

Filed: August 5, 2002

UNITED STATES COURT OF APPEALS

FOR THE FOURTH CIRCUIT

No. 01-2113
(CA-01-152-F)

aaiPharma Incorporated,

Plaintiff - Appellant,

versus

Tommy G. Thompson, etc., et al.,

Defendants - Appellees.

O R D E R

The court amends its opinion filed July 10, 2002, as follows:

On page 21, first full paragraph, line 19 -- "FTC" is corrected to read "FDA."

For the Court - By Direction

/s/ Patricia S. Connor
Clerk

PUBLISHED
UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

AAIPHARMA INCORPORATED,
Plaintiff-Appellant,

v.

TOMMY G. THOMPSON, Secretary of
Health and Human Services;
BERNARD SCHWETZ, DVM, Ph.D.,
Acting Commissioner of the United States Food and Drug
Administration; UNITED STATES
FOOD AND DRUG ADMINISTRATION,
Defendants-Appellees No. 01-2113

BARR LABORATORIES, INCORPORATED;
PHARMACEUTICAL, INCORPORATED,
Intervenors.

Appeal from the United States District Court
for the Eastern District of North Carolina, at Wilmington.

James C. Fox, Senior District Judge.

(CA-01-152-F)

Argued: February 25, 2002

Decided: July 10, 2002

Before MICHAEL, Circuit Judge, Raymond A. JACKSON,
United States District Judge for the Eastern District of Virginia,
sitting by designation, and Jerome B. FRIEDMAN, United States
District Judge for the Eastern District of Virginia, sitting by
designation.

Affirmed by published opinion. Judge Michael wrote the opinion, in which Judge Jackson and Judge Friedman joined.

COUNSEL

ARGUED: James C. Burling, HALE & DORR, L.L.P., Washington, D.C., for Appellant. Howard Stanley Scher, Appellate Staff, Civil Division, UNITED STATES DEPARTMENT OF JUSTICE, Washington, D.C., for Appellees. **ON BRIEF:** Mark A. Heller, HALE & DORR, L.L.P., Washington, D.C.; James D. Myers, Richard P. Vitek, MYERS, BIGEL, SIBLEY & SAJOVEC, P.A., Cary, North Carolina, for Appellant. Robert D. McCallum, Jr., Assistant Attorney General, Douglas N. Letter, Appellate Staff, Civil Division, UNITED STATES DEPARTMENT OF JUSTICE, Washington, D.C.; Daniel E. Troy, Chief Counsel, Eric M. Blumberg, Deputy Chief Counsel for Litigation, Michael N. Druckman, Associate Chief Counsel for Enforcement, UNITED STATES FOOD AND DRUG ADMINISTRATION, Rockville, Maryland, for Appellees. Dan Hartzog, Gregory Brown, CRANFILL, SUMNER & HARTZOG, L.L.P., Raleigh, North Carolina; George C. Lombardi, Christine J. Siwik, James F. Hurst, WINSTON & STRAWN, Chicago, Illinois; Robert W. Spearman, PARKER, POE, ADAMS & BERNSTEIN, L.L.P., Raleigh, North Carolina; Edgar H. Haug, Daniel G. Brown, FROMMER, LAWRENCE & HAUG, L.L.P., New York, New York, for Intervenors.

OPINION

MICHAEL, Circuit Judge:

The Federal Food, Drug, and Cosmetic Act (FFDCA) requires the manufacturer of a brand name drug approved by the Food and Drug Administration (FDA) to provide the FDA with a listing of all patents that claim the approved drug or a method of using the drug. *See* 21 U.S.C. § 355 (b)(1), (c)(2). The FDA publishes these listings in its *Approved Drug Products With Therapeutic Equivalence Evaluations*, a publication commonly known as the Orange Book. The plaintiff, aaiPharma Inc., has sued the FDA, contending that the agency has a

duty to ensure the accuracy of Orange Book listings and that the agency's refusal to do so violates the Administrative Procedure Act (APA). The district court rejected aaiPharma's APA challenge, concluding that the FDCA assigns the FDA a purely ministerial role regarding Orange Book listings. We affirm.

I.

Orange Book listings play an important role in the statutory and regulatory framework created by the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. §§ 355, 360cc and 35 U.S.C. §§ 156, 271, 282), commonly known as the Hatch-Waxman Act (Hatch-Waxman or the Act). Hatch-Waxman amended both the FDCA and the patent laws in an effort to strike a balance between "two conflicting policy objectives: to induce name-brand pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market." *Abbott Labs. v. Young*, 920 F.2d 984, 991 (D.C. Cir. 1990) (Edwards, J., dissenting on other grounds).

Prior to Hatch-Waxman's passage in 1984, both pioneer (brand name) and generic drug manufacturers who wished to bring a drug to market were required to file a New Drug Application (NDA) with the FDA. This requirement posed a formidable barrier to market entry for generic drug companies because preparation of an NDA requires expensive clinical studies demonstrating the proposed drug's safety and effectiveness. In addition, a generic manufacturer could not begin the necessary research and clinical studies until any patents on the brand name drug it sought to copy had expired because its research efforts would have infringed the patents held by the pioneer drug company. This meant that a pioneer drug company's monopoly on its brand name drug was effectively extended to include not only the terms of any patents on the brand name drug, but also the time it took generic competitors to complete the NDA process after these patents had expired. Hatch-Waxman addressed these problems by creating a streamlined procedure for FDA approval of generic drugs. A drug company that wishes to market a generic version of a brand name drug may now submit an Abbreviated New Drug Application (ANDA) to the FDA. See 21 U.S.C. § 355(j). By filing an ANDA, a

generic manufacturer can rely on the clinical studies performed by the pioneer drug manufacturer and is not required to prove the safety and effectiveness of its generic drug from scratch. Instead, the generic manufacturer must prove only that its drug is bioequivalent to the brand name drug it wants to copy. *See id.* § 355(j)(2)(A). In addition, Hatch-Waxman amended the patent laws so that a generic drug manufacturer no longer infringes the patents on a brand name drug by performing acts necessary to prepare an ANDA. *See* 35 U.S.C. § 271(e)(1).

Hatch-Waxman also contains a complex set of provisions designed to protect the intellectual property rights of pioneer drug companies and others holding patents on brand name drugs. The Act requires each drug company filing an NDA to include in its application a list of all the patents that "claim[] the drug for which the applicant submitted the application or which claim[] a method of using such drug and with respect to 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." 21 U.S.C. § 355(b)(1). If the FDA approves the application, the agency is required to publish this list in the Orange Book.¹ An NDA applicant must also amend its application to include information about any new patents claiming its drug that issue while the NDA is pending. *Id.* In addition, the holder of an approved NDA is required to submit to the FDA for Orange Book listing any new patents that claim the approved drug within thirty days of their issuance. *Id.* § 355(c)(2). With respect to each patent listed in the Orange Book for a pioneer drug, an ANDA applicant seeking to copy that drug must make one of the following four certifications in its initial application for FDA approval: (I) that no patent information for the pioneer drug has been submitted to the FDA (a "paragraph I certification"), (II) that the patent has expired (a "paragraph II certification"), (III) that the patent will expire on a specific date (a "paragraph III certification"), or (IV) that the patent "is

¹ For ease of reference, we will refer to those patents that meet the statutory criteria for Orange Book listing with respect to a given drug as patents that claim the drug. We need not explain the statutory criteria in any detail, but the general idea is that a patent claims a drug under 21 U.S.C. § 355(b)(1) if the patent might be infringed by a generic version of that drug.

invalid or will not be infringed by the manufacture, use, or sale of the new drug" for which the ANDA applicant seeks approval (a "paragraph IV certification"). *Id.* § 355(j)(2)(A)(vii)(I)-(IV). An ANDA applicant must also make an additional certification as to any new patent listed in the Orange Book while its application is pending, so long as the NDA holder submits the new patent to the FDA for listing no more than thirty days after the patent's issuance. 21 C.F.R. § 314.94(a)(12)(vi). The certification made by the ANDA applicant determines the date on which FDA approval of the application can become effective. ANDAs containing paragraph I or II certifications may be approved immediately if the FDA finds that all the relevant scientific and regulatory requirements have been met. 21 U.S.C. § 355(j)(5)(B)(i). An ANDA that contains a paragraph III certification becomes effective on the patent's expiration date, assuming that other FDA requirements have been satisfied. *Id.* § 355(j)(5)(B)(ii). Thus, certifications under paragraphs I, II, and III tell the FDA that it need not worry about the patent law implications of the generic drug because the drug will not enter the market until any relevant patents have expired. In contrast, an ANDA applicant making a paragraph IV certification intends to market its product before the relevant patents have expired. The effective date for an ANDA containing a paragraph IV certification is determined by the outcome of the following sequence of events.

An ANDA applicant making a paragraph IV certification with respect to a patent must give notice of this certification to both the NDA holder and the patent holder (often, but not always, these will be the same party) and must explain in detail why it believes that the patent is invalid or will not be infringed by the generic drug for which it seeks approval. *Id.* § 355(j)(2)(B). Hatch-Waxman provides that the act of filing a paragraph IV certification with respect to a patent creates a cause of action for patent infringement in the patent holder. *See* 35 U.S.C. § 271(e)(2)(A) ("It shall be an act of infringement to submit . . . [an ANDA] . . . if the purpose of such submission is to obtain [FDA] approval . . . to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent . . . before the expiration of such patent."). Once the patent holder receives notice of the certification, it has forty-five days in which to file a suit for patent infringement. Failure to file within this forty-five day period means that the FDA may approve the ANDA without delay. 21 U.S.C.

§ 355(j)(5)(B)(iii). But if the patent holder files suit, FDA approval of the ANDA is automatically stayed for up to thirty months.² Together, these provisions protect the holder of a patent that claims a brand name drug by giving the patent holder a chance to vindicate its intellectual property rights before the FDA approves a generic version of the drug. *See Bristol-Myers Squibb Co. v. Royce Labs., Inc.*, 69 F.3d 1130, 1135 (Fed. Cir. 1995). Orange Book listing of a patent is important because it is the trigger for this protection. If a patent is not listed in the Orange Book, ANDA applicants do not have to file a paragraph IV certification, and the patent holder is unable to take advantage of the thirty-month stay.

II.

On July 10, 2001, aaiPharma received a patent (the '853 patent) on a polymorphic variant of the active ingredient in Prozac, a widely prescribed antidepressant drug manufactured by Eli Lilly & Company (Lilly). U.S. Patent No. 6,258,853. Lilly's claim of exclusivity for Prozac under the patent laws was scheduled to expire on August 2, 2001. Several generic drug manufacturers (including intervenors Barr Laboratories, Inc. and Par Pharmaceuticals, Inc.) were set to begin marketing generic versions of Prozac the next day. aaiPharma was concerned that its new patent might be infringed by these generic drugs, and the company therefore sought to have its '853 patent included in the Orange Book listing for Prozac. As explained above, Orange Book listing of the '853 patent would confer significant benefits on aaiPharma. An ANDA applicant seeking to market a generic version of Prozac before the expiration of the '853 patent would be required to make a paragraph IV certification regarding the patent. aaiPharma would then have the ability to trigger the thirty-month stay (and so delay FDA approval of the ANDA applicant's generic version of Prozac) by filing a patent infringement suit against the applicant.³

² More precisely, the stay continues until the earliest of (1) the expiration of the patent, (2) judicial resolution of the patent infringement suit, or (3) thirty months from the patent holder's receipt of notice. 21 U.S.C. § 355(j)(5)(B)(iii). In addition, a court in which a patent suit is pending may order a shorter or longer stay if "either party to the action fail[s] to reasonably cooperate in expediting the action." *Id.*

³ As the district court observed, aaiPharma does not have a drug of its own ready for market. The record does not disclose the reasons for aai-

Because only the NDA holder can submit patents claiming its approved drug for listing in the Orange Book, aaiPharma asked Lilly to submit the '853 patent to the FDA. Lilly refused.⁴ aaiPharma then sent a letter to the FDA asking the agency to "contact Lilly to confirm the correctness of Lilly's omission of information about the '853 patent from the list of Prozac-related patents in the Orange Book." aaiPharma suggested that if Lilly persisted in its refusal to list the '853 patent, the FDA had an obligation to intervene. The FDA, however, has determined that it will not become an arbiter of the correctness of Orange Book listings. Its regulations implementing the Hatch-Waxman Act provide only a very limited mechanism for resolving disputes regarding those listings. *See* 21 C.F.R. § 314.53(f). Consistent with its regulation, the FDA responded to aaiPharma's request by sending a letter to Lilly requesting that Lilly confirm the correctness of its Orange Book listing for Prozac. The letter explained that the FDA would make no change to the listing unless Lilly asked it to do so. The record does not indicate whether Lilly has responded to this letter.

Having failed in its efforts to secure Orange Book listing for the '853 patent by contacting Lilly and the FDA, aaiPharma brought this lawsuit under the Administrative Procedure Act in the Eastern District of North Carolina on August 2, 2001, only hours before the FDA was set to approve the marketing of several generic versions of Prozac. aaiPharma alleged that the FDA's failure to require Lilly to list the '853 patent in the Orange Book was "arbitrary, capricious . . . or otherwise not in accordance with law" under § 706(2)(A) of the APA and asked the court to order the FDA to require Lilly to submit the '853 patent for listing in the Orange Book. aaiPharma also filed a motion for preliminary relief under Fed. R. Civ. P. 65. It sought a temporary

Pharma's avid interest in securing the thirty-month stay. We decline to speculate about aaiPharma's motives as they are not material to the resolution of this case.

⁴ Lilly would have benefitted significantly from any delay in the introduction of generic Prozac, and so it had a strong financial incentive to grant aaiPharma's request that the '853 patent be listed in the Orange Book. There is nothing in the record to indicate why Lilly refused aaiPharma's request despite this financial incentive.

restraining order and a preliminary injunction that would prevent the FDA from approving any ANDAs for generic Prozac until the court could determine whether the FDA had a duty to require the listing of the '853 patent. The district court held a non-evidentiary hearing on August 2, 2001, and denied the motion for preliminary relief from the bench. In a subsequent opinion dated August 13, 2001, the court explained that it had denied aaiPharma's request for preliminary relief primarily on the ground that there was no likelihood of success on the merits because the FDA's interpretation of the relevant statutes was not only reasonable, but correct. *See Blackwelder Furniture Co. of Statesville, Inc. v. Seilig Mfg. Co.*, 550 F.2d 189, 195 n.3 (4th Cir. 1977) (stating that the probability of success on the merits is the most important factor in evaluating a motion for a preliminary injunction when there is no decided imbalance of hardship in the plaintiff's favor if the injunction is denied). The court reasoned that Hatch-Waxman places the responsibility for deciding which patents to list in the Orange Book solely on NDA holders like Lilly and that the FDA's role in Orange Book listings is purely ministerial: "Congress decided that the FDA's task simply is to publish — without question — whatever patent information . . . is supplied to it by the NDA holder pursuant to the statute." Although the court had given no notice to the parties of any intention to enter final judgment in the case, the court noted in the conclusion of its opinion that it was "effectively . . . ruling against [aaiPharma] on the merits." The court therefore directed the clerk "to enter judgment and to close [the] file." aaiPharma appeals on both procedural and substantive grounds. Specifically, it contends that the district court erred procedurally by entering a final judgment on the merits without providing aaiPharma with notice and an adequate opportunity to be heard and that the court erred substantively by upholding the FDA's policy of non-intervention in Orange Book listing disputes.

III.

We first address the procedural question of whether the district court, after holding a hearing on aaiPharma's motion for preliminary relief, erred by entering judgment against the company without giving notice that it was considering final disposition on the merits. Although Fed. R. Civ. P. 65(a)(2) allows a district court to order consolidation of a preliminary injunction hearing with a trial on the mer-

its, we have long held that before consolidation is ordered, "the parties should normally receive clear and unambiguous notice to that effect either before the hearing commences or at a time which will still afford the parties a full opportunity to present their respective cases." *Gellman v. Maryland*, 538 F.2d 603, 604 (4th Cir. 1976) (internal quotation marks and citation omitted). The notice requirement is necessary because "the facts adduced [at a preliminary injunction hearing] often will not be sufficient to permit an informed determination of whether a direction for the entry of judgment is appropriate." *Berry v. Bean*, 796 F.2d 713, 719 (4th Cir. 1986) (quoting 11 Charles Alan Wright & Arthur R. Miller, *Federal Practice and Procedure* § 2950 at 492 (1973)). As a result, "a party addressing only issues of preliminary relief should not ordinarily be bound by its abbreviated and only partially informed presentation of the merits." *Id.* Here, the district court gave the parties no notice of any kind that it might enter judgment on the merits after the hearing on the motion for preliminary relief. Although this case turns completely on legal issues, and aaiPharma has not pointed to any factual evidence that it might have presented to the district court, the company contends that it did not have the opportunity to present the district court with the full battery of legal arguments in favor of its position. Specifically, aaiPharma claims that if it had received notice that the district court intended to rule on the merits, it would have submitted further briefing addressing such issues as "the Hatch-Waxman Act's application to non-NDA holders [and] the mandatory nature of NDA holders' obligations under the Act to provide information on eligible patents to [the] FDA." Brief for Appellant at 20. We agree with aaiPharma that the district court's spontaneous entry of final judgment was error because it deprived aaiPharma of a full and fair opportunity to present its case. *Cf. U. S. Dev. Corp. v. Peoples Fed. Sav. & Loan Ass'n*, 873 F.2d 731, 736 (4th Cir. 1989) (stating that "regardless of a claim's merits, a district court may not *sua sponte* enter summary judgment against it until the claim's proponent has been given notice and a reasonable opportunity to be heard"). Ordinarily, the proper course would be to vacate the district court's judgment and to remand for that court to decide the merits of the case after the parties have had a fair chance to develop their positions.

In this case, however, special circumstances allow us to put aside the district court's procedural error and render a decision on the mer-

its. First, aaiPharma acknowledges that it has now presented us with all the legal arguments that it would have made to the district court if given the opportunity. Indeed, aaiPharma's counsel stated at oral argument that his client "would welcome" a decision on the merits from this court. This, we conclude, amounts to a waiver of aaiPharma's objection to the district court's procedural error. Second, the case turns wholly on the legal question of whether the FDA's refusal to police the correctness of Orange Book listings violates the APA. If we were to remand the case, we would likely find ourselves reviewing the district court's ruling on this issue next year in light of the same record and the same arguments we have before us now. Under these circumstances, we conclude that it is appropriate to reach the merits of the case. We therefore turn to the question of whether the FDA's refusal to conduct any independent inquiry into the correctness of Orange Book listings is arbitrary, capricious, or otherwise not in accordance with law.

IV.

Because Lilly's NDA for Prozac was approved long before aaiPharma obtained the '853 patent, 21 U.S.C. § 355(c)(2) determines Lilly's obligations with respect to that patent. It provides that for patents issued after the approval of an NDA, the NDA holder

shall file with the [FDA] the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to 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. . . . [I]f the [NDA holder] could not file [the required patent information as part of its application] because no patent had been issued when an application was filed or approved, the holder shall file [the required information regarding the new patent] not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the [FDA] shall publish it.

21 U.S.C. § 355(c)(2). It is clear, then, that if (as aaiPharma asserts) the '853 patent "claims" Prozac in the sense provided in § 355(c)(2), Lilly is obligated to submit the '853 patent for listing in the Orange Book, and the FDA is required to publish the submitted listing.⁵ It is unclear, however, whether there is any effective way to enforce an NDA holder's obligation to submit for Orange Book listing every patent that claims its approved drug (or its corresponding obligation not to submit patents that do not claim its approved drug).

The question is important because, as we explained earlier, listing of a patent in the Orange Book triggers the availability of the thirty-month stay. If there is no enforcement mechanism to ensure that an NDA holder complies with its statutory obligations, an NDA holder can abuse the Orange Book listing process in such a way that (1) the NDA holder enjoys the protection of the thirty-month stay when it is not entitled to do so, or (2) a third party patentee (a person or entity other than the pioneer drug company that holds a patent claiming a pioneer drug) fails to receive the protection of the stay even though it is entitled to receive that protection. The first (and more serious) problem arises when an NDA holder wrongly lists a patent in the Orange Book that does not actually claim its approved drug under the standard set forth in § 355(c)(2). Once the patent is listed, the NDA holder can delay an ANDA applicant's entry into the marketplace for up to thirty months (and extend its monopoly power) simply by filing a patent infringement suit. The NDA holder receives this benefit regardless of whether the patent meets the statutory criteria for Orange Book listing. Thus, the absence of any mechanism for ensuring the accuracy of Orange Book listings means that "the patentee/NDA holder [can receive] almost automatic injunctive relief for even marginal infringement claims." Terry G. Mahn, *Patenting Drug Products: Anticipating Hatch-Waxman Issues During the Claims Drafting Process*, 54 Food Drug Cosm. L.J. 245, 250 (1999). The harm to generic drug manufacturers, and ultimately to the consuming public, is obvious. The second problem arises when an NDA holder refuses to submit an eligible third-party patent for listing in the Orange Book. This is the wrong complained of by aaiPharma.

⁵ We express no opinion, of course, on the question of whether the '853 patent meets the statutory criteria for inclusion in the Orange Book listing for Prozac.

Although an improper refusal to list a patent in the Orange Book is less obviously threatening to the public interest than an improper listing of a patent, we agree with aaiPharma that third-party holders of patents claiming an approved drug are also entitled to the thirty-month stay. Accordingly, aaiPharma has a legitimate grievance if Lilly has wrongfully refused to list the '853 patent in the Orange Book.

We are not the first court to consider whether parties aggrieved by an NDA holder's Orange Book listings have any remedy. Generic drug manufacturers have brought suits against NDA holders to compel them to delist certain patents on the ground that the patents did not claim the approved drug under the statutory criteria in §§ 355(b)(1) and (c)(2). It is now well established, however, that "a generic drug manufacturer cannot bring a declaratory judgment action or an injunctive action against a NDA holder under either the FDCA or the patent laws requiring it to take steps to 'delist' a patent from the Orange Book." *Andrx Pharm., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1373-74 (Fed. Cir. 2002). If a generic manufacturer cannot sue an NDA holder to compel delisting of a patent, it follows that a third-party patentee cannot sue an NDA holder to compel listing of a patent. This is why aaiPharma has brought suit against the FDA rather than against Lilly. The Federal Circuit, however, has acknowledged that a party aggrieved by an NDA holder's Orange Book listing could properly bring a lawsuit under the APA raising a challenge to the FDA's practice of "refusing to inquire into the correctness of [an Orange Book] listing." *Id.* at 1379 n.8. This is that case.

The FDA's policy regarding Orange Book listing disputes is codified in § 314.53(f) of the regulations implementing Hatch-Waxman:

Correction of patent information errors. If any person disputes the accuracy or relevance of patent information submitted to the agency under this section and published by the FDA in the list [the Orange Book], or believes that an applicant has failed to submit required patent information, that person must first notify the agency in writing stating the grounds for disagreement. . . . The agency will then request of the applicable new drug application holder that the correctness of the patent information or omission of patent

information be confirmed. *Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list.*

21 C.F.R. § 314.53(f) (emphasis added). The regulation goes on to say that ANDA applicants must make a proper certification regarding each patent listed in the Orange Book "despite any disagreement as to the correctness of the patent information." *Id.* In short, the FDA's position is that if the NDA holder stands on its Orange Book listing, aggrieved parties are out of luck. The FDA defends this purely ministerial conception of its role in the Orange Book listing process by explaining that it lacks both the resources and the expertise to police the correctness of Orange Book listings. aaiPharma acknowledges that the FDA has no responsibility to independently evaluate the correctness of every patent listing submitted by an NDA holder. It simply argues that if a party alerts the FDA to concerns that an NDA holder has incorrectly failed to list a patent, the FDA must do more than simply ask the NDA holder to look into the matter and accept whatever it says. Specifically, aaiPharma contends that upon learning of a dispute about the correctness of an Orange Book listing, "the FDA is required to make a substantive determination about eligibility and to take remedial measures against the NDA holder if it determines that the patent should be listed." Reply Brief for Appellant at 6 n.1. According to aaiPharma, the FDA's refusal to inquire into the correctness of Orange Book listings improperly delegates the FDA's statutory duties to NDA holders.⁶

In evaluating the FDA's interpretation of its governing statute, we

⁶ The parties frame the central issue in this case somewhat differently. aaiPharma says that the issue is whether the FDA has a duty to ensure that all eligible patents are listed in the Orange Book. In contrast, the FDA says the issue is whether it has a duty to ensure that Orange Book listings are correct (neither underinclusive nor overinclusive). For reasons that we explain below, *see infra* at 18-19, we do not think these different formulations of the issue have any impact on the outcome of this case because we conclude that if the FDA has a duty to police improper refusals to list patents, it must also have a duty to police improper listings of patents.

employ the familiar two-step analysis established by the Supreme Court in *Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842-45 (1984). In step one of the *Chevron* analysis, we ask whether "Congress has directly spoken to the precise question at issue." Here, that question is whether the FDA has an obligation to police the correctness of an NDA holder's Orange Book listings. "If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Id.* at 842-43. If, on the other hand, we find that "the statute is silent or ambiguous with respect to the specific issue, the question . . . is whether the agency's answer is based on a permissible construction of the statute." *Id.* at 843.

Both aaiPharma and the FDA claim that this case can be resolved at step one of the *Chevron* analysis because Congress has clearly expressed its intentions about the proper role of the FDA in Orange Book listing disputes. The FDA relies on the language of 21 U.S.C. § 355(c)(2), which says:

[I]f the holder of an approved [new drug] application could not file patent information [for a patent claiming the new drug] because . . . no patent had been issued when an application was filed or approved, the holder shall file such information . . . not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the [FDA] shall publish it.

According to the FDA, this statute clearly indicates that the NDA holder bears the sole responsibility for filing the required information on all the patents that claim its approved drug and that the FDA's role in the process is completely passive. aaiPharma relies on two different provisions, 21 U.S.C. §§ 355(d)(6) and (e)(4), to claim that Congress clearly intended for the FDA to play some role in ensuring that all eligible patents are listed in the Orange Book. Subsection (d) outlines the various grounds on which the FDA may refuse to approve an NDA. It states, among other things, that if, after notice and an opportunity for hearing, the FDA finds that "(6) the application failed to contain the patent information prescribed by subsection (b) of this section [a list of the patents claiming the drug] . . . [it] shall issue an order refusing to approve the application." 21 U.S.C. § 355(d). Simi-

larly, § 355(e) says that, after notice and opportunity for hearing, the FDA "shall . . . withdraw approval of an application" if it finds that "(4) the patent information prescribed by subsection (c) of this section was not filed within thirty days after the receipt of written notice from the [FDA] specifying the failure to file such information." *Id.* § 355(e). According to aaiPharma, these provisions indicate that the FDA has a duty to ensure that a pioneer drug company has submitted all the patents eligible for inclusion in the Orange Book.

Considered in isolation, the provisions cited by the FDA and aaiPharma could arguably qualify as clear expressions of congressional intent about the proper role of the FDA in Orange Book listing disputes. Step one of *Chevron*, however, requires us to look to the statute as a whole to determine whether Congress has unambiguously expressed its intent. *See Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1067-68 (D.C. Cir. 1998). Because subsection (c)(2) appears to conflict with subsections (d)(6) and (e)(4), we conclude that Congress has failed to express clearly its intent about the FDA's role in the Orange Book listing process. Accordingly, we proceed to step two of *Chevron* and ask whether the FDA's interpretation of its role as purely ministerial rests on a permissible construction of § 355.

There can be no question that the FDA's reading of subsection (c)(2) is reasonable. Indeed, that provision's requirement that the FDA "shall file" the patent information submitted by NDA holders is most naturally read to suggest that Congress intended for the FDA to play a purely ministerial role. The harder question is whether the apparent reasonableness of the FDA's position is undermined by the language of subsections (d)(6) and (e)(4).

Subsection (d)(6) requires the FDA to refuse to approve an NDA that fails to contain the patent information required by § 355(b)(1), namely, a listing of the patents that claim the drug for which the application was submitted. According to aaiPharma, this provision obligates the FDA to independently determine whether the NDA applicant has listed all the patents that meet the statutory criteria for Orange Book listing. We conclude, however, that the statute can reasonably be read to impose only a much more limited duty on the FDA. This is because an NDA's "failure to contain the patent information prescribed by subsection (b)" can be understood in two differ-

ent ways. On the reading proposed by aaiPharma, an NDA applicant fails to file the required patent information whenever its submissions for Orange Book listing fail to properly identify those patents that meet the statutory criteria. In other words, aaiPharma reads subsection (d)(6) to say that an NDA must be denied whenever the NDA applicant's patent law judgments are incorrect. There is, however, a far more modest interpretation of subsection (d)(6). On this more modest reading, an NDA applicant fails to file the required patent information only when it completely fails to submit a list of patents or a declaration that its drug is not claimed by any current patents. *See* 21 C.F.R. § 314.53(c)(3). In other words, the FDA's duty is not to ensure the correctness of the list of patents submitted for Orange Book listing, but simply to ensure that either a patent list has been filed or a declaration has been made that there are no patents to be listed. This second reading of subsection (d)(6) is at least as reasonable as the first. Further, aaiPharma's reading of subsection (d)(6) leads to an implausibly broad account of the FDA's duties under Hatch-Waxman. aaiPharma concedes that the Act does not require the FDA to assess the correctness of every determination by an NDA applicant that a patent claims or fails to claim its drug. Instead, aaiPharma contends that the FDA must make its own determination about whether a patent is eligible for listing only if a dispute is brought to the FDA's attention. We find it difficult, however, to read subsection (d)(6) as imposing only this relatively limited enforcement obligation on the FDA. If the statute requires the FDA to police the correctness of Orange Book listings at all, the obligation is far broader than aaiPharma is prepared to acknowledge. Subsection (c)(1)(A) requires the FDA to "approve [an NDA] if [it] . . . finds that none of the grounds for denying approval specified in subsection (d) of this section applies." This means that the FDA has an obligation to evaluate *every* NDA for compliance with the standards in subsection (d), including the requirement in subsection (d)(6) that the application "contain the patent information prescribed in subsection (b) of this section." If as aaiPharma contends, subsection (d)(6) commands the FDA to second-guess the NDA applicant's judgments about which patents claim its drug, that command is not limited to cases in which a third party has questioned the correctness of those judgments. In short, aaiPharma's reading of subsection (d)(6) must be wrong because it would require the FDA to "screen the universe of patents to determine which ones

should be listed" - a result aaiPharma explicitly disclaims. Reply Brief for Appellant at 9. We conclude that on the better reading of subsection (d)(6), the FDA is required only to ensure that each NDA applicant has submitted either a list of patents claiming its drug or a declaration that there are no patents to be listed.

Section 355(e)(4) says that the FDA shall withdraw approval of an NDA if "the patent information prescribed by subsection (c) of this section [a list of patents claiming the approved drug] was not filed within thirty days after the receipt of written notice from the [FDA] specifying the failure to file such information." According to aaiPharma, this provision allows the FDA to make a written demand that an NDA holder submit a patent for listing and to enforce compliance with that demand by threatening to withdraw approval of an NDA. The company argues that the FDA must necessarily have made a prior determination that a patent is eligible for listing before making such a written demand. This means, aaiPharma says, that the FDA has a duty to ensure that all eligible patents are listed in the Orange Book. The argument is somewhat more persuasive than aaiPharma's argument regarding subsection (d)(6). It sounds plausible to say that because subsection (e)(4) concerns the withdrawal of a previously approved NDA, its reference to an NDA holder's failure to file the patent information prescribed by subsection (c) must mean that the NDA holder has failed to list some specific patent that is eligible for listing. The conclusion appears to follow because an NDA that failed to contain a list of patents (or a declaration that there were no patents to be listed) would never have been approved in the first place. We note, however, that subsection (c)(2) requires the submission of patent information by holders of approved NDAs in two different situations. The situation emphasized by aaiPharma occurs when a new patent claiming a pioneer drug is issued after the NDA for that drug has been approved. In this situation, the NDA holder is obligated to submit the new patent for Orange Book listing no later than thirty days after the patent is issued. However, subsection (c)(2) also addresses the situation of drug companies whose NDAs were approved before the passage of the Hatch-Waxman Act. Such companies had never submitted information about patents claiming their drugs to the FDA because they were not required to do so. Subsection (c)(2) required these NDA holders to submit patents for listing in the Orange Book no later than thirty days after September 24, 1984, the date of Hatch-Waxman's

enactment. We think it likely that in drafting subsection (e)(4), Congress intended to provide the FDA with a means to ensure that holders of NDAs approved prior to the Act's passage would comply with the new patent listing requirements. Accordingly, we conclude that, just as in subsection (d)(6), the "failure to file the required patent information" discussed in subsection (e)(4) can reasonably be read to mean that the pioneer drug company has failed to submit a list of patents claiming the drug or a declaration that there are no patents to be listed. It follows that subsection (e)(4) does not undermine the reasonableness of the FDA's reading of 21 U.S.C. § 355.

Two additional points support the reasonableness of the FDA's reading of the statute. First, aaiPharma's appeals to subsections (d)(6) and (e)(4) derive much of their force from the way in which aaiPharma frames its argument. According to aaiPharma, the "failure to contain" and "failure to file" language in these subsections indicates that the FDA has a duty to intervene when pioneer drug companies fail to submit an eligible patent for listing in the Orange Book. In other words, aaiPharma explicitly claims only that the FDA has a duty to ensure that all eligible patents are listed in the Orange Book and takes no position on whether the FDA also has a duty to ensure that ineligible patents are not listed in the Orange Book. The company's argument ignores an important point. We think it clear that if Congress had intended to impose any duty on the FDA to police Orange Book listings, it would have required the FDA to ensure that ineligible patents are not listed in the Orange Book. This is because, as we noted earlier, improper listing of patents in the Orange Book is a far more serious problem than the improper refusal to list patents. By taking advantage of the thirty-month stay, a pioneer drug company that improperly lists a patent can cost consumers millions of dollars by keeping its generic competitors from bringing their products to market. In contrast, a drug company's improper refusal to list an eligible patent held by a third party like aaiPharma principally harms only the third party by depriving it of its statutory right to receive the protection of the thirty-month stay.⁷ As a result, it is hard to believe that

⁷ It is important to recognize that the third-party patentee can still pursue patent infringement suits against generic manufacturers. It is simply deprived of the opportunity to litigate its infringement claims under the shelter of the thirty-month stay.

Congress would impose a duty on the FDA to police the improper refusal to list patents without also imposing a duty to police the improper listing of patents. This means that for aaiPharma's argument to succeed, the company must show that subsections (d)(6) and (e)(4) require the FDA to ensure that Orange Book listings are correct: neither underinclusive nor overinclusive. Once this point is appreciated, aaiPharma's appeal to these subsections loses much of its force. The "failure to contain" and "failure to file" language in subsections (d)(6) and (e)(4) makes sense if, as we suggest, these provisions simply require the FDA to ensure that patent lists are submitted in a timely fashion. It might also make sense if Congress had intended to require the FDA to police only improper refusals to list patents in the Orange Book. But it seems odd language in which to articulate a general FDA duty to ensure that Orange Book listings are correct. We conclude that if Congress had meant for the FDA to ensure that Orange Book listings are neither underinclusive nor overinclusive, it would have not have used the language it did in subsections (d)(6) and (e)(4).

Second, the FDA's reading of the statute is reasonable in light of the division of intellectual labor established by the Hatch-Waxman Act. The FDA points out that the whole point of the Act's paragraph IV certification scheme is to let private parties sort out their respective intellectual property rights through patent infringement suits while the FDA focuses on its primary task of ensuring that drugs are safe and effective. This division of labor is appropriate because the FDA has no expertise in making patent law judgments. It seems unlikely, then, that Congress intended to require the FDA to take on the responsibilities urged upon it by aaiPharma. For all these reasons, we conclude that the FDA's conception of its role in Orange Book listings as purely ministerial rests on a permissible construction of § 355.

aaiPharma also contends that the FDA's refusal to police the correctness of Orange Book listings is arbitrary and capricious in violation of the APA because it delegates the FDA's statutory responsibilities to private parties. aaiPharma claims that it is arbitrary for the FDA to allow NDA holders, in their unreviewable discretion, to determine whether eligible patents are listed in the Orange Book. According to aaiPharma, the inevitable result of the FDA's policy is that similarly situated patent holders will be treated differently. We

are unpersuaded. The first problem with the argument is that by accusing the FDA of wrongfully delegating its statutory duties to NDA holders, aaiPharma assumes that the FDCA imposes these statutory duties on the FDA in the first place. This, of course, is the very question at issue. As we have already explained, the FDA's conclusion that it has no statutory duty to police the correctness of Orange Book listings rests on a permissible construction of the statute. Further, we think that the FDA has provided a reasoned explanation for its policy that is sufficient to satisfy the standard of review set forth in *Motor Vehicle Mfrs. Ass'n of the United States, Inc. v. State Farm Mutual Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). In *State Farm* the Supreme Court explained that the scope of review under the arbitrary and capricious standard is narrow. We must ensure that "the agency [has] examine[d] the relevant data and articulate[d] a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *Id.* (internal quotation marks and citation omitted). An agency rule would normally be arbitrary and capricious, however, if "the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Id.* In issuing its final rules regarding the patent listing requirements imposed by Hatch-Waxman, the FDA explicitly considered objections to its proposed § 314.53(f). Two commenters argued that the FDA should "ensure that the patent information submitted to the agency is complete and applies to a particular NDA." Abbreviated New Drug Application Regulations, Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,345 (Oct. 3, 1994). The FDA responded that it did not have "the resources or the expertise to review patent information for its accuracy and relevance to an NDA." *Id.* It also pointed out that an NDA applicant's potential liability for submitting untrue statements of fact to the agency would provide some check against abuse of the listing process. Finally, the agency observed that the informal procedure described in § 314.53(f) had proven effective in the past because "most NDA holders have amended or corrected their patent information after FDA has informed them of a dispute." *Id.* These explanations of the FDA's position are not especially detailed, but we cannot say the agency's

decision making was arbitrary and capricious. As we have explained, the FDA was asked by commenters to take on enforcement responsibilities that are not clearly imposed by its governing statute. When an agency has discretion about whether to take on enforcement responsibilities, an explanation that it lacks the resources and the expertise to do so is enough to satisfy the requirement of reasoned agency decision making articulated in *State Farm*.

None of this is to say that we are unsympathetic to aaiPharma's concerns. We agree with aaiPharma that Hatch-Waxman protects the intellectual property rights of third-party patentees and that, if the '853 patent claims Prozac, aaiPharma is entitled to enjoy the benefits of the thirty-month stay. Ultimately, aaiPharma's argument boils down to the plausible claim that if NDA holders have a statutory obligation to submit the correct list of patents for publication in the Orange Book and the failure to comply with that obligation deprives third parties of benefits conferred by Congress, there must be some mechanism to enforce this obligation. Because the FDCA clearly does not allow private enforcement of an NDA holder's listing obligations, aaiPharma concludes that enforcement responsibility must fall on the FDA and that the agency's refusal to accept that responsibility is arbitrary and capricious. Although we find some force in this argument, we cannot accept the proposition that an agency's failure to fill an enforcement gap created by a statute is necessarily arbitrary and capricious.⁸ We conclude that until Congress takes further action to address the enforcement gap in Hatch-Waxman's patent listing provisions, the FDA may persist in its purely ministerial approach to the Orange Book listing process.

⁸ We are encouraged to learn that there does appear to be at least one mechanism for enforcing an NDA holder's obligation not to list patents that do not claim its approved drug. Generic drug manufacturers, state agencies, and consumer groups have begun to bring antitrust suits against NDA holders who seek to use improper Orange Book listings to extend their monopoly power. See *In re Buspirone Patent Litigation*, 185 F. Supp. 2d 363 (S.D.N.Y. 2002). The Federal Trade Commission has also begun to address the potentially anticompetitive effects of improper Orange Book listings. See Prepared Statement of the Federal Trade Commission Before the Committee on Commerce, Science, and Transportation, United States Senate (April 23, 2002), available at www.ftc.gov/os/2002/04/pharmtestimony.htm.

V.

For the foregoing reasons, the district court's order rejecting aai-Pharma's APA challenge is affirmed.

AFFIRMED

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