DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN 7 2011

Christina M. Markus
King & Spalding LLP
1700 Pennsylvania Ave., NW
Suite 200
Washington, DC 20006-4707

Re: Docket No. FDA-2011-P-0127

Dear Ms. Markus:

This letter responds to your citizen petition submitted on behalf of Baxter Healthcare Corporation, Baxter International Inc., and Baxter Healthcare SA (collectively, Baxter), which was received by the Food and Drug Administration (FDA or Agency) on March 1, 2011 (Petition). Your petition requests that FDA confirm that it will stay approval of abbreviated new drug application (ANDA) 90-363 for a generic version of Suprane (desflurane, USP), absent another specified event under 21 U.S.C. 355(j)(5)(B)(iii) or (iv) (section 505(j)(5)(B)(iii) or (iv) of the Federal Food, Drug, and Cosmetic Act (the Act)), for 30 months from June 23, 2009, the date Baxter asserts it received notice of a paragraph IV certification[1] from Minrad, Inc. (Minrad), related to U.S. Patent No. 5,617,906 (the '906 patent).[2]

We have carefully considered your petition, comments to your petition submitted by Reed Smith LLP on behalf of Minrad, dated April 7, 2011 (Minrad Comments) and May 28, 2011, and comments submitted by you on behalf of Baxter, dated May 10, 2011 (Baxter Comments). For the reasons described below, your petition is granted in part, and denied in part. FDA will recognize the 30-month stay. That stay will end on January 7, 2012, based on the documentation submitted to FDA by Minrad.

[1] A "paragraph IV certification" is a certification under section 505(j)(2)(A)(vii)(IV) of the Act that states that the patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted. When a paragraph IV certification is submitted, the approval of the ANDA is not delayed by the patent unless a 30-month stay applies under section 505(j)(5)(B)(iii) of the Act. Whether such a stay applies here is the issue addressed in the Petition, and in this response.

[2] 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 docket by you and in comments submitted in response to your petition at Docket No. FDA-2011-P-0127. Existence of any pending abbreviated new drug application at issue in the Petition has been disclosed or acknowledged by virtue of notice of paragraph IV certifications.

FDA-2011-P-0127

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I. BACKGROUND

A. Baxter's NDA for Suprane

FDA approved Baxter's new drug application (NDA) 20-118 for Suprane (desflurane, USP), on September 18, 1992. Suprane is an anesthetic gas delivered to the patient through a vaporizer and is indicated for induction and/or maintenance of anesthesia in adults and for maintenance of anesthesia in pediatric patients following induction with agents other than Suprane and intubation. Suprane is not recommended for induction of anesthesia in pediatric patients.

In connection with its NDA for Suprane, Baxter submitted patent information for the '906 patent for listing in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) (Petition at 1-2; Minrad Comments at 1). The '906 patent was listed in the Orange Book on February 14, 2006, and is coded as a product patent. Specifically, it claims the finished dosage form of desflurane and a closure system that constitutes the drug product (Petition at 1-2). The '906 patent expires on April 8, 2014, and pediatric exclusivity expires on October 8, 2014.[3]

B. Minrad's ANDA for a Generic Version of Suprane

Minrad[4] submitted ANDA 90-363 to market a generic version of Suprane and submitted a paragraph IV certification to the '906 patent on November 24, 2008 (Petition at 2; Minrad Comments at 2). Minrad sent notice to Baxter of its ANDA and its paragraph IV certification to the '906 patent, which Baxter received on December 12, 2008 (Petition at 2; Minrad Comments at 2). Within 45 days of being notified, on January 23, 2009, Baxter initiated a patent infringement action against Minrad asserting infringement of the '906 patent (Petition at 2 and Attachment 1; Minrad Comments at 2 and Exhibit A).[5] This action triggered a 30-month stay on the Agency's approval of ANDA 90-363 beginning on December 12, 2008 (Petition at 2; Minrad Comments at 2). That 30-month stay expires on June 12, 2011.

Subsequently, Minrad changed the container closure system for its drug product and, on June 23, 2009, submitted an amendment to ANDA 90-363 to include the revised drug product closure system (Petition at 2; Minrad Comments at 2). Minrad also submitted a second paragraph IV certification to the '906 patent and sent a notice to Baxter of the same on June 23, 2009 (Petition at 2; Minrad Comments at 2).[6]

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[3] The Orange Book.

[4] Minrad is now Piramal Critical Care, Inc., effective December 31, 2009 (Minrad Comments at 2). For purposes of this response, however, we refer to the ANDA applicant as Minrad.

[5] *Baxter Healthcare Corporation, Baxter International Inc. and Baxter Healthcare SA v. Minrad, Inc.*, 09-054-GMS (D. Del.) (Jan. 23, 2009).

[6] There is some confusion with respect to the date of receipt by Baxter of this notice of paragraph IV certification. According to the Petition, Baxter received the notice on June 23, 2009 (Petition at 2). Minrad states that it provided the notice to Baxter on June 23, 2009 (Minrad Comments at 2), but in its comments, Minrad does not specify the date of receipt of that notice by Baxter.

According to the Petition, by letter dated July 2, 2009, Baxter advised Minrad that Baxter did not believe the notice of paragraph IV certification satisfied all applicable requirements (Petition at 1). Minrad disagreed, but sent a new notice of paragraph IV certification to Baxter dated July 6, 2009 (Petition at 1). As required by 21 CFR 314.95(e), Minrad submitted to FDA documentation of receipt of the notice. Within 45 days of receiving the notice (regardless of whether we use the June 23, 2009, or the July 6, 2009, notice as the operative notice), on August 6, 2009, Baxter initiated a second action for patent infringement of the '906 patent (Petition at 2 and Attachment 2; Minrad Comments at 2 and Exhibit B).[7] In the Petition, Baxter states that, to be conservative, it is using the June 23, 2009, notice date as the earliest relevant date for purposes of the requested 30-month stay (Petition at 1).

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 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).)

An ANDA 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). In the case of a patent(s) for which information was submitted to FDA before the date on which the ANDA is submitted, 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).

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[7] *Baxter Healthcare Corporation, Baxter International Inc. and Baxter Healthcare SA v. Minrad, Inc., Minrad International, Inc., Piramal Healthcare Limited, and Piramal Healthcare, Inc.*, 09-582-GMS (D. Del.) (Aug. 6, 2009).

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 amendment of the 30-month stay provision as part of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA).[8] 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 the 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 Act as amended by the MMA, a 30-month stay is available only when information concerning the patent(s) at issue in the paragraph IV-related litigation was submitted by the NDA holder to FDA before the ANDA was submitted (section 505(j)(5)(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 first submitted following the submission of the ANDA (FDA draft 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* (Draft Guidance), at 8 (Oct. 2004)).[9] As noted in the Draft Guidance, "[t]he 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 (Draft Guidance at 8). The Draft 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.
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> (Draft Guidance at 8.) (Emphasis in original; footnotes omitted.)

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[8] Pub. L. No. 108-173.

[9] The Draft Guidance is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072887.pdf. The Draft Guidance, when finalized, will represent FDA's current thinking on the topic.

The Draft Guidance cautions, however, that "[m]ultiple 30-month stays . . . may be possible in certain cases" (Draft Guidance at 8). One scenario envisioned by the Draft 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 (Draft Guidance at 8-9). 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 claim that the product originally covered by ANDA 90-363 was "replaced by the second, 'final' configuration presented to FDA [in an amendment to ANDA 90-363] on June 23, 2009" (Petition at 2). You also state that in response to the complaint you filed in the second patent infringement action regarding the '906 patent, Minrad described the revised product submitted in the ANDA amendment as "the final version of the bottle closure that Minrad will use in commerce" (Petition at 2-3). You assert that "[o]nly the second version (and not the first) is therefore pertinent for analysis under the statutory ANDA approval parameters" (Petition at 2). Thus, you claim that the 30-month stay of approval calculated from June 23, 2009, "is a 'superseding stay' and provides the earliest operative timeline for possible approval of ANDA 90-363" (Petition at 3).

In addition, you claim that the same result reached by FDA in response to a citizen petition submitted by Genzyme Corporation (Genzyme) regarding the drug product Hectorol (doxercalciferol injection) (Docket No. FDA-2010-P-0223) is legally required here (Petition at 3).[10] In that response, FDA confirmed that a second 30-month stay applied where the ANDA applicant filed an amendment to its ANDA covering the reformulation of the product, submitted a subsequent paragraph IV certification in connection with seeking approval of the revised product, sent a notice of that paragraph IV certification to the NDA holder, and the NDA holder subsequently sued the ANDA applicant for patent infringement within 45 days. Similarly, you assert that "[o]nce Minrad chose to change its product, submit a Second Paragraph IV Certification, and provide new notice to Baxter of its factual/legal basis for an assertion of non-infringement (which resulted in Baxter's filing of a separate infringement action within 45 days following receipt of the notice of Minrad's Second Paragraph IV Certification)," the statute dictates the result and a 30-month stay applies from the date of receipt of the notice of that certification (Petition at 3-4).[11]

We agree that Baxter is entitled to a 30-month stay stemming from Minrad's paragraph IV certification to the '906 patent submitted in connection with Minrad's revised product and Baxter's resulting patent infringement action. On June 23, 2009, Minrad changed the container closure system for its drug product and submitted an amendment to ANDA 90-363

[10] See Letter from FDA to Gerald F. Masoudi, Covington & Burling LLP (Oct. 19, 2010) (Genzyme Letter).

[11] You also assert that your interpretation is consistent with the Draft Guidance discussed in the text above, which acknowledges that multiple 30-month stays are possible in certain circumstances (Petition at 4).

to include the new closure system. Once Minrad submitted the second paragraph IV certification to the '906 patent in connection with the revised product and sent notice to Baxter, and Baxter subsequently sued Minrad within 45 days of receiving that notice, the statutory requirements for a 30-month stay with respect to this paragraph IV certification were met.[12]

The statute is unambiguous. When a paragraph IV certification has been made to a patent for which information was submitted to FDA before the ANDA was submitted, and an action is brought for infringement of the patent that is the subject of the certification before the expiration of 45 days of the date of receipt of notice of that certification, a 30-month stay dating from receipt of the notice applies (section 505(j)(5)(B)(iii) of the Act). Even if the statute were ambiguous, we would interpret it, consistent with its intent to provide an opportunity to litigate questions concerning patent infringement, to begin a 30-month stay when, as here, an ANDA is amended to include a new certification reflecting a change in the product covered by the ANDA.[13]

While we agree that Baxter is entitled to a 30-month stay of approval of Minrad's ANDA, it should be noted that this 30-month stay will end on January 7, 2012, not December 23, 2011 (i.e., 30 months from June 23, 2009), as requested in the Petition. As described previously in section I.B, Baxter advised Minrad in a letter dated July 2, 2009, that it did not believe the June 23, 2009, notice of paragraph IV certification satisfied all applicable requirements (Petition at 1). Minrad disagreed, but subsequently sent Baxter a new notice of paragraph IV certification dated July 6, 2009 (Petition at 1). 21 CFR 314.95(e) requires that the ANDA applicant submit to FDA documentation of receipt of the notice. Based on the documentation submitted to FDA by Minrad, the 30-month stay of approval will end on January 7, 2012.

Minrad presents several grounds to support its position that Baxter's request for confirmation of the 30-month stay should be denied. First, Minrad claims that a superseding 30-month stay is not available under section 505(j)(5)(B)(iii) of the Act for a subsequent paragraph IV certification that refers to the same reference listed drug and the same patent for the same version of the drug product (Minrad Comments at 4). Second, Minrad asserts that multiple 30-month stays are neither explicitly nor implicitly authorized under the Act and cannot be imposed when only one infringement action is pending (Minrad Comments at 5). Third, Minrad claims that FDA's response to the Genzyme citizen petition, discussed above, is not applicable to the facts at issue because, unlike the Genzyme matter, this case does not involve a paragraph IV certification in connection with a reformulated drug, relisted patents, or a supplemental NDA product (Minrad Comments at 5-7). Finally, Minrad argues that the Petition is "nothing more than another transparent and improper attempt to delay approval and

[12] We note that there is no dispute that, in accordance with section 505(j)(5)(B)(iii) of the Act, as amended by the MMA, Baxter submitted the information concerning the '906 patent to FDA prior to both Minrad's submission of its original ANDA in 2008 and its ANDA amendment in 2009.

[13] Minrad states on page 3 of its May 28, 2011, comment on the Petition that its second certification provided a second basis for asserting non-infringement relating to the change in the product, a basis apparently not available to it when it submitted the initial certification relating to the earlier version of its product. While Minrad argues that the litigation was not delayed by the second certification, there was presumably no opportunity to litigate the second basis before the second certification.

marketing of generic competition for [Baxter's] product, Suprane" (Minrad Comments at 1). We address each of these claims below.

First, we disagree with Minrad's claim that its second paragraph IV certification to the '906 patent relates to "the same version of the drug product" (Minrad Comments at 4). As we noted above, Minrad revised the container closure system for its drug product and submitted an amendment to the ANDA to include the new closure system. When Minrad changed the container closure system, it changed its product; it is, therefore, not accurate to describe, as Minrad does, the revised product as "the same version." Furthermore, FDA's recognition of the 30-month stay is dictated here by the statute itself — because the statutory requirements were met (see section 505(j)(5)(B)(iii) of the Act), a 30-month stay ensues. This would occur whether or not the Petition had been filed.

Second, Minrad's argument that no 30-month stay applies because there is only one patent infringement action pending is unpersuasive (Minrad Comments at 5). Baxter filed a second action for infringement of the '906 patent within 45 days of receiving notice of Minrad's second paragraph IV certification. The second patent infringement action is specific to the revised product described in Minrad's ANDA amendment. The fact that the court chose to consolidate the two infringement actions does not affect our reasoning. Furthermore, the court's Order consolidating the two actions states that the consolidation "is not intended to, and shall not, affect the calculation or duration of the automatic thirty-month stay imposed on defendant Minrad...." (Baxter Comments at 9, quoting Order dated July 14, 2010 (09-cv-00582-GMS) (D. Del.)). We also find Minrad's argument to be inconsistent with FDA's historical practice regarding patent issues. Indeed, "FDA has a longstanding policy not to get involved in patent disputes. It administers the Hatch-Waxman Amendments in a ministerial fashion simply following the intent of the parties that list patents" (*American Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1084 (D.C. Cir. 2001)).

Third, we disagree that the petition submitted on behalf of Genzyme (FDA-2010-P-0223) is inapplicable here. In response to that petition, we granted Genzyme a second 30-month stay of approval of Cobrek Pharmaceuticals' (Cobrek) ANDA for a generic version of Hectorol after Cobrek reformulated its product for vial rather than ampule delivery at FDA's request.[14] We concluded that once Cobrek submitted a paragraph IV certification in connection with seeking approval of the reformulated product, and Genzyme subsequently sued Cobrek for infringing the patent at issue within 45 days of receiving notice of the certification, the statutory requirements for a 30-month stay with respect to that paragraph IV certification were met.[15] Minrad asserts that, unlike the situation characterized in the Genzyme petition, here there was "an updated Paragraph IV Certification to the same patent and drug product" (Minrad Comments at 7). As we noted above, however, we consider the changes made to the container closure system to be changes to Minrad's product. The principles we set out in our response to the Genzyme petition are applicable to the facts at issue here; just as we concluded in that response, under these circumstances, the language of the Act is controlling

[14] See Genzyme Letter.

[15] Id. at 7-8.

(i.e., a 30-month stay from the date of receipt of the notice of paragraph IV certification applies).

Finally, we find unconvincing Minrad's argument that the Petition should be denied on the grounds that it is an attempt by Baxter "to 'game the system' and further delay the approval of a generic version of its branded product" (Minrad Comments at 7). Minrad argues that FDA should not grant the requested 30-month stay "based on a tortured interpretation of the statute to exploit a procedural anomaly," and that to do so "would serve only to deprive the public of access to generic desflurane long after any stay on the launch of such a product should have expired" (Minrad Comments at 8). The statute is, we believe, clear and controls here. As we stated in our response to the Genzyme petition,

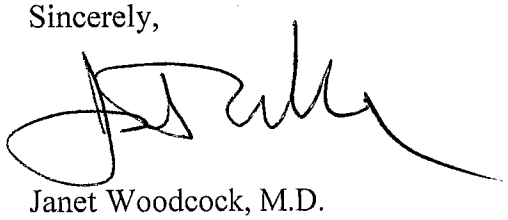
> FDA does not, however, have the latitude to ignore the language of the Act [to] achieve Congress's perceived policy objectives, even if it were possible to determine with certainty what those objectives would be in these circumstances. There is no evidence, from the statutory structure or otherwise, that Congress ever considered the particular set of circumstances presented here....[16]

Minrad chose to change its product when it changed the product's container closure system and submitted an amendment to ANDA 90-363, and submitted a paragraph IV certification to the '906 patent in connection with that product. In response to Minrad's notice of paragraph IV certification, Baxter sued Minrad within 45 days of receiving that notice. Under these circumstances, as discussed above, the statute dictates the result.

III. CONCLUSION

For the reasons stated above, your petition is granted in that FDA confirms that a 30-month stay applies to ANDA 90-363 based on Minrad's second paragraph IV certification and Baxter's resulting patent infringement action regarding the '906 patent. FDA thus confirms that it will stay approval of ANDA 90-363, absent another specified event under section 505(j)(5)(B)(iii) or (iv) of the Act, for a 30-month period. However, as noted above, this stay will end on January 7, 2012, based on the documentation submitted to FDA by Minrad.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[16] Id. at 8.