UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

TEVA PHARMACEUTICALS USA, Inc.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 08-0395 (RCL)
	)	
MICHAEL O. LEAVITT, Secretary of Health and Human Services, *et al*.,	)	
	)	
Defendants.	)	
	)	

DEFENDANTS' MEMORANDUM IN OPPOSITION TO PLAINTIFF'S MOTION FOR A PRELIMINARY INJUNCTION

INTRODUCTION

The instant case is about whether the U.S. Food and Drug Administration ("FDA") is permitted to use the most current information available when it ensures compliance with statutory patent listing and certification requirements. FDA believes that this is an appropriate method of ensuring compliance, while plaintiff Teva Pharmaceuticals, Inc. ("Teva") seeks to prevent FDA from doing so.

More than six years ago, Teva, a generic drug manufacturer, withdrew a purported certification to a patent that it conceded then had been "delisted." See February 26, 2008, Letter from Janet Woodcock to Deborah A. Jaskot ("FDA Pet. Resp.," attached as Ex. 2 to P.I. Mem. and Ex. 5 to the complaint). Teva now asks that this Court enter mandatory emergency relief against the FDA requiring that the patent be retroactively "relisted," claiming that "time is of the essence." P.I. Mem. at 6.[1]

[1] Michael O. Leavitt, Secretary of Health and Human Services, and Andrew C. von Eschenbach, Commissioner of Food and Drugs, are also named defendants.

There are numerous reasons to deny Teva's request. First, Teva is not likely to succeed on the merits. The Federal Food, Drug, and Cosmetic Act ("FDCA") requires new drug application ("NDA") sponsors to submit patents to FDA that "claim" an innovator, or brand-name drug product. FDA is required to publish this information so that, among other things, generic drug manufacturers can decide whether their products might infringe such patents. The FDCA also requires these generic drug manufacturers to "certify" to these patents when they submit their applications to manufacture generic drugs (these applications are called abbreviated new drug applications, or ANDAs). When FDA receives an ANDA for filing, it reviews whether the application contains the information required. Among other things, FDA reviews whether the ANDA contains the appropriate patent certifications.

In this case, the NDA sponsor requested that the patent at issue, U.S. Patent Number 5,158,952 ("the '952 patent"), be "delisted" months before Teva submitted its ANDA. FDA delisted the patent from the electronic, or Internet, version of FDA's patent listing (also known as the Orange Book) before the submission of Teva's ANDA.[2] FDA informed Teva of this delisting when Teva submitted its ANDA, and Teva changed its certification accordingly. Teva does not dispute this, but argues that because the paper Orange Book was not changed to reflect this delisting until publication of the next annual edition in 2002 (which FDA does not dispute), Teva was permitted to rely on this incorrect listing (even though – after being told about the delisting – Teva acquiesced and did not object for six years).

Teva's contention is meritless. Contrary to Teva's arguments, neither the FDCA nor

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[2] The electronic Orange Book is, and at all times relevant to this dispute was, available via FDA's website, www.fda.gov.

FDA regulations limit FDA's publication of patent information to a paper version or preclude FDA from listing that information on its web site. In short, there is no statute or regulation that limits FDA's discretion in the manner urged by Teva. Nothing in 2001 (or today) prevents FDA from using the most recent information available when ensuring compliance with the FDCA. FDA's denial of Teva's citizen petition requesting FDA to "relist" the patent was eminently reasonable and not invalid under the Administrative Procedure Act ("APA").

Second, Teva cannot show irreparable harm in the event it is denied injunctive relief. Teva does not claim it will be barred entirely from the marketplace by FDA's refusal to relist the '952 patent. Rather, Teva's only claimed injury is the loss of 180 days of marketing exclusivity, which is far from the sort of harm necessary to justify preliminary injunctive relief.

Third, Teva has not shown that its requested relief would not harm third parties. Indeed, the very relief Teva seeks – denying approval to other generic applications for risperidone for six additional months – would plainly harm these other parties. See, e.g., Mem. in Supp. of Mylan's Motion to Intervene at 2-3, 7.

Fourth, Teva has not shown that an injunction would serve the public interest. The public benefits from competition among generic drug manufacturers in the form of lower prices, and granting Teva the relief it seeks would prevent consumers from receiving that benefit for at least six months.

In addition, Teva has provided no credible justification for its years-long delay. Although Teva suggests that it did not know of its supposed legal right to have the patent "relisted" until the decision in Ranbaxy Labs. Ltd. v. Leavitt, 469 F.3d 120 (D.C. Cir. 2006), that case addressed only the issue (not presented here) of whether a patent-holder may withdraw a patent "*after* a

generic manufacturer has filed an ANDA containing a paragraph IV certification." Id. at 125 (emphasis added). And even if Ranbaxy had any applicability here, Teva waited nine months after that decision to ask FDA to relist the patent at issue. Teva's lengthy delay after acquiescing in FDA's decision severely undermines its request for equitable relief, especially its allegation of irreparable harm. For all of these reasons, Teva's motion for a preliminary injunction should be denied.

BACKGROUND

I. Statutory And Regulatory Framework

Under the FDCA, pharmaceutical companies seeking to market "pioneer" or "innovator" drugs must first obtain FDA approval by filing an NDA containing extensive scientific data demonstrating the safety and effectiveness of the drug. 21 U.S.C. § 355(a), (b). An NDA applicant must also submit information on any patent that claims the drug, or a method of using the drug, and for which a claim of patent infringement could reasonably be asserted against an unauthorized party. 21 U.S.C. § 355(b)(1), (c)(2).

FDA must publish the patent information it receives, and does so both on paper and electronically, in the Orange Book. Id.; see also 21 C.F.R. § 314.53(e); FDA Pet. Resp. at 2-3. Neither the statute nor the regulation limits publication to paper only. The statute, 21 U.S.C. § 355(b)(1), simply requires FDA to "publish" the information. The regulation, 21 C.F.R. § 314.53(e), refers to publication of a "list," but does not limit this to a paper list. The regulation refers to a monthly "supplement to the list," but does not state that it must be paper only. Patent information submitted to FDA between monthly supplements is to be placed on public display at FDA. Id. The Orange Book itself refers to the electronic version of the patent listing. It states

that "[s]ince all parts of this publication are subject to changes, additions, or deletions, the Addendum must be used in conjunction with the most current 'Cumulative Supplement.'" FDA Pet. Resp. at 6. The inside cover notes that the Orange Book is updated by monthly supplements and on the internet. Id. at 7. Each Cumulative Supplement refers in turn to the availability of the electronic Orange Book. Id. at 6; P.I. Ex. 4 at § 1.3. FDA has been using its publicly available web site to keep the patent listing since 1998. Id. at 3.

The statutory provisions governing patent listings assign control over patent submissions to the NDA holder. 21 U.S.C. §§ 355(b)(1) and (c)(2). FDA interprets these provisions to afford FDA a ministerial role in the patent listing process, which includes patent listing and delisting. Rather than substantively review the accuracy of the patent listing itself – which the agency lacks the resources and expertise to do – FDA has established a "challenge" process whereby an outside party can express any doubts it has about the accuracy of a patent listing to the NDA holder through FDA. 21 C.F.R. § 314.53(f). Under this regulation, 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. FDA's ministerial approach to patent listings has been upheld against numerous challenges. See Apotex, Inc. v. Thompson, 347 F.3d 1335, 1347 (Fed. Cir. 2003); aaiPharma Inc. v. Thompson, 296 F.3d 227, 238-39, 241 (4th Cir. 2002); Alphapharm PTY Ltd. v. Thompson, 330 F.Supp.2d 1, 6-9 (D.D.C. 2004).

The Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Amendments"), codified at 21 U.S.C. §§ 355 and 35 U.S.C. §§ 156, 271, and 282, permits the submission of ANDAs for approval of generic versions of approved drug

products. 21 U.S.C. § 355(j).[3] The Hatch-Waxman Amendments were intended to balance encouraging innovation in drug development with accelerating the availability of lower cost alternatives to innovator drugs. See H.R. Rep. No. 98-857 (Part I), 98th Cong., 2d Sess. at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647-48; see also, e.g., Tri-Bio Labs., Inc. v. United States, 836 F.2d 135, 139 (3d Cir. 1987). ANDA applicants need not submit clinical data to demonstrate the safety and efficacy of the generic product, as in an NDA. See 21 U.S.C. § 355(j). Rather, an ANDA relies on FDA's previous findings that the product approved under the NDA is safe and effective, and the FDCA sets forth in detail the information an ANDA must contain. See 21 U.S.C. § 355(j)(2)(A). The timing for approval of ANDAs depends, in part, on patent protections for the innovator drug.

Among other things, an ANDA must contain one of four specified certifications for each patent that "claims the listed drug" or "a use for such listed drug for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(vii).[4] This certification must state one of the following:

> (I) that the required patent information relating to such patent has not been filed;
> (II) that such patent has expired;
> (III) that such patent will expire on a particular date; or

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[3] Congress amended 21 U.S.C. § 355(j) in 2003. See The Access to Affordable Pharmaceuticals provisions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003) (the "MMA"). The relevant provisions of these amendments do not apply to the patent certification at issue in this case because Teva's certification was submitted before the December 8, 2003, enactment date of the amendments. See id. § 1102(b)(1). Except where otherwise noted, this memorandum refers to the pre-December 2003 version of the statute.

[4] FDA has defined the "listed drug" to mean the approved new "drug product." 21 C.F.R. § 314.3(b).

> (IV) that such patent is invalid or will not be infringed by the drug for which approval is being sought.

21 U.S.C. § 355(j)(2)(A)(vii). If an applicant wishes to challenge the validity of a patent, or to claim that the patent would not be infringed by the product covered by the ANDA, the applicant must submit a certification pursuant to paragraph IV of this provision. See 21 U.S.C. § 355(j)(2)(A)(vii)(IV).[5] The applicant must also provide notice of its so-called "paragraph IV certification" to the NDA holder and the patent owner explaining the factual and legal basis for the applicant's opinion that the patent is invalid or not infringed. 21 U.S.C. § 355(j)(2)(B).

The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of infringement. 35 U.S.C. § 271(e)(2)(A). This enables the NDA holder and patent owner to sue the ANDA applicant. If such a suit is brought within 45 days of the date notice of the certification was received by the patent owner or NDA holder, FDA must stay approval of the ANDA for 30 months from that date (commonly referred to as the "30-month stay"), unless a final court decision is reached earlier in the patent case or the court orders a longer or shorter period. 21 U.S.C. § 355(j)(5)(B)(iii). If no action is brought within the requisite 45-day period, FDA may approve an ANDA with a paragraph IV certification effective immediately, provided that other conditions for approval have been met. 21 U.S.C. § 355(j)(5)(B)(iii); 21 C.F.R. § 314.107(f)(2).

In certain circumstances, the statute provides an incentive and reward to generic drug

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[5] If a certification is made under paragraph I or II indicating that patent information pertaining to the drug or its use has not been filed with FDA or that the patent has expired, the ANDA may be approved immediately. 21 U.S.C. § 355(j)(5)(B)(i). A paragraph III certification indicates that the ANDA applicant does not intend to market the drug until after the applicable patent has expired, and approval of the ANDA may be made effective on the expiration date. 21 U.S.C. § 355(j)(5)(B)(ii).

manufacturers that expose themselves to the risk of patent litigation. It does so by granting a 180-day period of marketing exclusivity (*vis-à-vis* other ANDA applicants) to the manufacturer who is first to file an ANDA containing a paragraph IV certification to a patent that claims the listed drug, provided certain conditions are met. 21 U.S.C. § 355(j)(5)(B)(iv); see Teva Pharm. Indus. v. Crawford, 410 F.3d 51, 52 (D.C. Cir. 2005); Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1064 (D.C. Cir. 1998). The statutory provision governing 180-day exclusivity provides:

> If the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification, the application shall be made effective not earlier than one hundred and eighty days after-
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> > (I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
> >
> > (II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed,
>
> whichever is earlier.

21 U.S.C. § 355(j)(5)(B)(iv).[6] Thus, under the statute, an ANDA applicant with a paragraph IV certification that is "previous" to all others for that patent may become eligible for a 180-day exclusivity period. During that period, it can market its product and approvals of other ANDAs for the same product are held in abeyance. This 180-day exclusivity is triggered by the earlier of (I) the ANDA applicant's first commercial marketing of the drug (the "commercial marketing

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[6] Courts have observed that the word "continuing" as it appears in the statute reflects a typographical error and should probably be read as "containing." See Purepac Pharm. Co. v. Friedman, 162 F.3d 1201, 1203 n.3 (D.C. Cir. 1998); Mova, 140 F.3d at 1064 n.3; see also 21 C.F.R. §§ 314.107(c)(1) & (2).

trigger"), or (ii) a decision of a court finding the patent at issue invalid or not infringed (the "court decision trigger"). Id.

The statute is clear that in the absence of ANDAs containing proper paragraph IV certifications, no ANDA applicant can obtain 180-day exclusivity. 21 U.S.C. § 355(j)(5)(B)(iv) ("If the application contains a [paragraph IV] certification . . . and is for a drug for which a previous application has been submitted [containing a paragraph IV certification], the application shall be made effective not earlier than one hundred and eighty days after . . ."). A paragraph IV certification can be submitted only to a patent that "claims the listed drug" or "a use for such listed drug for which the applicant is seeking approval." See 21 U.S.C. § 355(j)(2)(A)(vii); 21 C.F.R. § 314.94(a)(12). Absent such patent, there can be no exclusivity based on a paragraph IV certification. See 21 U.S.C. § 355(j)(5)(B)(iv).

II. Procedural History

On August 28, 2001, Teva submitted an ANDA for risperidone tablets. The reference listed drug for Teva's ANDA is Janssen Pharmaceutica's (Janssen) Risperdal tablets (NDA 20-272). The 1-milligram ("mg"), 2-mg, 3-mg, 4-mg, and 5-mg Risperdal tablets were approved in 1993. The 0.25-mg and 0.5-mg strengths were approved in 1999. After approval, the sponsor submitted information to FDA on U.S. Patent Number 4,804,663 ("the '663 patent") and the '952 patent for listing in the Orange Book entry for Risperdal tablets. The '663 patent expired on December 29, 2007, and pediatric exclusivity attached to that patent will expire on June 29, 2008.[7] The '952 patent will expire on October 27, 2009.

[7] The pediatric exclusivity statute, 21 U.S.C. § 355a, provides an additional six months of marketing exclusivity beyond the term of applicable patents and other marketing exclusivities to drug manufacturers that conduct pediatric studies at FDA's request.

By letter dated April 4, 2001, Janssen's parent company, Johnson & Johnson, requested that FDA remove the '952 patent from the Orange Book listing for 1-mg, 2-mg, 3-mg, and 4-mg Risperdal tablets. See FDA Pet. Resp. at 4. By letter dated June 11, 2001, Johnson & Johnson informed FDA that its April 4, 2001, correspondence also should have requested delisting of the '952 patent for 0.25-mg, 0.5-mg, and 5-mg Risperdal tablets, and requested removal of the '952 patent from the Orange Book listing for these strengths. Id. In response to Johnson & Johnson's request, FDA modified its patent listing database on June 11, 2001, to remove the '952 patent from the entries for Risperdal tablets in the above-referenced strengths. Id. The delisting of the '952 patent was reflected in the publicly available, electronic Orange Book shortly after June 29, 2001, and no later than July 20, 2001, the date of the next database update. Id.

Teva submitted its ANDA to FDA on August 28, 2001. Teva's ANDA contained a paragraph III certification to the '663 patent and a paragraph IV certification to the '952 patent. After reviewing Teva's application, FDA concluded that Teva had submitted a patent certification for a patent (the '952 patent) that no longer claimed Risperdal tablets. FDA then requested that Teva submit a revised patent certification, which Teva did by letter dated October 22, 2001. Id. at 5. Teva's letter stated: "U.S. Patent 5,158,952 with an expiration of October 27, 2009 has been officially delisted from the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), therefore only U.S. Patent 4,804,663 with an expiration of December 29, 2007 remains. Please find enclosed a patent certification revised accordingly." Id.; this letter is also attachment A hereto (it was exhibit 3 to Teva's citizen petition). The revised patent certification stated: "Paragraph III Certification: The undersigned hereby certifies that to the best of our knowledge and in TEVA Pharmaceuticals USA's opinion there is one

listed patent which claims the reference drug Risperdal Tablets, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg, U.S. Patent No. 4804663 Expiration December 29, 2007 . . . ." FDA Pet Resp. at 5. On October 24, 2001, FDA issued a standard acknowledgment letter to Teva indicating that Teva's ANDA for risperidone tablets had been received for substantive review.[8] Id

On August 3, 2007, Teva filed a Citizen Petition with FDA, requesting that FDA relist the '952 patent for the 0.25-mg, 0.5-mg, 1-mg, 2-mg, 3-mg, and 4-mg strengths of Risperdal tablets. See P.I. Mem., Ex. 1 at 1. Teva also asked FDA to confirm that Teva's eligibility for 180-day exclusivity was not affected by FDA's delisting of the '952 patent from the Orange Book, and to refrain from approving any other ANDAs for risperidone tablets until Teva's 180-days of exclusivity expires. Id.

FDA responded to Teva's citizen petition by letter dated February 26, 2008. See FDA Pet. Resp. FDA explained that the '952 patent had been delisted before Teva submitted its ANDA to FDA, and declined Teva's request to relist the patent. Id. at 1, 4. FDA also noted that the fact of the delisting was publicly available via the electronic Orange Book before Teva submitted its ANDA. Id. at 4. FDA informed Teva of this delisting soon after Teva had submitted its ANDA, and Teva withdrew this certification. Id. at 5. FDA also stated that its filing review of ANDAs "routinely includes a determination of whether the patent certifications contained in the ANDA correspond to the patents actually listed for the reference listed drug, as

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[8] As explained in FDA's regulations, when an ANDA is submitted, FDA reviews it to ensure that it is sufficiently complete to permit a substantive review. 21 C.F.R. § 314.101; FDA Pet. Resp. at 3 n.4. If an ANDA is incomplete when submitted, FDA does not simply reject or deny it, but typically undertakes a dialogue with the applicant (which may include telephone calls, etc.), to attempt to ensure that the application is complete. See, e.g., 21 C.F.R. § 314.101; FDA Pet. Resp. at 5; Attachment A hereto. Thus, FDA makes a distinction between when an application is received and when it is received for substantive review. FDA Pet. Resp. at 3 n.4.

assessed by the most current patent information the Agency has received." Id. at 8. FDA further stated that it "does not rely solely on the applicant's representation that the ANDA contains the required patent certifications; [FDA] conducts an independent review of the patent information . . . ." Id. FDA noted that this review pertains not only to the delisting of patents, but also to the addition of new patents. Id. at 8 n.14. Thus, FDA requires certification to newly-submitted patents even if the new patent has not yet appeared in any version of the Orange Book. Id. FDA stated that the Ranbaxy case cited by Teva was distinguishable because in Ranbaxy, the NDA holder's request to delist came almost two years after the ANDAs and paragraph IV certifications had been submitted. Id. at 8. FDA concluded that because "Teva's ANDA did not contain a paragraph IV certification for a listed patent, . . . Teva would not be eligible for 180-day exclusivity." Id. at 1-2.

Teva filed its complaint and Motion for a Preliminary Injunction on March 4, 2008.

ARGUMENT

Teva Is Not Entitled To A Preliminary Injunction

I. Legal Standard for a Preliminary Injunction

To obtain a preliminary injunction, a party must demonstrate that: (1) it has a substantial likelihood of success on the merits; (2) it will suffer irreparable injury in the absence of preliminary relief; (3) other interested parties will not be substantially injured if the requested relief is granted; and (4) granting such relief would serve the public interest. See Katz v. Georgetown Univ., 246 F.3d 685, 687-88 (D.C. Cir. 2001). The likelihood of success requirement is the most important of these factors. Id. Furthermore, the injunctive relief Teva seeks is demonstrably not to preserve the status quo, but to obtain far-reaching mandatory relief

that would reverse a course of action publicly taken more than six years ago. This peculiar request for relief presents an additional and very high hurdle for Teva. A court's power to issue such a mandatory injunction "should be sparingly exercised." Mylan Pharms., Inc. v. Shalala, 81 F. Supp.2d 30, 36 (D.D.C. 2000) ("Mylan (terazosin)"), quoting Dorfmann v. Boozer, 414 F.2d 1168, 1173 (D.C. Cir. 1969); see generally Mazurek v. Armstrong, 520 U.S. 968, 972 (1997); Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 215 (D.D.C. 1996).

As shown below, Teva has failed to satisfy any of the four elements needed to obtain a preliminary injunction. FDA appropriately denied Teva's citizen petition, all of Teva's purported injuries are economic injuries insufficient to meet the irreparable harm standard, and granting the requested relief would harm both the public and other risperidone ANDA applicants whose approvals would be delayed by at least 180 days.

II. Teva Is Not Likely to Succeed On The Merits

A. The Standard of Review Under the APA

FDA's administrative decisions are subject to review by the Court under the APA, and may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). This standard is highly deferential to the agency. Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 416 (1971). "There is a presumption in favor of the validity of the administrative action." Bristol-Myers, 923 F. Supp. at 216. Under this "arbitrary and capricious" standard, agency action must be upheld if the action is rational, based upon relevant factors, and within the agency's authority. Motor Vehicle Mfrs. Ass'n of the United States, Inc. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 42-43 (1983); see also Overton Park, 401 U.S. at 416; AT&T Corp. v. FCC, 349 F.3d 692, 698 (D.C. Cir. 2003).

Further, "under this narrow scope of review, 'the court is not empowered to substitute its judgment for that of the agency.'" Bristol-Myers, 923 F. Supp. at 216 (quoting Overton Park, 401 U.S. at 416); see also Motor Vehicle Mfrs. Ass'n, 463 U.S. at 43 (the "scope of review under the 'arbitrary and capricious' standard is narrow and a court is not to substitute its judgment for that of the agency.").[9]

When the Court is reviewing an agency's construction of statutory provisions, it is governed by the two-step analysis of Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837 (1984). First, the Court must inquire "whether Congress has directly spoken to the precise question at issue;" if Congress's intent is clear, the Court "must give effect to [such] unambiguously expressed intent." Id. at 842-43. Formulated another way, the Court must initially decide "whether the statute unambiguously forbids the Agency's interpretation." Barnhart v. Walton, 535 U.S. 212, 218 (2002). When, as here, Congress has not "directly" addressed "the precise question at issue," the Court may not "impose its own construction on the statute." Chevron, 467 U.S. at 843. Rather, it must determine if the agency's interpretation is based on "a permissible construction of the statute." Id. Chevron deference is appropriate when "the interstitial nature of the legal question, the related expertise of the Agency, the importance of the question to administration of the statute, the complexity of that administration, and the careful consideration the Agency has given the question over a long period of time all indicate that Chevron provides the appropriate legal lens through which to view the legality of the Agency

[9] Also, review is limited to the Administrative Record. Camp v. Pitts, 411 U.S. 138, 142-43 (1973). Although FDA has not yet submitted the record in this case, sufficient portions of it are before the Court for consideration of Teva's request for preliminary relief. The most important portion of the record is FDA's response to Teva's citizen petition.

interpretation here at issue." Barnhart, 535 U.S. at 222. Thus, deference is appropriate in the drug approval context because of "the complexity of the statutory regime" and "FDA's expertise." Mylan Labs., Inc. v. Thompson, 389 F.3d 1272, 1280 (D.C. Cir. 2004).

Accordingly, the D.C. Circuit has repeatedly given Chevron deference to FDA's interpretation of the FDCA and its implementing regulations. See, e.g., Novartis Pharms. Corp. v. Leavitt, 435 F.3d 344, 349 (D.C. Cir. 2006) ("We have held on a number of occasions that FDA interpretations of the FDCA receive deference, as do its interpretations of its own regulations unless plainly erroneous or inconsistent with the regulations."); Mylan v. Thompson, 389 F.3d at 1281; Purepac Pharm. Co. v. Thompson, 354 F.3d 877, 883 (D.C. Cir. 2004); Serono Labs., Inc. v. Shalala, 158 F.3d 1313, 1319, 1320 (D.C. Cir. 1998) (citing Auer v. Robbins, 519 U.S. 452, 461 (1997)).[10] For this reason, FDA's decisions about where patent information may be published, whether patents claim listed products, and what information FDA may rely on when reviewing ANDAs are entitled to considerable deference.

B. FDA's Decision was Reasonable and Not in Violation of the APA

The FDA decision challenged in this case was reasonable and not arbitrary and capricious under the APA. As noted above, the statute requires NDA holders to submit patents to FDA that "claim" drug products, and requires generic applicants to certify to these patents. FDA did not abuse its discretion when it found that the '952 patent – which Johnson & Johnson had

[10] See also Apotex, Inc. v. Thompson, 347 F.3d at 1352 ("Deference is due to an administrative agency's regulations particularly when the subject matter of the regulatory authority is a 'highly detailed' regulatory program to which the agency has brought its 'specialized expertise,' . . . a characterization that aptly describes the FDA's role in the context of the regulatory scheme created pursuant to the Hatch-Waxman Act.") (quoting United States v. Mead Corp., 533 U.S. 218, 235 (2001)).

withdrawn and which FDA had removed from its electronic Orange Book – did not "claim" Risperdal and thus no exclusivity could be awarded based on the '952 patent.

FDA's position is that it is allowed to use the most current information available to ensure compliance with the statute. Teva, on the other hand, argues that FDA is precluded from doing so if the paper version of the Orange Book contains information that is inconsistent with the most current information. Teva's argument appears to be that it is permitted to rely on the paper Orange Book, even if an NDA holder has delisted a patent, FDA has removed it from the web site listing, and Teva knows about the delisting. Teva's argument is meritless; there is nothing about FDA's approach that is unreasonable or in violation of the APA or any other law.

In denying Teva's citizen petition, FDA explained that the '952 patent had been delisted before Teva submitted its ANDA. FDA Pet. Resp. at 1. FDA noted that the fact of the delisting was publicly available via the electronic Orange Book before Teva submitted its ANDA. Id. at 4-7. FDA also stated that, when reviewing ANDAs, it conducts an independent review of the required patent certifications and uses "the most current patent information the Agency has received." Id. at 8. In 2001, Teva did not take the position that this was an unreasonable approach. Indeed, when FDA informed Teva that the patent had been delisted, Teva readily acquiesced and certified that "to the best of our knowledge and in TEVA Pharmaceuticals USA's opinion" the '952 patent was not listed for Risperdal. Id. at 5. Teva removed its certification to the '952 patent and said nothing more about it until 2007.

Teva's primary argument in attacking this approach is its repeated assertion that the FDCA and an FDA regulation somehow limit FDA's discretion regarding what information it can rely on when reviewing ANDAs to ensure compliance with the statute. See, e.g., P.I. Mem.

at 9, 10, 18, 21-24. Teva's argument is that these provisions contemplate only paper publication of patents, and therefore it was entitled to rely on the paper Orange Book, and whatever was reflected in the electronic Orange Book was simply irrelevant (even when, as here, Teva knew about the delisting). See, e.g., id. at 20-21 ("Whether or not [it] is true" that the '952 patent was delisted from the electronic Orange Book, it is "legally immaterial."); see also id. at 23.

There are a number of reasons why Teva's arguments fail. First, as discussed above, neither the statute nor the regulation relied upon by Teva limits the listing of patents to a paper version. The statute, 21 U.S.C. § 355(b)(1), (c)(2), simply requires FDA to "publish" the information and does not specify that this must be paper only. The regulation, 21 C.F.R. § 314.53(e), refers to publication of a "list," and again does not specify that this list must be only on paper.

Thus, FDA is not limited to a paper listing of patents and there is nothing that prevents FDA's use of the Internet to comply with the statute. FDA's decision to do so is not arbitrary and capricious under the APA. Teva cites to numerous cases which it asserts establish that "there was never a shred of doubt that FDA formally discharged that duty [to publish patent information in the Orange Book] by printing the annual Orange Book and . . . issuing its printed Cumulative Supplements to the Orange Book." P.I. Mem. at 19. None of the cases cited by Teva, however, states that the Orange Book must only be in paper form, or makes any mention at all of what form the Orange Book must, or may, take. Teva's reliance on these cases is thus misplaced.

Teva's contention would lead to the absurd result that ANDA applicants would not have to certify to patents recently submitted to FDA that do not appear in a paper version of the

Orange Book. This is not only inconsistent with FDA's practice of requiring certification in such instances, FDA Pet. Resp. at 8 n.14, it is analogous to a claim that unless and until a court's opinion appears in a hard-bound court reporter, that opinion is not binding and has no precedential value. This argument is no more persuasive for patent listings than it is for court opinions. Teva's suggestion also defies common sense. FDA's use of the "most current patent information the Agency has received," id. at 8, is plainly a more appropriate manner of complying with the statutory requirement that ANDAs certify to patents that "claim" listed products.

Other ANDA applicants were aware of the electronic Orange Book. For example, a different applicant submitted an ANDA for risperidone in November 2001; this ANDA contained a printout from the electronic Orange Book, dated October 30, 2001, showing that the only patent listed for Risperdal tablets was the '663 patent. See FDA Pet. Resp. at 7 and Ex. 3. The November 2001 ANDA contained a patent certification only to the '663 patent (when, according to Teva, the '952 patent was still in the paper version). See id. at 7; P.I. Mem. at 18. Hence, others in the generic industry knew about, and relied on, the electronic Orange Book for patent information in 2001.

Moreover, as discussed supra, when FDA receives an ANDA, FDA does not assume the application is complete or automatically reject it if it is not complete. See id. at 5; 21 C.F.R. § 314.101. There is communication between the applicant and FDA in an attempt to make the application complete, such as happened in this case. See, e.g., FDA Pet. Resp. at 5, Attachment A hereto. The applicant does not have to guess what is required – especially regarding the listing of patents – and then, at its peril, submit its ANDA and hope it is complete. If the applicant has a

question, it can ask FDA. After such dialogue occurred in this case, Teva certified, among other things, that to the best of its knowledge and in its opinion, only the '663 patent was listed for Risperdal, and not the '952 patent. Id. at 5. FDA's conclusion that the '952 patent had been delisted and Teva's paragraph IV certification was improper was a reasonable one and not in violation of the APA.

Teva also places much reliance on language in the paper Orange Book that states that changes to the Orange Book are reflected in "the most current Cumulative Supplement" to the Orange Book. P.I. Mem. at 22. As noted above, however, both the Orange Book and the Cumulative Supplement refer to the electronic Orange Book. FDA Pet. Resp. at 6-7. Although these references state that the electronic and paper versions of the Orange Book would be updated concurrently, that was not the case in 2001 with patent delistings. At that time patent delistings were reflected in the electronic Orange Book, but not the paper monthly supplements. Id. at 6 n.12. Nonetheless, this does not make FDA's use of the most current information when it reviewed Teva's paragraph IV submission unreasonable.

Significantly, Teva does not appear to dispute that the '952 patent had in fact been delisted by the patent holder, nor does it appear to dispute that this fact was reflected in the electronic Orange Book. It argues that this is "legally immaterial." P.I. Mem. at 21. What Teva appears to be doing is attempting to game the system, using the fact that the '952 patent incorrectly remained in the paper Orange Book after it was removed from the electronic version to argue that the patent remained "listed" with FDA, and, as a result, FDA is bound to award Teva 180 days of exclusivity. As discussed above, however, when FDA requested that Teva withdraw its paragraph IV certification, FDA was relying on the most current patent information

it had, and that was not a violation of the APA or any other law. Teva does not even appear to dispute that FDA relied on the most current information; its argument is basically that FDA was not entitled to do so because the paper Orange Book did not contain the most current information. See, e.g., P.I. Mem. 5 ("Teva, in short, was legally entitled to rely on the 2001 Orange Book listing."). Teva's approach is plainly unreasonable.

Teva suggests that the D.C. Circuit's decision in Ranbaxy requires FDA to relist the '952 patent. See P.I. Mem. at 16-18. The factual predicate that gave rise to the Ranbaxy decision, however, is absent here. In Ranbaxy, all three of the patents held by Merck for Zocor (simvastatin) claimed the listed drug at the time Ivax and Ranbaxy submitted their ANDAs – containing paragraph IV certifications – for simvastatin. Ranbaxy, 469 F.3d at 123. Merck's request to delist the patents for simvastatin came almost two years *after* the Ranbaxy ANDA was submitted and almost three years *after* the Ivax ANDA was submitted. Ranbaxy Labs. Ltd. v. Leavitt, 459 F. Supp. 2d 1, 5 (D.D.C. 2006). In other words, it was undisputed that the ANDA filers properly qualified for exclusivity as of the time of their certifications, and the issue was whether a later withdrawal of the patents by the NDA holder could deprive the ANDA filers of exclusivity. 469 F.3d at 125 ("The "precise question at issue at *Chevron* step one is, in our view, whether the FDA may delist a patent upon the request of the NDA holder *after* a generic manufacturer has filed an ANDA containing a paragraph IV certification so that the effect of delisting is to deprive the applicant of a period of marketing exclusivity.") (emphasis added). Here, in contrast, Johnson & Johnson requested that the '952 patent for Risperdal be delisted months *before* Teva's ANDA for risperidone was submitted. Ranbaxy simply does not hold that a NDA-holder cannot withdraw a patent before an ANDA filer submits a paragraph IV

certification.

While Teva asserts repeatedly that it undertook the risk of litigation and therefore "deserves" 180 days of exclusivity, P.I. Mem. at 1, 12, 17, 25, in fact Teva faced no risk whatsoever of patent litigation upon submitting its risperidone ANDA because the NDA holder had already withdrawn the '952 patent. Teva does not argue – nor could it – that if a patent holder delisted a patent one day before the filing of a paragraph IV certification from all versions of the Orange Book, that paragraph IV applicant would still be entitled to 180 days of exclusivity. Thus, even if an ANDA applicant did a significant amount of work designing around a patent, that effort would not entitle the applicant to 180 days of exclusivity if the patent were delisted. For this reason, FDA's decision to rely upon the most current information when it accepted Teva's ANDA must be analyzed without reference to any alleged "effort" by Teva to "design around" the '952 patent.

For all of these reasons, Teva has no likelihood of success on the merits of this action. It has failed to demonstrate that FDA's use of the most current information available when ensuring compliance with its own statute was in violation of the APA.[11]

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[11] Although Teva presents its claim as an APA claim, Complaint ¶ 38, it seems to suggest an estoppel claim. See, e.g., P.I. Mem. 5 ("Teva, in short, was legally entitled to rely on the 2001 Orange Book listing."). Even if it were to assert and pursue such a claim, this argument would fail. Estoppel will very rarely, if ever, lie against the federal government. See Office of Pers. Mgmt. v. Richmond, 496 U.S. 414, 422 (1990); ATC Petroleum, Inc. v. Sanders, 860 F.2d 1104, 1111 (D.C. Cir. 1988) ("we are aware of no case in which this court has applied the doctrine [of estoppel] against the government."). Even if estoppel were available against the government, estoppel requires reasonable reliance, see, e.g., Smith v. United States, 277 F.Supp.2d 100, 115 (D.D.C. 2003), and Teva's reliance on the printed Orange Book alone is not reasonable. In addition, nowhere in the record does Teva claim that it was completely unaware of the existence of electronic Orange Book, which raises the question of whether Teva actually relied solely on the printed Orange Book. Finally, Teva has not shown that it relied to its detriment on FDA's failure to remove the '952 patent from the August 2001 printed supplement. There is no

III. Teva Will Not Suffer Irreparable Harm Without Injunctive Relief

Courts insist that only irreparable harm justifies the issuance of a preliminary injunction. "The *sine qua non* of granting any preliminary injunctive relief is a clear and convincing showing of irreparable injury to the plaintiff." Experience Works, Inc. v. Chao, 267 F.Supp.2d 93, 96 (D.D.C. 2003). Because Teva is not likely to succeed on the merits, Teva "would have to make a very substantial showing of severe irreparable injury" to prevail on its motion. Nat'l Pharm. Alliance v. Henney, 47 F.Supp.2d 37, 41 (D.D.C. 1999); see also Apotex, Inc. v. FDA, 2006 U.S. Dist. LEXIS 20894, *54 (D.D.C. Apr. 19, 2006). "Irreparabilty of injury is a very high standard." Bristol-Myers, 923 F.Supp at 220. The injury alleged must be certain, great, actual, and imminent. See Wisconsin Gas Co. v. FERC, 758 F.2d 669, 674 (D.C. Cir. 1985).

Teva has failed to provide a valid explanation for why it waited more than six years to challenge FDA's delisting of the '952 patent, and now, incredibly, argues that its alleged harm is irreparable. This delay in seeking relief defeats plaintiff's claim that it has suffered irreparable injury. In Sandoz, Inc. v. FDA, 439 F.Supp.2d 26 (D.D.C. 2006), this Court held that Sandoz' delay of less than two months – until the "last minute" – to challenge the result of the district court decision in Ranbaxy (the same Ranbaxy case relied on by Teva) undercut its claim of irreparable injury. Id. at 30-31. See also Tough Traveler, Ltd. v. Outbound Prods., 60 F.3d 964, 968 (2d Cir. 1995) (delay "may, 'standing alone, . . . preclude the granting of preliminary injunctive relief.'") (quoting in part Majorica, S.A. v. R.H. Macy & Co., 762 F.2d 7, 8 (2d Cir. 1985)); Fund for Animals v. Frizzell, 530 F.2d 982, 987 (D.C. Cir. 1975) ("Our conclusion that

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evidence in the record as to any action that Teva undertook between the date that FDA allegedly failed to delist the patent and the time Teva submitted its ANDA.

an injunction should not issue is bolstered by the delay of the appellants in seeking one."); Mylan (terazosin), 81 F.Supp.2d at 43 ("Mylan's delay in bringing this action further undercuts its allegation of irreparable harm.").

It is also well settled that mere economic loss in and of itself does not constitute irreparable harm: "Mere injuries, however substantial, in terms of money, time and energy necessarily expended" are inadequate. Wisconsin Gas, 758 F.2d at 674 (quoting Virginia Petroleum Jobbers Ass'n v. FPC, 259 F.2d 921, 925 (D.C. Cir. 1958)); Sandoz, Inc. v. FDA, 439 F.Supp.2d at 32. Even irrecoverable economic loss does not rise to the level of irreparable harm unless "the denial of injunctive relief would likely cause the business to collapse." Amtote Int'l, Inc. v. PNGI Charles Town Gaming LLC, 998 F.Supp. 674, 678 (N.D. W.Va. 1998) (citing Wisconsin Gas, 758 F.2d at 674); see also Experience Works, Inc., 267 F.Supp.2d at 96 ($21.1 million reduction in funding is a serious financial blow, but one frequently faced by other similar entities, and not an economic loss that threatens survival of the business); Sociedad Anonima Viña Santa Rita v. Dep't of Treasury, 193 F.Supp.2d 6, 14 (D.D.C. 2001) ("financial harm alone cannot constitute irreparable injury unless it threatens the very existence of the movant's business"); Gulf Oil Corp. v. Dep't. of Energy, 514 F.Supp. 1019, 1025 (D.D.C. 1981) (claimed economic injury must be "sufficiently large in proportion to the plaintiff's operations that the loss of the amount of money involved would also cause extreme hardship to the business, or even threaten destruction of the business."); Mylan (terazosin), 81 F.Supp.2d at 42 ("Because Mylan is alleging a non-recoverable monetary loss, it must demonstrate 'that the injury [is] more than simply irretrievable, it must also be serious in terms of its effect on the plaintiff.'" (quoting in part Gulf Oil Corp., 514 F.Supp. at 1026)); Bristol-Myers Squibb, 923 F.Supp. at 221 & n.12

(alleged loss of 50-70 percent of $97,000,000.00 product sales not irreparable harm because it would be only a small percentage of plaintiff's total sales).

In its attempt to demonstrate irreparable harm, Teva alleges that the potential loss of "revenue opportunities" incurred from competition with other FDA-approved generic versions of risperidone would be "massive." See P.I. Mem. at 28, 29. Teva does not allege, however, that these lost sales would threaten its business, much less cause it to collapse. Indeed, Teva would be hard pressed to claim its alleged injury would even have a severe detrimental impact given that Teva, one of the world's largest generic drug manufacturers, will unquestionably survive any impact of competition with other generic versions of risperidone.[12] In 2007 Teva posted record annual net sales of $9.4 billion, up 12 percent from the prior year, without the sale of a generic version of risperidone.[13] Allegations of lost sales and a lost opportunity to gain certain market advantages are a far cry from the required demonstration of a "serious" loss that "would significantly damage its business above and beyond a simple diminution in profits." Mylan Pharms. Inc. v. Thompson, 139 F. Supp. 2d 1, 27 (D.D.C. 2001), rev'd on other grounds, 268 F.3d 1323 (Fed. Cir. 2001); Mylan (terazosin), 81 F. Supp. 2d at 42-43. Thus, the alleged loss of potential sales that may result from competition with other generic versions of risperidone do not constitute irreparable harm. See Varicon Int'l v. Office of Personnel Mgmt., 934 F. Supp. 440, 447-48 (D.D.C. 1996) (finding no irreparable harm due to lost contract where movant's revenue

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[12] See The History of Teva, available at http://www.tevapharm.com/about/history.asp ("Today, Teva is among the top 20 pharmaceutical companies in the world and one of the largest generic pharmaceutical companies in the world.").

[13] See Teva Reports Fourth Quarter and Full Year 2007 Reports, available at http://www.teva.co.il/pr/2008/pr_731.asp ("Record annual and quarterly net sales of $9.4 billion and $2.6 billion, up 12 percent and 13 percent, respectively.").

would decline by 10%); TGS Tech., Inc. v. United States, Civ. No. 92-0062, 1992 U.S. Dist. LEXIS 195, at *10 (D.D.C. Jan. 14, 1992) (finding no irreparable harm where lost contract constituted 20% of movant's business).

The cases that Teva claims support its contention that the loss of exclusivity alone suffices to show irreparable harm actually belie this argument. P.I. Mem. at 28. In Mova, the district court granted a preliminary injunction both because Mova would be harmed by the loss of its exclusivity *and* because "Mova's small size put it at a particular disadvantage." Mova, 140 F.3d at 1067 n.6; see also Sandoz, Inc. v. FDA, 439 F.Supp.2d at 32 (holding that Sandoz failed to carry its burden of demonstrating irreparable harm because the claimed injury was "merely economic" and did not "threaten the company's very existence."); Apotex, 2006 U.S. Dist. LEXIS 20894, *54-*57 (same). Furthermore, this is not a case in which Teva is being denied entrance into the market to compete with other generic companies, as in Torpharm, Inc. v. Shalala, Civ. No. 97-1925, 1997 U.S. Dist. LEXIS 21983, *13-*15 (D.D.C. Sept. 15, 1997). Rather, Teva would simply enter the market on June 29, 2008, at the same time as any and all other companies with approved ANDAs, assuming, of course, that Teva's ANDA can be and is approved at that time. Because Teva has not shown that it will suffer an irretrievable loss that would significantly damage its business, its allegations fall well short of the showing necessary to support a finding of irreparable injury.

IV. The Requested Relief Would Harm The Public

Finally, Teva has failed to show that any potential harm to its interests in the absence of injunctive relief outweighs the potential harm to other parties, or that the entry of the relief it seeks would further the public interest – the third and fourth requirements for preliminary

injunctive relief. Although FDA has no commercial stake in the outcome of this litigation, FDA is the government agency charged with implementing the statutory scheme governing the approval of generic drugs. As such, FDA's interest coincides with the public interest.

As Teva itself acknowledges, in enacting the Hatch-Waxman Amendments, "Congress sought to get generic drugs into the hands of patients at reasonable prices – fast." In re Barr Labs., Inc., 930 F.2d 72, 76 (D.C. Cir. 1991). Moreover, "the public has a well-recognized interest 'in receiving generic competition to brand-name drugs as soon as possible,' and 'a delay in the marketing of [the generic] drug could easily be against the public interest in reduced prices.'" Apotex Inc. v. FDA, 508 F.Supp.2d 78, 88 (D.D.C. 2007), quoting in part Boehringer Ingelheim Corp. v. Shalala, 993 F.Supp. 1, 3 (D.D.C. 1997), and Schering Corp. v. Sullivan, 782 F.Supp. 645, 652 (D.D.C. 1992). Relisting a patent in the Orange Book when the patent holder had requested its removal prior to the submission of any paragraph IV certifications unnecessarily delays competition for generic risperidone for at least 180 days. This harms both other generic drug manufacturers with ANDAs waiting for approval and the public, who benefit from competition by lower generic drug prices. Moreover, there can be no public interest in giving Teva exclusivity as a reward for challenging a non-listed patent.

FDA must implement the statutory scheme governing exclusivity determinations and the approval of generic drugs. For the reasons stated above, FDA has concluded that it properly delisted the '952 patent, properly declined to relist that patent on Teva's request, and properly concluded that Teva is not "entitled" to 180-day exclusivity. Because Teva has failed to establish that it has any rights at issue that are being threatened, public interest "would be better served by denying the plaintiff's motion." Boehringer Ingelheim Corp., 993 F.Supp. at 3.

CONCLUSION

For the foregoing reasons, Teva's motion for a preliminary injunction should be denied.

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