formulation is no longer being manufactured. Genzyme has also indicated to FDA that it plans to discontinue the product once the current supply of ampules is exhausted in the marketplace.

B. Cobrek's ANDA for a Generic Version of Hectorol

Cobrek⁶ submitted an ANDA for doxercalciferol injection, 2 mcg/mL, on October 13, 2007 (ANDA 90-040), citing Genzyme's Hectorol injection 2 mcg/mL formulation aseptically processed in ampules as the reference listed drug (RLD). The ANDA contained paragraph IV certifications to the '116 patent among other patents.⁷ Under section 505(j)(2)(B)(i)-(ii) of the Act, Cobrek notified Genzyme of its ANDA and its paragraph IV certification regarding the '116 patent, among other listed patents. Within 45 days of being notified, Genzyme initiated a lawsuit against Cobrek asserting the '116 patent.⁸ This lawsuit triggered a 30-month stay on the Agency's approval of ANDA No. 90-040. Cobrek states that because the '116 patent contains only method-of-use claims that cover the approved indications for Hectorol, it asserted only invalidity of the '116 patent in its notice letter to Genzyme (Cobrek's Comments at 3). Moreover, Cobrek also states that throughout the resulting patent litigation it has asserted only invalidity of the '116 patent, having admitted infringing the '116 patent (Cobrek's Comments at 3).

Shortly after Genzyme's NDA supplement was approved and the '211 patent was listed in the Orange Book, Cobrek submitted to FDA a paragraph IV certification to the newly listed '211 patent and notified Genzyme of the same. Genzyme did not initiate patent litigation against Cobrek based on this paragraph IV certification as it believed that Cobrek's ampule formulation for which it was seeking approval at the time would not infringe the '211 patent claims.

Soon thereafter, FDA informed Cobrek that ANDA 90-040 could not be approved because the ampule formulation was not qualitatively and quantitatively (Q-and-Q) the same as Genzyme's reformulated RLD in vials. FDA recommended that Cobrek reformulate its test product to be Q-and-Q the same as Genzyme's reformulated RLD product. Cobrek reformulated its product as recommended and amended its ANDA in 2009 to include the reformulated product.

FDA subsequently informed Cobrek that its amendment to its ANDA would not be accepted for review unless accompanied by new patent certifications to both the '211 and the '116 patents. FDA also informed Cobrek that it had the option of seeking approval for the prior ampule formulation by filing a citizen petition in accordance with the regulations in 21 CFR 314.161. Under the regulations, Cobrek could request that FDA provide a determination on whether the ampule formulation of Hectorol had been

⁶ ANDA 90-040 was originally filed by Pentech Pharmaceuticals, Inc. Cobrek subsequently acquired all rights to the ANDA.

⁷ The other patents to which Cobrek filed a paragraph IV certification were Patent Nos. 6,903,083 and 5,707,980 (the '083 and '980 patents, respectively). Genzyme has since requested that FDA delist both of these patents from the Orange Book.

⁸ *Bone Care International LLC et al. v. Pentech Pharmaceuticals, Inc.*, 08-cv-1083 (N.D. Ill.).

withdrawn for safety or effectiveness reasons.⁹ Cobrek, however, chose to continue to seek approval of its reformulated product and certified to the ‘116 and the ‘211 patents in its ANDA amendment submission. Concurrently, Cobrek informed Genzyme in its notice letter that it was seeking approval of a generic version of Genzyme’s reformulated vial product under ANDA 90-040, and that it had submitted two paragraph IV certifications with respect to the ‘116 and ‘211 patents. Within 45 days of receiving this notice letter, Genzyme filed a suit on January 7, 2010, alleging infringement of both patents.¹⁰

C. Statutory and Regulatory Requirements

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) of the Act. See also 21 CFR 314.94(a)(12)(i)(A).)

⁹ FDA received a petition under 21 CFR 314.161 from a third party (Lachman Consultant Services, Inc.) on February 17, 2009 (Docket No. FDA-2009-P-0088), requesting that the Agency determine whether the ampule formulation had been voluntarily withdrawn or withheld from sale for safety or efficacy reasons (Lachman Petition). This petition also requested that FDA determine whether the ampule formulation approved under an ANDA would be considered therapeutically equivalent to the vial formulation.

FDA determined that the ampule formulation was safe and effective for the labeled conditions of use and was not withdrawn from the market for reasons of safety or efficacy, and thus ANDAs that refer to the ampule formulation as the RLD may be approved by the Agency if all other legal and regulatory requirements for the approval of ANDAs are met (Letter from FDA to Lachman Consultant Services, Inc., July 29, 2010, at 1 (Docket No. FDA-2009-P-0088) (FDA Response to Lachman Petition)). The Agency also determined that any doxercalciferol injection ampule formulation approved under an ANDA would be considered therapeutically equivalent to the vial formulation approved on December 5, 2008, and thus would receive an AP rating in the Orange Book (FDA Response to Lachman Petition at 3). An AP rating granted to an injectable aqueous solution signifies that FDA considers the product therapeutically equivalent and, therefore, substitutable where permitted by the prescriber.

¹⁰ *Genzyme Corporation v. Cobrek Pharmaceuticals, Inc.*, No. 1:10-cv-00112 (N.D. Ill.).

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) of the Act). 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 receipt of the notice, unless a court orders otherwise (section 505(j)(5)(B)(iii) of the Act).

Until August 18, 2003, section 505(j)(5)(B)(iii) of the Act permitted a 30-month stay regardless of when the patent at issue was submitted to FDA. This resulted in ANDAs being subjected to multiple overlapping 30-month stays, as NDA holders submitted new patents to FDA well after the ANDA had been submitted and after the initiation of an earlier 30-month stay (see Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study*, at iv-v (July 2002), available on the Internet at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>). Concern over the significant delays in generic drug approvals resulting from multiple 30-month stays led to passage of the MMA. The MMA included provisions modifying section 505(j)(5)(B)(iii) of the Act to reduce the availability of 30-month stays (149 Cong. Rec. S15882 at S15884 (Nov. 25, 2003) (statement of Senator Kennedy that Hatch-Waxman provisions of MMA “will stop the multiple, successive 30-month stays that the Federal Trade Commission identified as having delayed approval of generic versions of several blockbuster drugs and cost consumers billions of dollars”)).

Under the FFDC Act as amended by the MMA, a 30-month stay is available only when the patent at issue in the paragraph IV-related litigation was submitted by the NDA holder to FDA before the ANDA was submitted (section 505(j)(2)(B)(iii) of the Act). No 30-month stay is available when the NDA holder or patent owner sues as a result of a paragraph IV certification to a patent for which information is submitted following the submission of the ANDA (FDA guidance for industry on *Listed Drugs, 30-Month Stays, and Approval of ANDAs and 505(b)(2) Applications Under Hatch-Waxman, as Amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Questions and Answers* (Guidance), at 9 (Oct. 2004)). As noted by the Guidance, “the MMA generally precludes multiple 30-month stays for those applications to which it applies” but does not preclude multiple 30-month stays in all circumstances (Guidance at 8). The Guidance explains that:

[t]he relevant provisions of the MMA apply to patents submitted to FDA on or after August 18, 2003. For ANDAs and 505(b)(2) applications with paragraph IV certifications to a patent submitted to FDA on or after August 18, 2003, the MMA provides that a 30-month stay may be available for litigation related to that patent only if the patent was submitted to FDA before the date that the ANDA or 505(b)(2) application (excluding an amendment or supplement) was submitted.

In other words, the MMA precludes 30-month stays for later listed patents, that is, those patents submitted to FDA on or after the date the ANDA or 505(b)(2) application was submitted. Because of this limitation, in most cases, ANDAs and 505(b)(2) applications will be subject to no more than one 30-month stay.

(Guidance at 8.)

The Guidance cautions, however, that “[m]ultiple 30-month stays . . . may be possible in certain cases” (Guidance at 8). One scenario envisioned by the Guidance in which multiple 30-month stays are possible is one in which an ANDA containing a paragraph III and a paragraph IV certification (to patents submitted after August 18, 2003, and before the ANDA was submitted) is amended by the ANDA applicant to convert the paragraph III certification to a paragraph IV certification (Guidance at 8). In such a scenario, both the original paragraph IV certification and the new paragraph IV certification could give rise to separate 30-month stays.

II. ANALYSIS

You assert that under section 505(j)(5)(B) of the Act, each paragraph IV certification to a patent that claims the drug at issue requires a separate 30-month-stay analysis, which entails determining whether all the statutory requirements for a 30-month stay have been met (Petition at 1). You thus claim that just as Genzyme’s first infringement action asserting the ‘116 patent with respect to the ampule product triggered its own 30-month stay, the Act requires a 30-month stay beginning on November 24, 2009, based on Cobrek’s paragraph IV certification asserting invalidity of the ‘116 patent with respect to the vial product (Petition at 7).

You claim that the plain and unambiguous language of section 505(j)(5)(B)(iii) of the Act provides that when an ANDA applicant submits a paragraph IV certification and the patent holder brings an infringement action within 45 days of receipt of notice of the paragraph IV certification, approval of the ANDA is stayed for 30 months (Petition at 6). You recognize, however, that under this same statutory provision, a 30-month stay is available under the MMA only if the patent that is the subject of the certification was submitted for listing in the Orange Book before the ANDA was submitted to the FDA (Petition at 6). You note that these additional restrictions on 30-month stays set forth in the 2003 MMA amendments apply only to patents listed in the Orange Book on or after August 18, 2003.¹¹ Accordingly, you take the position that because “the ‘116 patent was initially listed in the Orange Book in 1999, the pre-MMA provisions apply in this instance (Petition at 7). You nevertheless argue that, even if the MMA applied, the additional criterion for a 30-month stay would be satisfied because Genzyme listed the ‘116 patent before Cobrek submitted ANDA 90-040 to FDA (Petition at 7).

¹¹ The MMA provisions relating to 30-month stays “apply with respect to any patent information submitted under subsection (b)(1) or (c)(2) of section 505 of the [Act] on or after August 18, 2003.” Pub. L. 108-173, Section 1101(c)(3).

Cobrek, on the other hand, argues that the MMA does apply here, apparently because patent information on the ‘116 patent was submitted a second time with respect to the amendment covering the reformulation of this drug on December 26, 2008, after the August 18, 2003 effective date of the MMA with respect to submission of patent information. Determination of whether or not the MMA applies thus depends on whether one concludes that the operative submission of patent information was in 1999 or in 2008. Because we conclude that the relief requested in your petition must be granted even if the MMA applies, we need not resolve the issue of whether or not that amendment applies.

You assert that under the plain language of the statute, a 30-month stay is appropriate as all the requirements for a 30-month stay are met — Cobrek filed a paragraph IV certification on November 24, 2009, asserting the invalidity of the ‘116 patent, and Genzyme timely brought an infringement action based on this paragraph IV certification regarding a patent for which information was submitted to the FDA before the date on which the ANDA was submitted (Petition at 7).¹² You claim that this infringement suit is specific to the reformulated product, but distinct from the litigation regarding the original product (even though the method-of-use claims asserted are the same) (Petition at 7). You thus conclude that Genzyme is entitled to a 30-month stay to resolve the infringement suit brought in response to the paragraph IV certification regarding the ‘116 patent made in 2009 in connection with the reformulated product (Petition at 8).

We agree that Genzyme is entitled to a 30-month stay stemming from Cobrek’s paragraph IV certification made in connection with the reformulated product and Genzyme’s resulting patent infringement. Genzyme is entitled to this 30-month stay regardless of the fact that Cobrek was relying on an invalidity defense in both lawsuits, or that, as Cobrek contends, reformulation of its product would have no impact on the ongoing litigation regarding the validity of the ‘116 patent (see Cobrek’s Comments at 4).¹³ Once Cobrek made the paragraph IV certification, and Genzyme subsequently sued Cobrek for infringing the ‘116 patent, the statutory requirements for a 30-month stay with respect to this paragraph IV certification were met, as the information concerning the ‘116 patent was submitted to FDA before either the original submission of the ANDA to

¹² Any argument concerning this point would require adoption of a certain illogic: Either what is at issue is the ANDA itself, in which case the 1999 patent information submission preceded the 2007 ANDA submission, or the amendment covering the reformulation, in which case the 2008 resubmission of the patent information preceded the 2009 amendment. Cobrek does not, in its comments, argue that the words of the statute result in a denial of the 30-month stay. Instead, as discussed in the text, it argues that the Act should be interpreted in light of “the overall structure of the statute” (Cobrek’s Comments at 5).

¹³ In its comment, Cobrek argues not only that it should not have been required to submit a second paragraph IV certification, but also that it should now be permitted to withdraw that certification. A comment on a petition may support or oppose the petition, but may not request alternative or different administrative action (21 CFR 10.30(d)). In any case, if Cobrek wished to argue that no paragraph IV certification was required when it filed its amendment for its new formulation, the time to make that argument was at that point. Once Cobrek did file the additional certification and provided notice to Genzyme that resulted in litigation, the language of the Act is controlling, i.e., a 30-month stay from the date of receipt of the notice of that certification applies.

FDA in October 2007, or the submission of the ANDA amendment in 2009. We reach this conclusion regardless of whether the MMA applies to the facts at hand.

Cobrek argues that the relief requested in your petition would be “inconsistent with the plain language of the MMA once the overall structure of the statute is properly considered” (Cobrek's Comments at 5) and that granting your petition would permit innovators to obtain multiple 30-month stays by reformulating their injectable drug products (*id.*, at 7). Cobrek argues that the 30-month stay requested here should be denied because recognizing that stay would be inconsistent with a Congressional desire to prevent the use of multiple 30-month stays to inappropriately delay generic approvals. FDA does not, however, have the latitude to ignore the language of the Act achieve Congress’s perceived policy objectives, even if it were possible to determine with certainty what those objectives would be in these circumstances. There is no evidence, from the statutory structure or otherwise, that Congress ever considered the particular set of circumstances presented here, in which the two stays at issue related to separate formulations of the product. Ultimately, Cobrek chose to seek approval of a copy of the reformulated product rather than follow the alternative route, offered by FDA, of seeking approval of the original formulation. Based on that choice, Cobrek filed the paragraph IV certification at issue here. Once it did so, as discussed above, the statute dictates the result.

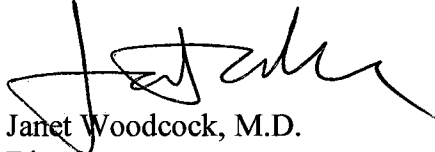
Moreover, the legal bases of either Genzyme’s first or second lawsuits against Cobrek do not affect our reasoning. Cobrek argues that as the reformulation of the product has no impact on the validity of the method-of-use claims in the ‘116 patent, there is no legitimate reason for Genzyme to initiate a second lawsuit on the ‘116 patent (Cobrek’s Comments at 7). Thus, Cobrek concludes that FDA should deny your petition. Cobrek’s arguments are unconvincing and are inconsistent with FDA’s historical practice regarding patent issues. FDA’s role in listing patents and patent information in the Orange Book is ministerial (see *American Bioscience v. Thompson*, 269 F.3d 1077, 1080 (D.C. Cir. 2001)), and just as the Agency relies on the NDA applicant to provide an accurate patent submission, it does not contest the NDA applicant’s decisions on which listed patents it should include in a patent infringement suit resulting from a paragraph IV certification.

III. CONCLUSION

For the reasons stated above, your petition is granted in that FDA confirms that the Act requires a 30-month stay beginning November 24, 2009, based on Cobrek’s paragraph IV certification and Genzyme’s resulting patent infringement suit regarding the ‘116 patent. FDA thus confirms that it will stay approval of ANDA 90-040 for doxercalciferol

injection, absent another specified event under section 505(j)(5)(B)(iii) of the Act, for 30 months from November 24, 2009.

Sincerely,

A handwritten signature in black ink, appearing to read 'Janet Woodcock', written over a faint, illegible background.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research