

ATTACHMENT C

No. 06-5154

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

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RANBAXY LABORATORIES LIMITED, *et al.*,

Plaintiffs-Appellees,

and

IVAX PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

v.

MICHAEL O. LEAVITT, Secretary of Health and Human Services, *et al.*,

Defendants-Appellants.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

BRIEF FOR THE APPELLANTS

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**Statement of Subject Matter and
Appellate Jurisdiction**

Both Ranbaxy Laboratories Limited, *et al.* (Ranbaxy) and Ivax Pharmaceuticals, Inc. (Ivax) invoked the district court's jurisdiction under 28 U.S.C. 1331. JA 4 ¶ 13; 379 ¶ 7. The district court (Richard W. Roberts) entered a final order disposing of all claims in favor of Ranbaxy and Ivax on April 30, 2006 (JA 522), and issued an opinion dated April 30, 2006, which was entered May 1, 2006 (JA 523). The government filed a timely notice of appeal from the

amend its paragraph IV certification to a paragraph III, reflecting the fact that it will not be eligible for final approval until expiration of the patent. *Id.* FDA's practice of considering the status of the patents and paragraph IV certifications at the time of making its exclusivity determinations is fully consistent with the statute and has been upheld. See *Dr. Reddy's Labs.*, 302 F. Supp.2d at 353.¹³

In sum, the pre-MMA version of the statute provides no guidance for resolution of the delisting issue presented here. No provision addresses the possibility of delisting; nor does any pre-MMA provision otherwise provide an answer for how delisting affects patent certification or generic exclusivity. As a result, there was a statutory gap to be filled regarding delisting, and the gap was filled by 21 C.F.R. 314.94(a)(12)(viii)(B).

B. FDA's Delisting Regulation is a Reasonable Interpretation of the FDCA.

1. 21 C.F.R. 314.94(a)(12)(viii)(B) states as follows:

If a patent is removed from the list, any applicant with a pending application (including a tentatively approved application with a delayed effective date) who has made a certification with respect to such patent shall amend its certification. The applicant shall certify under paragraph (a)(12)(ii) of this section that no patents described in paragraph (a)(12)(i) of this section claim the drug or, if other relevant

¹³ In addition, a patent certification must also be amended if for any reason the original certification is no longer accurate. 21 C.F.R. 314.94(a)(12)(viii)(C). See also JA 291.

patents claim the drug, shall amend the certification to refer only to those relevant patents. In the amendment, the applicant shall state the reason for the change in certification (that the patent is or has been removed from the list). 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 delay in effective dates of approval is ended. An applicant shall submit an amended certification. Once an amendment or letter for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (a)(12)(i)(A)(4) of this section.

Under this regulation, with one limited exception (when the patent is the subject of a lawsuit), patents may be delisted at the NDA holder's request, and upon such delisting, ANDA applicants must amend their patent certifications to reflect the change in patent listing.

As FDA explained in its response to the citizen petitions, the agency could have adopted a number of approaches to patent delisting, including: (1) maintaining the patent in the Orange Book if any ANDA has filed a paragraph IV certification, (2) immediately delisting the patent upon request, regardless of the existence or status of any litigation, or (3) withdrawing the patent in some circumstances but not in others. The agency rejected the first option because no ANDA applicant has a "vested" right in exclusivity upon the mere submission of a paragraph IV certification, regardless of the later status of the patent listing or

paragraph IV certifications. JA 291. FDA rejected the second option to avoid the unjust result that would occur if an ANDA applicant who is eligible for exclusivity prevails in the patent litigation but loses exclusivity when the NDA holder delists as a result of the litigation. JA 294. See also Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,348 (1994) (“If a patent were removed from the list immediately upon a court decision that the patent is invalid or unenforceable, an applicant with a subsequently filed application might seek to certify that there is no relevant patent and seek an immediately effective approval.”). The agency thus adopted the third option as the one that best carried out the language and intent of the statute. See also pp. 15-16, *supra*.

The regulation, moreover, is consistent with another important consideration, namely, FDA’s view that it has only a ministerial role in the patent listing process and that, accordingly, control over patent listing is generally in the hands of the NDA holder, a position that the courts have uniformly upheld. See *Apotex, Inc. v. Thompson*, 347 F.3d 1335 (Fed. Cir. 2003); *aaiPharma Inc. v. Thompson*, 296 F.3d 227 (4th Cir. 2002); *Alphapharm PTY Ltd. v. Thompson*, 330 F. Supp.2d 1 (D.D.C. 2004). The agency lacks the resources and expertise to substantively review the accuracy of patent listings, see *id.*, and there are many

reasons why an NDA holder might delist a patent, including, for example, that the NDA holder no longer believes that the patent meets the criteria set forth in 21 U.S.C. 355(b)(1) & (c)(2) and at 21 C.F.R. 314.53, that a settlement with the FTC requires delisting (JA 170-72, 287), or that the NDA holder reevaluated the patents in light of FDA's revised regulations on the criteria for patent listing, see 68 Fed. Reg. 36676, 36703-05 (2003), revising 21 C.F.R. 314.53 (JA 287).

Given its lack of expertise in patent matters and its lack of resources, FDA relies on a process which it created whereby an outside party can express any doubts it has about the accuracy of a patent listing to the NDA holder through FDA. See 21 C.F.R. 314.53(f). Under this process, if a challenge is made, the NDA holder is given an opportunity to correct the listing. If the NDA holder does not alter or amend the listing, the patent remains listed. However, if a patent is delisted, an ANDA applicant who has certified to that patent must amend its certification. Significantly, this regulation recognizes that a patent holder may generally amend its patent listings as a result of the challenge, which is a result that could not occur if, as the district court here ruled, FDA were required to keep a patent listed when any paragraph IV certification has been filed to that patent. See JA 297.

Accordingly, when an NDA holder, such as Merck, delists a patent in the absence of patent infringement or declaratory judgment litigation (litigation referred to in 21 C.F.R. 314.107(c)), ANDAs with paragraph IV certifications must be amended in accordance with the change in listing status, and no ANDA applicant will be eligible for a period of generic exclusivity as to the delisted patents. The result treats the patent (or patents) at issue as though it (they) had never been listed (JA 300), and this interpretation is entitled to deference as a permissible construction of the statute. See, e.g., *Purepac Pharm. Co.*, 354 F.3d at 883; *Mylan Laboratories, Inc. v. Thompson*, 389 F.3d 1272, 1279-80 (D.C. Cir. 2004).

Indeed, *Mylan* is instructive as to deference because the Court extended *Chevron* deference to FDA's exclusivity determination, which was embodied in a letter decision, a less formal pronouncement than FDA's citizen petition response in this case. The Court explained that deference was appropriate because of "the complexity of the statutory regime under which FDA operates, the FDA's expertise or the careful craft of the scheme it devised to reconcile the various statutory provisions," and because "FDA's decision made no great legal leap but

relied in large part on its previous determination of the same or similar issues and on its own regulations” (*id.* at 1280) — the same factors present here.¹⁴

2. FDA also took into account important policy objectives in promulgating its regulation. See *Arizona Pub. Serv. Co. v. EPA*, 211 F.3d 1280, 1287 (D.C. Cir. 2000) (“As long as the agency stays within Congress’ delegation, it is free to make policy choices in interpreting the statute, and such interpretations are entitled to deference.”) (internal quotation marks and alterations omitted); *Apotex, Inc. v. FDA*, ___ F.3d ___, 2006 WL 1528871 at *4 (D.C. Cir., June 6, 2006) (same, quoting *Arizona Pub. Serv. Co.*). In its response to the citizen petitions, FDA emphasized that its regulation furthers the goals of the Hatch-Waxman Amendments by (1) maintaining appropriate exclusivity incentives, (2) properly removing listed patents that would otherwise serve as unjustified barriers to entry, and (3) not unduly placing control of exclusivity in the NDA holder’s hands. JA 296-99.

First, “as a general rule, the benefit derived from maintaining exclusivity does not justify the delay in generic drug approvals that would arise from leaving a

¹⁴ FDA also pointed out that it has been consistent in applying its delisting regulation. JA 300-02. The agency identified a number of examples of delisting when there was no patent litigation, many of which came soon after the agency’s revision of 21 C.F.R. 314.53 (see p. 31, *supra*), which describes the kinds of patents that may be listed in the Orange Book.

patent listed when the NDA holder has requested that the patent be withdrawn.”

JA 298. The narrow exception applicable when the patent has been the subject of a lawsuit “serves to continue to provide an incentive to the first applicant to pursue its patent litigation by assuring the applicant that the exclusivity reward will not be extinguished if the patent is removed from the Orange Book as a result of success in that litigation.” JA 299.

In addition, patent delisting is “relatively uncommon,” and the unavailability of exclusivity in the event of patent delisting is not likely to be a significant deterrent to the filing of ANDAs with paragraph IV certifications. JA 298. Further, all ANDA applicants who challenge patents are aware of the risk that, even if they are first to file a paragraph IV certification and thus may be eligible for exclusivity in the future, they may not have an opportunity to take advantage of that exclusivity period. As previously noted, exclusivity can be lost in a number of ways that are outside the control of the ANDA applicant who might be otherwise eligible. The patent could expire, see *Dr. Reddy's*, 302 F. Supp.2d at 353-54, or the exclusivity could be triggered (and expire before the first-filer is in a position to use it) by a court decision in litigation brought by a subsequent ANDA applicant before the first ANDA applicant can market its drug, see *Teva Pharm., USA, Inc. v. FDA*, 182 F.3d 1003, 1005 n.3 (D.C. Cir. 1999) (“The court-

decision trigger can be activated by any subsequent ANDA applicant's litigation whether or not the first applicant has enjoyed a period of exclusivity." See JA 291-92, 298.

Second, FDA considered the effect of maintaining or delisting a patent on generic drug entry in general. JA 296-98. Listed patents can result in exclusivity and thus delay market entry for subsequent ANDA applicants — because of the potential 30-month stays, the statutory 180-day generic exclusivity delay, and the possible delay in marketing the drug by the ANDA applicant eligible for exclusivity. *Id.* However, a delisted patent — like an expired patent — should not bar generic drug approval and should thus permit earlier entry of generic competition. This result is as though the patent had not been listed in the first place. JA 292, 300.¹⁵

In addition, if, notwithstanding an NDA holder's request to delist, FDA continued the listing, such listing would impose significant burdens on subsequent ANDA applicants because they would be required to certify to such patents. JA

¹⁵ Even if FDA's regulation had provided that a patent should be delisted only after expiration of the 180-day exclusivity period, ANDA applicants might still be required to wait for long periods before exclusivity is triggered — if, for example, the applicant eligible for 180-day exclusivity is unable to obtain approval of its ANDA, or fails to begin marketing. JA 297, 300. Significantly, the MMA (see n.2, *supra*) amended the FDCA to address forfeiture of exclusivity in circumstances involving the latter scenario. See 21 U.S.C. 355(j)(5)(D)(i)(I).

296 ("If a patent remains listed, any applicant submitting an ANDA for the drug product after the NDA holder requests delisting must nonetheless comply with the patent certification requirements of section 505(j)(2) [21 U.S.C. § 355(j)(2)].").

Certification would require the ANDA applicant to undertake a patent analysis if it intended to market a drug before patent expiration, and articulate why its drug product would not infringe the patent or why the patent is invalid or unenforceable. *Id.* Neither Ranbaxy nor Ivax is in a position to argue that these administrative burdens are de minimis, since both seek exclusivity based solely on their having gone to the trouble of complying with these requirements.

Continued listing would also render FDA's patent challenge process, 21 C.F.R. 314.53(f), "largely ineffective." JA 297. Pursuant to the regulation, any party with doubts about the correctness of a patent listing can submit a statement to FDA challenging the patent listing, which FDA then forwards to the NDA holder. The NDA holder then has an opportunity to correct the patent listing, either by withdrawing or amending the patent. As FDA observed, often little time passes between listing a patent and submission of ANDAs containing paragraph IV certifications. *Id.* If a patent cannot be removed from the Orange Book for any reason once a paragraph IV certification has been filed, there is "little, if any, time for meaningful use of the patent challenge process." *Id.*

Third, in deferring to the NDA holder's request to delist a patent except in the limited circumstance of patent litigation, FDA is not unduly placing control of exclusivity in the NDA holder's hands. JA 297-98. The statute gives unfettered control to the NDA holder over patent listing (but not discretion as to which patents must be listed), and as FDA has always maintained, it is in no position to second-guess a listing — or delisting — determination. *Id.*; see also pp. 30-31, *supra*. In any event, there is nothing wrong with an interpretation of the statute that permits an NDA holder to delist a patent that does not meet the statutory and regulatory requirements for listing.

In this connection, it is unlikely that an NDA holder would abuse the patent withdrawal process. JA 298. First, NDA holders have no discretion to list or delist a patent, but must make such decisions based on statutory and regulatory criteria. JA 297-98. Second, an NDA holder has no economic incentive to delist because it will lose the 30-month stay of generic approval provided in 21 U.S.C. 355(j)(5)(B)(iii) when it sues for patent infringement. JA 298. And, it is unlikely that an NDA holder would delist merely to deprive a first-filer of its generic exclusivity because an NDA holder would ordinarily prefer generic competition to be limited to one generic for the 180-day period, since prices fall further when additional competitors enter the market — a duopoly preserves more market

power than open competition. *Id.*; see also JA 169-70. Thus, even if an NDA holder had discretion to abuse the patent listing process, it would have little, or no, economic incentive to do so.¹⁶

* * * * *

In sum, 21 C.F.R. 314.94(a)(12)(viii)(B) reasonably “reconciles the statutory provisions governing patent listings and 180-day exclusivity” and “is consistent with the policy considerations underlying the Hatch-Waxman Amendments.” JA 302. The regulation also “maintain[s] a reasonable balance between allowing NDA applicants to correct patent listings and protecting the incentive for ANDA applicants to challenge listed patents.” *Id.*

C. FDA’s Approach to Patent Listing and Its Effect on Generic Exclusivity Has Been Upheld in Cases Involving Closely Related Issues.

FDA’s approach to patent listing and the generic exclusivity period — which are embodied in the decision at issue here — has been upheld in two cases addressing extremely similar issues and resolving the issues based on principles that support the agency’s decision here. In *Dr. Reddy’s Labs., Inc. v. Thompson, supra*, the plaintiff (Reddy) argued that it was entitled to exclusivity based on its

¹⁶ Moreover, drug manufacturers are aware that the FTC has been concerned about and will investigate improper listing practices. See JA 170-72, 298.

Conclusion

For the foregoing reasons, the district court's judgment should be reversed, and consistent with this Court's June 1, 2006 order granting expedition (see p.18, *supra*), we respectfully request the Court to do so as promptly as possible in order to permit FDA to approve other ANDAs whose approvals have been delayed by the district court decision.

Respectfully submitted,

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