DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-306

NOV 0 3 2006

Rakoczy Molino Mazzochi Siwik, LLP
Attention: Christine J. Siwik and William A. Rakoczy
6 West Hubbard Street
Suite 500
Chicago, IL 60610

Dear Mr. Rakoczy and Ms. Siwik:

This responds to your letter dated August 29, 2006, in which you request on behalf of Apotex Corporation that the Food and Drug Administration (FDA) consider the start of 180-day exclusivity for ondansetron hydrochloride tablets 4 mg and 8 mg (ondansetron) to have been triggered by the dismissal of a patent infringement suit.

As you are aware, FDA interpreted the relevant statutory provision in a letter dated April 11, 2006 (FDA letter decision) (attached). FDA's letter decision expressly states that the dismissal of a patent suit in and of itself is not sufficient to trigger the start of a 180-day exclusivity period; rather a court order must reflect a holding on the merits by the court that the patent at issue is invalid, not infringed, or unenforceable ("holding-on-the-merits" standard). The FDA letter decision explains in detail the legal grounds and policy justifications for the holding-on-the-merits standard. Apotex sued the agency, challenging the FDA letter decision as arbitrary and capricious, and the District of Columbia Circuit Court of Appeals ruled in the agency's favor, summarily affirming the district court's denial of Apotex's motion for a preliminary injunction. *See Apotex, Inc. v. FDA*, 449 F.3d 1249, 1253 (D.C. Cir. 2006). Apotex petitioned for a rehearing *en banc* by the court, which the court denied on August 17, 2006. On October 3, 2006, Apotex entered into a stipulation of dismissal ending the litigation.

In accordance with the FDA letter decision, we deny your request for the reasons detailed briefly below, and refer you to that decision for further guidance on this matter.

I. Apotex's request.

Apotex now asks the FDA to confirm that: "(1) Apotex will, subject to all other substantive requirements for approval, receive final approval of its ondansetron ANDA [abbreviated new drug application] upon expiration of U.S. Patent No. 4,753,789 ("the '789 patent"); (2) Apotex's final approval will not be delayed by any unexpired 180-day exclusivity associated with U.S. Patent No. 5,344,658 ("the '658 patent"); and (3) any 180-day exclusivity associated with the '658 patent was triggered by the May 25, 2005 Order dismissing Glaxo Group Limited's and SmithKline Beecham Corporation's (collectively, "GSK") patent infringement action against Apotex Inc. [for infringement of the '658 patent]." In essence, you argue that the dismissal of the GSK lawsuit triggered any 180-day exclusivity arising from the '658 patent with respect to ondansetron, that any such 180-day exclusivity has now expired and, therefore, no unexpired 180-day exclusivity arising from the '658 patent could delay approval of Apotex's ANDA upon expiration of the '789 patent.

II. The May 25, 2005 Order.

Apotex's ANDA for ondansetron includes a "paragraph IV" certification[1] in which Apotex alleges that the '658 patent is not infringed and/or is not valid. Having received notice of this paragraph IV certification in December 2004, GSK sued Apotex for infringement of the '658 patent in January 2005. You enclosed with your August 31, 2005 letter a copy of "the stipulation of dismissal pursuant to Fed. R. Civ. P. 41" filed May 25, 2005, dismissing the GSK suit (stipulation of dismissal).

The stipulation of dismissal states that the plaintiffs (GSK)

> . . . stipulate and agree that the ondansetron hydrochloride tablets that are the subject of and described in Apotex Inc.'s ANDA No. 77-306 do not infringe, and if imported, manufactured, used, sold, or offered for sale in the United States would not infringe, any claim of GlaxoSmithKline's U.S. Patent No. 5,344,658 ("the '658 patent"); and
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> . . . [have] represented that [they] will not sue Apotex for infringement of the '658 patent based on the importation, manufacture, use, sale or offer for sale of ondansetron hydrochloride tablets that are the subject of and described in ANDA No. 77-306;

and the parties

> . . . stipulate and agree to dismissal of the parties' respective claims and counterclaims with prejudice . . . .

The stipulation is signed on behalf of GSK and Apotex, and is signed as "so ordered" by the court.

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[1] An NDA applicant must notify FDA of patents the applicant believes claim the drug or an approved use of the drug. 21 U.S.C. §§ 355(b)(1), 355(c)(2). FDA relies on these notifications to post information on these patents in *Approved Drug Products with Therapeutic Equivalence Evaluations* (informally referred to as the Orange Book). 21 U.S.C. §§ 355(b)(1), 355(c)(2), 355(j)(7)(A)(iii). An ANDA applicant must then make one of four certifications with respect to each patent that claims the drug or any use of the drug for which the ANDA applicant is seeking approval. These certifications are commonly referred to by the four sub-paragraphs of section 505(j)(2)(A)(vii) establishing them:

- a "paragraph I" certification that patent information has not been filed;
- a "paragraph II" certification that the patent has expired;
- a "paragraph III" certification of the date the patent will expire; or
- a "paragraph IV" certification that the patent is invalid, not infringed, or not enforceable.

21 U.S.C. § 355(j)(2)(A)(vii); 21 C.F.R. § 314.94(a)(12)(i)(A). A paragraph I or II certification indicates that the applicant believes that the patent does not bar immediate approval of the ANDA. A paragraph III certification indicates that the applicant is not challenging the validity or applicability of the patent and that the applicant is seeking ANDA approval only after the patent expires. A paragraph IV certification indicates that the ANDA applicant disputes the applicability or validity of that patent. If an ANDA applicant makes a paragraph IV certification, the applicant must the notify the holder of the approved NDA and the patent owner. 21 U.S.C. § 355(j)(2)(B).

III. 180-day exclusivity and FDA letter decision.

Section 505(j)(5)(B)(iv) of the Act establishes 180-day exclusivity. This exclusivity provides a potential reward to the first ANDA applicant to submit a paragraph IV certification to a patent pursuant to section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act and thus to expose itself to the risk of being sued for infringing the patent.

Section 505(j)(5)(B)(iv)(II) provides that the start of 180-day exclusivity can be triggered as of "the date of a *decision of a court . . . holding the patent which is the subject of the certification to be invalid or not infringed.*"[2] (Emphasis added.) This mechanism for initiating 180-day exclusivity is commonly referred to as the "court decision trigger."

The FDA letter decision announced the holding-on-the-merits standard to assess whether an action of a court qualifies as a court decision trigger to start the running of 180-day exclusivity. As the introduction to that letter states (and the body of that letter explains in detail):

> FDA interprets the language of the court decision trigger provision, "the date of a decision of a court . . . holding the patent which is the subject of the certification to be invalid or not infringed," to require a court decision with an actual "holding" on the merits that the patent is invalid, not infringed, or unenforceable. The holding must be evidenced by language on the face of the court's decision showing that the determination of invalidity, noninfringement, or unenforceability has been made by the court. . . . FDA's "holding-on-the-merits" interpretation adheres closely to the language of the statute, and will provide a bright line that is more easily administrable by FDA and that will enable industry to make appropriate business planning decisions.

FDA letter decision at 2.[3] FDA adopted this bright-line standard to provide clarity, reduce the likelihood of litigation over whether a court action triggers 180-day exclusivity, and promote greater marketplace certainty.

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[2] Congress amended 21 U.S.C. § 355(j) in late 2003. *See* The Access to Affordable Pharmaceuticals provisions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003) ("MMA"). None of the amendments pertaining to 180-day exclusivity enacted through the MMA bear upon the determination of whether the stipulation of dismissal for the GSK suit triggered 180-day exclusivity for ondansetron, however, because the earliest ANDA containing a paragraph IV certification for this drug was submitted before the December 8, 2003, enactment date of the MMA. *See id.* § 1102(b)(1).

[3] Provisions of the MMA inapplicable to the 180-day exclusivity determination for ondansetron (*see* MMA § 1102(b)(1)) eliminated the court-decision trigger provision, but provided for forfeiture of exclusivity in certain circumstances. One event that can trigger forfeiture under the MMA is a "a settlement or consent decree that enters a final judgment that includes a finding that the patent is invalid or not infringed." 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(BB) (2006). The holding-on-the-merits standard under the pre-MMA statute does not reflect an agency view as to the proper scope or interpretation of this forfeiture provision or any other forfeiture provision in the MMA.

IV. Analysis

The GSK suit was dismissed by an agreement between the parties; the court never issued a holding on the merits of the patent claim. It is clear, therefore, that this dismissal does not constitute a court decision trigger under the holding-on-the-merits standard. *See Apotex*, 449 F.3d at 1253.[4]

You assert that the stipulation of dismissal satisfies the holding-on-the-merits standard because, *inter alia*, it expressly reflects GSK's judgment that the patent at issue is not infringed and GSK's commitment not to sue. Your conclusion is not correct. It is not enough that the order reflects the views and commitments of the parties. The court itself has to have made a substantive determination on the merits of the patent claim. As its title ("Stipulation of Dismissal Pursuant to Fed. R. Civ. P. 41") reflects, the stipulation of dismissal was the mechanism by which the parties sought and received dismissal of the case because, in their view, there was nothing left for the court to decide. The court was not asked to resolve the dispute on the merits and did not do so. In short, the stipulation of dismissal does not reflect a holding by the court on the merits of the patent claim.[5]

[4] Although the holding-on-the-merits standard was announced in relation to a declaratory judgment action, the standard is equally applicable to affirmative patent infringement suits, such as the GSK suit at issue here. The standard looks to whether the court has made a holding on the merits of the patent claim; it does not consider the manner by which the dispute came before the court.

This letter does not address the arguments made in your prior letter of August 31, 2005, to support your claim that the GSK stipulation of dismissal satisfies an estoppel-based interpretation of the court decision trigger. As explained in greater detail in the FDA letter decision, the agency has rejected this standard in favor of the holding-on-the-merits standard. Accordingly, this letter addresses only the arguments you made in your letter dated August 29, 2006, that the GSK stipulation of dismissal satisfies the holding-on-the-merits standard.

[5] We note that you raised additional arguments in telephone conversations with the agency that you chose not to submit in writing. These arguments relate to FDA's decision in *Granutec, Inc. v. Shalala*, 139 F.3d 889, 1998 WL 153410 (4th Cir. Apr. 3, 1998) (unpublished opinion), as well as whether FDA's interpretation of section 505(j)(5)(B)(iii) is consistent with its interpretation of section 505(j)(5)(B)(iv). In this letter, however, we are only addressing the question that Apotex set forth in writing, *i.e.*, whether the ondansetron dismissal constitutes a court decision trigger under FDA's "holding-on-the-merits" standard. We do not believe that the additional arguments not submitted in writing are pertinent to making that determination, which simply looks to whether the court has held on the merits of a patent claim.

V. Conclusion

The stipulation of dismissal did not trigger any 180-day exclusivity for ondansetron that may arise from another ANDA applicant's paragraph IV certification to the '658 patent. The agency is not aware of any judicial action to date qualifying as a court decision trigger of 180-day exclusivity for ondansetron. Accordingly, 180-day exclusivity may delay approval of Apotex's ANDA for ondansetron hydrochloride tablets 4 mg and 8 mg upon expiration of the '789 patent.[6]

Sincerely,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure

cc: Elizabeth Dickinson, Office of Chief Counsel
Applicants with Pending ANDAs for Ondansetron HCl Tablets, 4 mg and 8 mg

[6] FDA does not make its exclusivity determinations until an ANDA is ready for final approval, which will not occur for ondansetron until at least December 24, 2006, when the pediatric exclusivity associated with the '789 patent will expire. Pediatric exclusivity is intended as an incentive to sponsors to conduct and submit to FDA studies requested by the agency on the use of drugs in pediatric populations. It is a six-month exclusivity that attaches to any listed patent or exclusivity for the drug studied. 21 U.S.C. § 355a. Apotex assumes that another ANDA applicant will be entitled to 180-day exclusivity for ondansetron, which the agency neither confirms nor denies.