WELSH & KATZ, LTD.

Attorneys at Law

120 SOUTH RIVERSIDE PLAZA · 22ND FLOOR
CHICAGO, ILLINOIS 60606-3912

TELEPHONE (312) 655-1500
FACSIMILE (312) 655-1501

www.welshkatz.com

A. SIDNEY KATZ*
RICHARD L. WOOD*
JEROLD B. SCHNAYER
JOSEPH R. MARCUS
GERALD S. SCHUR
GERALD T. SHEKLETON
JAMES A. SCHEER
DANIEL R. CHERRY
ROBERT B. BREISBLATT
JAMES P. WHITE
R. MARK HALLIGAN
HARTWELL P. MORSE, III
EDWARD P. GAMSON, PH.D.
KATHLEEN A. RHEINTGEN
THOMAS W. TOLPIN*
RICHARD W. McLAREN, JR.
ELLIOTT C. BANKENDORF
ERIC D. COHEN
JOHN L. AMBROGI
JULIE A. KATZ
JON P. CHRISTENSEN
WALTER J. KAWULA, JR.
LEONARD FRIEDMAN
STEVEN E. FELDMAN
JEFFREY W. SALMON
LOUISE T. WALSH
PAUL M. VARGO, PH.D.
JOSEPH E. CWIK

J. ARON CARNAHAN
ERIK B. FLOM, PH.D.
JAMES B. RADEN
ALAN S. WERNICK*

RICHARD J. GURAK
DANIEL M. GURFINKEL
MICHELE S. KATZ*
BRIAN J. SODIKOFF
BRETT M. TOLPIN
GEORGE S. PAVLIK
MICHAEL A. KROL, PH.D.
SHERRY L. ROLLO
CRAIG M. KUCHII
STEPHEN P. BENSON
GREGORY J. SKONY

OF COUNSEL
LAURIE A. HAYNIE
JAMES J. MYRICK
THOMAS R. VIGIL
PHILIP D. SEGREST, JR.**
WALLACE L. OLIVER, PH.D.
LAURA A. LABEOTS, PH.D.

DONALD L. WELSH (1925-1998)

* ALSO ADMITTED IN DISTRICT OF COLUMBIA
** ALSO ADMITTED IN ALABAMA

April 4, 2007

HAND DELIVERED

Food and Drug Administration
Office of Generic Drugs, HFD-600
Attn: Gary J. Buehler, Director
7519 Standish Place
Rockville, MD 20855

Re: Apotex Inc. -- ANDA 76-719 (Amlodipine Besylate Tablets)

Dear Mr. Buehler:

This letter is submitted on behalf of our client Apotex Inc. (formerly TorPharm) and responds to the five questions set forth in your letter to Mr. John Ley of Apotex Corp, agent for Apotex Inc.

1. **What date controls FDA's giving effect to the decision in *Pfizer Inc. v. Apotex, Inc.*, No. 2006-1261 (Fed. Cir. March 22, 2007) ("*Apotex* decision") holding that Pfizer's patent 4,879,303 ("the '303 patent") is invalid? Can FDA treat the '303 patent as invalid as of March 22, 2007, or must FDA await the issuance of the mandate? Is the answer the same for all purposes, that is, for determining the applicability of pediatric exclusivity, the triggering of 180-day exclusivity, and the eligibility of other ANDA applicants for final approval?**

a. The operative date of giving effect to the *Apotex* decision should be March 22, 2007, the date of the Federal Circuit's decision and judgment. FDA should regard the patent as invalid as of that date and should have deemed it to have been delisted from the Orange Book as a matter of law as of that date. *See* Answer to Question 3 below.

The FDC Act's 30-month delay of final ANDA approval provision, 21 U.S.C. § 355(j)(5)(B)(iii) (as amended by the MMA for all pending matters, MMA § 1101(c)(1)), provides that, where (as here) the district court upholds the patent but the Federal Circuit reverses, the operative date is the date of the Federal Circuit's decision. 21 U.S.C. § 355(j)(5)(B)(iii)(II)(aa)(AA). FDA should use that date – which was selected by Congress for a closely related provision – here.

b. It is appropriate for FDA to give effect to the Federal Circuit's decision and judgment as of March 22 because that decision is a final decision from which no appeal can be taken. Rehearing and rehearing *en banc* by the Federal Circuit are discretionary, as is Supreme Court review pursuant to a writ of *certiorari*. Neither is an "appeal," which is a matter of right.

The fact that the Federal Circuit's March 22 decision and judgment could be vacated and Pfizer's patent ultimately upheld pursuant to a request for rehearing or rehearing *en banc* is immaterial, as the Federal Circuit rarely grants rehearing.[1] Using similar reasoning, FDA has long recognized that reversal by the Supreme Court pursuant to a writ of *certiorari* is unlikely and should be disregarded. *See* 59 Fed. Reg. 50,338, 50,355 (Oct. 3, 1994).

c. In its petition for stay of action (Docket No. 2007P-0116), Mylan asserts that the operative date should be, at the earliest, the date of the Federal Circuit's mandate. Mylan Petition at 2, n.1. As authority, Mylan cites to a March 2000 guidance. Reliance on that guidance is misplaced for several reasons.

First, and most importantly, that guidance predates the MMA and Congress's adoption of the date of the Federal Circuit's decision – not the date of mandate – in a closely related statutory provision. Thus, the March 2000 guidance does not necessarily reflect FDA's *current* thinking.

---

[1] A review of petitions for rehearing submitted to the Federal Circuit over a 16-month period demonstrated that the Federal Circuit grants petitions for rehearing by the panel less than 3% of the time, while petitions for rehearing *en banc* are granted only about 0.6% of the time. *See* George Quillin & Jacqueline Wright, *Rare Success Upon Filing Petitions for Rehearing by the Panel or En Banc at the Federal Circuit vs. Certiorari at the Supreme Court*, CORPORATE COUNSEL OUTSIDE PERSPECTIVES, July 2004, at A6, http://www.foley.com/files/tbl_s31Publications/FileUpload137/2090/Quillin - Wright FINAL.pdf. Further, the Federal Circuit itself has expressed this view, stating in official guidance documents that "Rehearings are rarely granted." *See Guide for Pro Se Petitioners and Appellants*, p. 7, available at http://fedcir.gov/pdf/guide.pdf.

Second, the March 2000 guidance (65 Fed. Reg. 16,922; March 30, 2000) was based in turn on a *former* regulation, which provided in relevant part:

> (e) *Court actions*. (1) References to actions of "the court" in paragraphs (b) and (c) of this section are to the court that enters final judgment from which no appeal can be or has been taken.
>
> (2) For purposes of establishing the effective date of approval based on a court judgment, the following dates shall be deemed to be the date of the final decision of the court on the patent issues:
>
> (i) If the district court enters a decision that the patent is invalid, unenforceable, or not infringed, and the decision is not appealed, the date on which the right to appeal lapses.
>
> (ii) If the district court enters a decision that the patent is invalid, unenforceable, or not infringed, and the decision is appealed, the date of the first decision or order by a higher court holding or affirming the decision of the district court that the patent is invalid, unenforceable, or not infringed.
>
> (iii) If the district court enters a decision that the patent is infringed, and the decision is appealed, the date on which the district court enters a judgment that the patent is invalid, unenforceable, or not infringed pursuant to a mandate issued by a court of appeals.

21 C.F.R. § 314.107(e) (2000) (removed in 65 Fed. Reg. 43,233 (July 13, 2000)).

The quoted former regulation distinguished between two situations:

- If the district court ruled against the patentee and the Federal Circuit affirmed, the operative date was the date of the Federal Circuit decision. Former 21 C.F.R. § 314.107(e)(2)(ii).

- If (as here), the district court upheld the patent and the Federal Circuit reversed, the operative date was the date of the district court's judgment following issuance of the mandate. Former 21 C.F.R. § 314.107(e)(2)(iii).[2]

In its rulemaking preamble for that former regulation, FDA did not provide any explanation for the disparate treatment of these two situations (depending on whether the district court had ruled for or against the patentee). The quoted C.F.R. language was not part of FDA's proposed rule, *see* 54 Fed. Reg. 28,872 (July 10, 1989), and appeared for the first time in the final rule without any explanation for the differing treatment, *see* 59 Fed. Reg. at 50,355. We respectfully submit that FDA provided no explanation because there is none. FDA should so recognize at this time because the situation in the *Pfizer v. Apotex* is different in that the Federal Circuit decision is a reversal without a remand to the district court.

d. FDA asked whether the same operative date should apply for all purposes. In our view, the answer is yes. A consistent approach promotes simplicity that benefits both industry and the agency. More importantly, Apotex does not believe that there is a basis for differentiating between the purposes cited by FDA in this question.

For purposes of determining the date of the "court decision trigger" for 180-day exclusivity for ANDAs governed by pre-MMA law (such as here for generic versions of Norvasc), Congress adopted the following standard:

> [T]he term "decision of a court" as used in clause (iv) of section 505(j)(5)(B) of that Act 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.

MMA, § 1102(b)(3). For the reasons discussed, the Federal Circuit's March 22 decision is a "final decision of a court from which no appeal...can be taken." Thus, our suggested interpretation properly implements the intent of Congress with regard to the "court decision trigger" for pre-MMA ANDAs.

---

[2] In the event FDA ultimately adopts the interpretation that the date of the Federal Circuit's mandate is controlling, there is no need to wait until the date of the district court's judgment following issuance of the mandate in this case. Here, the Federal Circuit reversed, and did not remand for any further proceedings. Thus, the district court only has the ministerial act of closing its case. *See* 28 U.S.C. § 2106.

2. If FDA must await the issuance of the mandate, does pediatric exclusivity bar approval of all unapproved ANDAs in the meantime?

Assuming for discussion purposes that FDA determines that the operative date of delisting a patent that has been held invalid by the Federal Circuit is the date the Federal Circuit issues a mandate under Fed. R. App. P. 41, the pediatric exclusivity will not apply to all ANDA applicants equally. As discussed below, Apotex is not now blocked from receiving final approval, but all other sponsors are blocked at this time by pediatric exclusivity. Apotex is treated differently because it now has a decision and judgment from the Federal Circuit in its favor.

At the time of patent expiration, each pending (unapproved) ANDA will have a Paragraph III or Paragraph IV certification to an Orange Book patent. By operation of the plain language of the pediatric exclusivity statute, 21 U.S.C. § 355a(c)(2)(A)(ii), final approval of Paragraph III ANDAs is delayed by six months (unless the patent is delisted before then, *see* Answer to Question 3 below).

The effect of pediatric exclusivity on a Paragraph IV ANDA depends on the status of its patent litigation. There are three possibilities that must be examined separately.

First, if the ANDA sponsor has lost in patent litigation (whether at the district court or appellate level), such that "in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed," 21 U.S.C. § 355a(c)(2)(B), final approval is blocked for six months (again, unless FDA delists the patent earlier). Respect for the judgments of district courts requires those judgments finding the patent valid and infringed be given full weight with respect to each applicant until such a time as those judgments are reversed or vacated by either the Federal Circuit or the district court.

Second, if the ANDA sponsor has prevailed in patent litigation, whether at the district court or appellate level (such as Apotex, and only Apotex, here), the situation is governed by what is, in essence, the "flip side" of § 355a(c)(2)(B). In this circumstance, the ANDA sponsor would have a final judgment in its favor pursuant to Fed. R. Civ. P. 58 or Fed. R. App. P. 36 holding the patent invalid, unenforceable, or not infringed. Final approval is not delayed by pediatric exclusivity because the relevant court judgment must be given effect as of the date of judgment.

Third, where there is no judicial decision in patent litigation against a Paragraph IV sponsor as of the date of patent expiration, or no patent suit at all, the sponsor's Paragraph IV certification is converted to a Paragraph II certification. Thereafter, as discussed above, final approval is delayed by pediatric exclusivity under § 355a(c)(2)(A)(ii). This approach was upheld in *Ranbaxy Laboratories v. FDA*, 307 F. Supp.2d 15 (D.D.C.), *aff'd.*, 96 Fed. App. 1 (D.C. Cir. 2004).

When these principles are applied to the current situation, Apotex is the only sponsor of a pending ANDA that is not blocked by pediatric exclusivity. Apotex is entitled to immediate final approval. Apotex is so situated because it is the only sponsor that has a judgment in its favor in patent infringement litigation (the March 22 Federal Circuit judgment in the *Apotex* case). All other sponsors of pending amlodipine besylate ANDAs have Paragraph III certifications, have Paragraph IV certifications and were not sued or have unresolved patent litigation, or lost before the District Court in Paragraph IV infringement litigation. For the reasons discussed above, final approval for these sponsors are all delayed by pediatric exclusivity, unless Pfizer's patent is delisted before pediatric exclusivity ends.

3. If and when the *Apotex* decision is implemented, what is the effect of the decision that the '303 patent is invalid on the obligation of an ANDA applicant to change its certification? Must Pfizer delist its patent, so that certifications can be withdrawn? Or can FDA treat an invalid patent as delisted as a matter of law, and presume the withdrawal of the certifications? Or must the ANDA applicants file paragraph II certifications stating that the '303 patent has expired?

a. Immediately upon implementation of the *Apotex* decision (for purposes of this letter we understand FDA to mean when it gives the *Apotex* decision legal effect), FDA should deem Pfizer's '303 patent to be delisted as a matter of law. This approach would be consistent with longstanding agency practice, under which FDA delists patents upon the expiration of any associated 180-day exclusivity or upon patent expiration, whichever occurs first. *See* 21 C.F.R. § 314.94(a)(12)(viii)(B) and Answer to Question 5 below.

Waiting for Pfizer to request that its patent be delisted is both unnecessary and contrary to the goal of getting generic drugs on the market quickly. For example, Pfizer might engage in a detailed legal and management "review" that could take weeks or months. Or, Pfizer could simply refuse to act, on the basis that no explicit statutory or regulatory provision requires it to request delisting of its patent. In either case, American consumers, generic companies like Apotex, and third party payors (including federal and state governments) would be the losers; only Pfizer and Mylan would benefit by limiting generic competition.

Once the '303 patent is deemed delisted as a matter of law, nothing prevents FDA from presuming the withdrawal of Paragraph IV certifications by the respective ANDA sponsors except for Apotex who prevailed in its Paragraph IV certification and can be approved immediately. This approach, rather than requiring ANDA sponsors to submit amendments or correspondence withdrawing their Paragraph IV certifications, would promote active generic competition and thereby benefit the public. In *Mylan Laboratories, Inc. v. Thompson*, 389 F.3d 1272 (D.C. Cir. 2004) (involving fentanyl patch), the court upheld FDA's authority to convert Mylan's Paragraph IV certification to a Paragraph II certification, thereby subjecting Mylan to pediatric exclusivity and

delaying its final approval for six months. If FDA has such authority in a situation where its actions are adverse to the interests of the ANDA sponsor whose patent certification was being converted, the agency surely has the authority to modify patent certifications in the current situation, where such modifications are in the interest of the affected ANDA sponsors.[3]

Moreover, deeming Pfizer's '303 patent to be "delisted as a matter of law" and "presum[ing]" the withdrawal of Paragraph IV certifications are both ministerial acts, which are consistent with FDA's longstanding, judicially sanctioned view that FDA only plays a ministerial role in the listing of patents in the Orange Book.

b. There is no statutory, regulatory, or policy basis for requiring ANDA applicants to file Paragraph II certifications stating that the '303 patent has expired. In fact, such a requirement would be contrary to 21 C.F.R. § 314.94(a)(12)(viii)(B), which expressly provides that no certification is needed to address a patent that has been delisted. *See* Answer to Question 5 below.

4. If and when the *Apotex* decision is implemented and the patent is treated as invalid, does pediatric exclusivity attach to the '303 patent with respect to any unapproved ANDAs? Does it matter whether the ANDA applicant filed a paragraph III or IV certification before patent expiration?

Once the *Apotex* decision is implemented and the '303 patent is delisted from the Orange Book (*see* Answer to Question 3 above), it follows that there is no pediatric exclusivity that attaches to that patent which blocks final approval of any ANDAs. It makes no difference whether an ANDA sponsor had a Paragraph III certification or a Paragraph IV certification before patent expiration. Under the plain language of the pediatric exclusivity provision, pediatric exclusivity only attaches in connection with, in relevant part, a "listed patent." 21 U.S.C. § 355a(c)(2). Once the patent is deemed to be delisted, it is, of course, no longer a "listed patent."

---

[3] In *Mylan Pharmaceuticals, Inc. v. Thompson*, 207 F. Supp.2d 476 (N.D. W. Va. 2001) (involving nifedipine), FDA had deemed Mylan's Paragraph IV patent certification to be "effectively changed" to a Paragraph III, thereby resulting in the loss of 180-day exclusivity, as a result of Mylan's settlement with the innovator company under which Mylan marketed an "authorized generic." The district court rejected FDA's action, on the basis that it was sanctioned by neither the statute nor any FDA regulation. That case is easily distinguished and in no way stands for the proposition that FDA cannot deem patent certifications to be revised without requiring any action by the affected ANDA sponsors. In the West Virginia case, FDA's attempted action by itself had the effect of rendering Mylan ineligible for 180-day exclusivity and represented a new interpretation of the statute. In comparison, in the present case, deeming Paragraph IV (or Paragraph III) certifications in the affected ANDAs to be deleted is nothing more than a ministerial act. No company is being disadvantaged, and no company has any legitimate basis for complaint.

5. Does 180-day exclusivity triggered before a patent expires continue to bar approvals of other ANDAs after the patent expires, even if other ANDA applicants change their certifications to paragraph II or withdraw their certifications altogether?

a. No. It is well settled that 180-day exclusivity cannot extend beyond patent expiration. There are two steps to the analysis.

In the first step of the analysis, it has always been FDA's view that a patent will be removed from the Orange Book upon expiration (if not before, where appropriate). FDA's regulation has provided, since its initial promulgation in 1994, in relevant part:

> A patent that is the subject of a lawsuit under § 314.107(c) shall not be removed from the list until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, *that the patent has expired, or* that any such period of delays in effective dates of approval is ended.

21 C.F.R. § 314.94(a)(12)(viii)(B) (emphasis added). FDA's use of the term "or" in the quoted language clearly shows that patent expiration, by itself, is sufficient reason to remove a patent from the Orange Book. FDA explained in its rulemaking preamble:

> This means that a patent is deemed to be relevant under § 314.94(a)(12)(ii) until the end of the term of the patent or applicable 180-day exclusivity period, whichever occurs first.

59 Fed. Reg. at 50,348.

In 1999, FDA published a proposed rule to revise its 180-day exclusivity regulations to include the concept of a "triggering period." 64 Fed. Reg. 42,873 (Aug. 6, 1999). Of relevance here, the agency stated in the rulemaking preamble:

> 5. Patent Expiration and 180-Day Exclusivity
>
> The agency is *clarifying* that once the patent for which the first applicant has filed a paragraph IV expires, the first applicant is no longer eligible for exclusivity. When the first applicant is no longer eligible for exclusivity, FDA may approve all otherwise eligible ANDA's. FDA regulations at § 314.94(a)(12)(viii) *currently* provide that exclusivity cannot extend beyond the term of the patent.

64 Fed. Reg. at 42,877 (emphasis added). (FDA subsequently withdrew that proposed regulation for unrelated reasons. 67 Fed. Reg. 66,593 (Nov. 1, 2002)).

In the second part of the analysis, as noted under § 314.94(a)(12)(viii) (quoted above), a patent can be removed from the Orange Book upon expiration. Once a patent is removed from the Orange Book, sponsors of pending ANDAs no longer have any obligation to certify to the patent. Thus, Apotex (and other sponsors of pending amlodipine besylate ANDAs) can delete their Paragraph IV certifications to the '303 patent as of the date of patent expiration.

b. Mylan should have lost its final approval when the court in the W.D. of Pennsylvania (02-cv-1628) found the patent valid and infringed and entered judgment against Mylan. However, if Mylan were the holder of a fully approved ANDA, it was under no obligation to amend its Paragraph IV certification upon patent expiration. But that does not help Mylan. Under the plain language of the statute, the 180-day exclusivity of the first Paragraph IV ANDA sponsor only delays the final approval of subsequent Paragraph IV ANDA sponsors. *See* 21 U.S.C. § 355(j)(5)(B)(iv). Here, after expiration of the '303 patent, there can be no Paragraph IV ANDA certifications because once the patent expires then the paragraph IV certifications are converted to paragraph III certifications which are not delayed by Mylan's 180-day exclusivity (even if such exclusivity were deemed to continue).[4]

c. The D.C. Circuit has suggested, in *dictum*, that 180-day exclusivity does not survive patent expiration: "We note ... the text and structure of the statute suggest a distinction... such that the first generic applicant may no longer retain exclusivity when the patent has expired. *Ranbaxy Laboratories Limited v. Leavitt*, 469 F.3d 120, 126 at n.* (D.C. Cir. 2006) (citations omitted).

d. FDA's longstanding view that 180-day exclusivity cannot extend beyond patent expiration is supported by sound policy considerations. It is beyond dispute that the purpose of 180-day exclusivity is to encourage generic firms to challenge patents on innovator products by providing them with a "reward" to do so. Once an Orange Book patent has expired, that patent no longer represents a bar to generic competition. Thus, allowing 180-day exclusivity to extend beyond patent expiration would contradict the intent of the Hatch-Waxman Act and provide an unnecessary windfall to the company that failed to have a patent held invalid or non-infringed before the patent expired. Such a windfall hurts American consumers, by depriving them of the lower prices that result when multiple generic firms compete after a patent expires.

---

[4] Apotex believes that there are serious questions as to whether Mylan was entitled to *any* 180-day exclusivity because it lost its own patent case. However, that issue is beyond the scope of FDA's five questions.

e. Mylan contends in its March 26, 2007 petition for stay of action (Docket No. 2007P-0116) that the current situation is unique and is not covered by prior agency pronouncements because those pronouncements do not apply to a situation (such as here) "where the 180-day exclusivity has already been awarded and triggered." Mylan Petition at 3.

For example, in its petition, Mylan attempts to distinguish *Dr. Reddy's Laboratories, Inc. v.*, 302 F.Supp. 2d 340 (D.N.J. 2003), and several FDA administrative determinations (involving fentanyl patch, cisplatin, and omeprazole) as involving ANDAs that were only tentatively approved at the time of patent expiration. That purported distinction misses the point. There is nothing in the regulation and preambles quoted above that can be read to support a distinction between a situation where 180-day exclusivity has been triggered (such as here), and one where it has not been triggered as of patent expiration. Moreover, there is nothing in either FDA longstanding interpretation that 180-day exclusivity ends with patent expiration or public policy considerations that support Mylan's view that it is entitled to a full 180-day exclusivity period solely because it triggered its exclusivity before patent expiration.

Mylan should not be rewarded for failing to bring the issue of the patent's validity to a conclusion before the patent expired, so as to enjoy during the patent's life whatever first filer exclusivity to which it was entitled.

* * *

We appreciate the agency's attention to this important matter.

Respectfully submitted,

Robert B. Breisblatt
A. Sidney Katz
Steven E. Feldman
Welsh & Katz, Ltd.
120 South Riverside Plaza, 22nd Floor
Chicago, Illinois 60606
(312) 655-1500
(312) 655-1501 (telecopy)

Arthur Y. Tsien
Olsson, Frank and Weeda, P.C.
1400 16th Street, N.W., Suite 400
Washington, DC 20036-2220
(202) 789-1212
(202) 234-3550 (telecopy)

Counsel to Apotex Inc.

OFW:jdc