UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

BIOVAIL CORPORATION, *et al.*, Plaintiffs, v. U.S. FOOD AND DRUG ADMINISTRATION, *et al.*, Defendant, ANCHEN PHARMACEUTICALS, INC., Intervenor-Defendant, and TEVA PHARMACEUTICALS USA, INC. and IMPAX LABORATORIES, INC., (Proposed) Intervenors-Defendants.	Case No. 06-1487 (RMU)

JOINT OPPOSITION OF INTERVENORS TEVA PHARMACEUTICALS USA, INC. AND IMPAX LABORATORIES, INC. TO BIOVAIL'S MOTION FOR A TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

Jay P. Lefkowitz (D.C. Bar No. 449280)
Michael D. Shumsky (D.C. Bar No. 495078)
KIRKLAND & ELLIS LLP
655 15th Street N.W., Suite 1200
Washington, DC 20005
(202) 879-5000

Counsel for Intervenors-Defendants Teva Pharmaceuticals USA, Inc. and Impax Laboratories, Inc.

December 29, 2006

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Rules

INTRODUCTION

This case represents Biovail's latest attempt to forestall generic competition and protect its monopoly in the market for extended-release bupropion hydrochloride tablets ("bupropion"), an antidepressant that Biovail has patented and manufactures, and which its business partner GlaxoSmithKline ("GSK") markets under the trade-name Wellbutrin XL®. But this attempt comes a day late and a dollar short: defendant U.S. Food and Drug Administration ("FDA") has already granted intervenor-defendant Anchen Pharmaceuticals, Inc. ("Anchen") final approval for the sale of its generic bupropion drug products in both 150-mg and 300-mg dosages, and the agency likewise has granted proposed intervenor-defendant Impax Laboratories, Inc. ("Impax") final approval for the sale of its generic bupropion drug product in 300-mg dosages and tentative approval for the sale of its generic bupropion drug product in 150-mg dosages. Pursuant to an agreement between those companies and an affiliate of proposed intervenor-defendant Teva Pharmaceuticals USA, Inc. ("Teva"), Anchen has "selectively waived" its 180-day exclusivity for generic 300-mg bupropion tablets to Impax, and Teva has already begun to commercially market Impax's 300-mg product on an exclusive basis. The injunctive relief Biovail seeks thus would not only irreparably harm Teva, Impax, and Anchen, but also would come at a tremendous expense to the millions of Americans who depend on bupropion and finally have access to an affordable generic alternative. Additionally, Biovail seeks such extraordinary injunctive relief against the backdrop of an action in which it has ***no chance of success on the merits***.

Biovail's principal claim is that FDA abused its discretion in approving the abbreviated new drug applications ("ANDA") filed by Anchen and Impax for generic bupropion drug products, because the label on Anchen's generic bupropion product is not "the same" as the label on the "listed drug" referenced in the ANDA (Wellbutrin XL®), as required by the statute. The

purported difference, according to Biovail, is that neither Anchen nor Impax conducted independent trials to demonstrate bioequivalency with two ***different*** drugs – the standard-release ("SR") and immediate-release ("IR") versions of bupropion, as Biovail did in gaining initial new drug approval for Wellbutrin XL®. Because Anchen and Impax did not perform these studies, Biovail contends, the labels on their generic bupropion products do not indicate such bioequivalency and are not "the same" as that of Wellbutrin XL®. As an initial matter, Biovail's argument is factually incorrect – the generic labels do in fact contain the same statements as WELLBUTRIN XL® regarding bioequivalence between extended release bupropion, and standard-release and immediate-release bupropion. Further, Biovail cannot claim that the placement of this statement on the generic labels is misleading, because such an argument is inconsistent with the clear requirements of the statute and FDA's own governing regulations.

Put another way, Biovail's argument is just a distraction from the real issue in this case, which is whether the statute requires Anchen and Impax to independently demonstrate the bioequivalence of their drug products to Biovail's Wellbutrin SR® and Wellbutrin IR® drug products despite the fact that neither of those products is a reference listed drug product for the Anchen and Impax generic bupropion drug products. The answer to this question is a resounding "no." The statute requires an ANDA applicant to demonstrate bioequivalency ***only*** between the proposed generic drug and the listed drug for which it is to be substituted. An applicant need not show bioequivalency with any other drug, including other generic drug products or other drugs that have shown to be bioequivalent with the "listed drug." Biovail's argument to the contrary is an attack to the very core of the statute, which ensures that generic drugs are "substitutable" for the listed drug but explicitly does not require that both drugs undergo the same clinical testing.

Moreover, for all of Biovail's overblown rhetoric about the dangers its own drug poses to

the public health and welfare, it challenges neither FDA's expert scientific determination that both the Anchen and Impax formulations are safe and effective for public consumption, nor FDA's expert legal determination that neither company was required independently to demonstrate the bioequivalence of their respective drug products to Biovail's Wellbutrin SR® and Wellbutrin IR® drug products under the plain text of the statute.

Those determinations were well within FDA's discretion. After all, the statute requires ***only*** that the manufacturer of a proposed generic drug demonstrate the generic drug product's bioequivalence ***to the reference listed drug***, and there is no indication that Congress intended the statutory labeling requirements to impose ***additional*** testing and bioequivalence requirements through the proverbial back-door. To the contrary, the statute expressly forbids the agency from requiring a generic drug's manufacturer to demonstrate its product's bioequivalence to any drug other than the listed drug. In essence, then, Biovail is seeking to have the labeling tail wag the bioequivalence dog, and FDA did not remotely abuse its substantial discretion in interpreting the statute to avoid that absurd (and plainly unlawful) result. As a consequence, FDA's interpretation of the statute warrants deference under *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), and Biovail has not come close to undermining FDA's expert determination that the Anchen and Impax formulations are safe, effective, and commercially marketable.

In addition to having no chance of succeeding on the merits, Biovail has not shown that the equities of the case favor granting injunctive relief. Indeed, this Court squarely rejected each of Biovail's putative claims of irreparable injury the last time Biovail sought a TRO from this Court in this case (only a few months ago)—which, presumably, is why Biovail first sought relief from the U.S. District Court for the District of Maryland (instead of this Court) after FDA

approved the Anchen and Impax ANDAs. But that strategy failed when the Maryland court rejected each of Biovail's equitable claims for the same reasons previously given by this Court. There is no basis for allowing Biovail to bring the same claims once again. Litigants are not ordinarily entitled to three bites at the apple, and given that Biovail's claims now have been rejected twice, its claims should not detain this Court for long. As both this Court and the District of Maryland already have recognized, Biovail's purported injuries from FDA's approval of the Anchen and Impax generic bupropion drug products are merely financial, and monetary injuries can always be compensated with monetary damages.

Instead, the only irreparable harms at issue here are the ones that would befall Teva, Impax and Anchen. The 180-day exclusivity period granted by statute to ANDA first filers began to run the day Anchen first marketed its drug product, and it cannot be tolled. If this Court enjoins Teva's continued commercial marketing of Impax's approved 300-mg generic bupropion product pending resolution of the merits, Teva and Impax would be deprived of the 180-day exclusivity period. It is well-settled that "[o]nce th[at] statutory entitlement has been lost, it cannot be recaptured," *Apotex, Inc. v. FDA*, No. Civ. A. 06-627-JDB, 2006 WL 1030151, at *17 (D.D.C. April 19, 2006), *summarily affirmed by published opinion*, 449 F.3d 1249 (D.C. Cir. 2006), and it would be manifestly inequitable to punish Anchen, Teva and Impax for relying on FDA's final approval and commencing commercial marketing of the Anchen and Impax generic bupropion drug products. *See, e.g., Mylan Pharms., Inc. v. Shalala*, 81 F. Supp. 2d 30, 48 (D.D.C. 2000). And any delay that prevents Anchen—or any of its potential business partners—from commencing commercial marketing of the 150-mg drug product could potentially cause that company to lose its 180-day exclusivity period for sales of that drug. *See* 21 U.S.C. § 355(j)(5)(D)(I)(aa)(AA).

Likewise, Biovail has not shown that the balance of hardships weighs in favor of granting injunctive relief. Whatever monetary injuries Biovail alleges, it has shown at best that "the hardships [it] may suffer if the emergency injunctive relief is denied are equal to the hardships that Teva will suffer…. Either way, some party may face significant economic disadvantage." *Teva Pharms. USA, Inc. v. FDA*, 404 F. Supp. 2d 243, 246 (D.D.C. 2005). Thus, as explained below, Teva and Impax have made an irrecoverable investment of ***millions of dollars*** to produce and begin distributing some ***seventy million doses*** of 300-mg bupropion to consumers. Entering an injunction at this stage of the proceedings jeopardizes Teva and Impax's significant investment in the development and production of this product. Moreover, temporary injunctive relief would impose substantial hardships on Teva and Impax by disrupting their current production schedules, staffing decisions, and related business plans for both bupropion and other drugs in the companies' respective pipelines.

But whatever hardships may befall the various parties and (proposed) intervenors in this proceeding, those with the most at stake are the millions of Americans who depend on bupropion to relieve symptoms of their depression. Entry of a TRO or preliminary injunction would extend Biovail's monopoly hold on the market. With the full blessing of the Nation's public health regulators, Teva and Impax have launched a safe, effective, and affordable generic version of 300-mg bupropion and now are delivering much-needed price relief to consumers. Given the considerable burden that entry of an injunction would impose on consumers, this Court should deny Biovail's meritless motion for a TRO or preliminary injunction.

BACKGROUND

A. Statutory Framework

The Food, Drug, and Cosmetic Act ("FDCA" or "the statute"), as modified by the Hatch-Waxman and Medicare Modernization Acts ("HWA" and "MMA," respectively), establishes an

expedited FDA approval process for generic drugs, and creates significant incentives for manufacturers to develop affordable generic alternatives. To that end, the statute authorizes FDA to promptly approve a proposed generic drug product if its manufacturer demonstrates that the proposed drug product is bioequivalent to a "listed drug" that previously has been deemed safe and effective.

In order to do so, a generic manufacturer must submit an ANDA to FDA for each proposed generic version of a previously-approved drug (called a "reference listed drug" or "RLD"). *See* 21 U.S.C. § 355(j) (2003); *see also* 21 C.F.R. § 314.3 ("Reference listed drug means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its [proposed generic drug product]."). If an ANDA for a generic version of an RLD adequately demonstrates the proposed generic drug's bioequivalence to the RLD, the manufacturer need not repeat the safety and efficacy studies that accompanied the new drug application ("NDA") for the listed drug; FDA can simply approve the generic drug product for commercial marketing. 21 U.S.C. § 355(j)(2)(A); *see also Dr. Reddy's Labs., Inc. v. Thompson*, 302 F. Supp. 2d 340, 343 (D.N.J. 2003).

As a general matter, ANDA applicants must also propose to include with their approved drug product "the same" labeling that accompanies the RLD. 21 U.S.C. § 355(j)(2)(A)(v). This provision is not without exception; the statute expressly permits labeling variances where two products have a different route of administration, dosage form, or strength, and where those products are manufactured or marketed by different companies. *Id*. By regulation, FDA has construed these statutory exceptions to permit labeling "differences [based on] expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect

of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act." 21 C.F.R. § 314.94(a)(8)(iv). Those longstanding regulations never have been challenged previously, and Biovail does not challenge them here.

Finally, an applicant's ANDA must include a "certification" regarding each of the patents that the NDA holder has listed with FDA as claiming the reference listed drug. Of the various certifications an ANDA applicant might include in their filing, the most important is a "paragraph IV" certification. Paragraph IV certifications assert that a given patent is invalid or will not be infringed by the proposed generic drug product, *see* 21 U.S.C. § 355(j)(2)(A)(vii)(IV), and therefore indicate that the applicant either has developed a viable legal challenge to the validity of a competition-blocking patent or has engineered a non-infringing pathway around such a patent. By design, and in order to help clear the "patent thicket" and speed the onset of market competition, the statute rewards applicants who submit paragraph IV certifications. Congress recognized that the first generic drug company to engineer a generic pathway bears significant research and legal costs when they attack a patent directly or design their way around it. Congress also recognized that the first ANDA filer faces a significant risk that it will be sued for patent infringement. To encourage generic manufacturers to assume those risks, Congress chose to reward the first applicant to file a paragraph IV certification with eligibility for a 180-day period of marketing "exclusivity," during which it holds the right to market the generic product without competition from other generic manufacturers. *See, e.g.*, *Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 879 (D.C. Cir. 2004); *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1064 (D.C. Cir. 1998); *Sandoz, Inc. v. FDA*, 439 F. Supp. 2d 26, 29 (D.D.C. 2006); *see also* 21 U.S.C. § 355(j)(5)(B)(iv) ("180-day exclusivity period"). The exclusivity period runs from the date on which the first ANDA applicant to file a

paragraph IV certification commercially markets its generic drug product following final FDA approval (the "commercial marketing trigger"). *Id*. § 355(j)(5)(B)(iv)(I).

B. Factual Background

Biovail currently owns the patent rights to and manufactures extended-release bupropion, a dopamine reuptake inhibitor used to counter depression. Its business partner, GlaxoSmithKline, markets that drug in 150-mg and 300-mg dosages under the trade name Wellbutrin XL®. Two patents are listed as claiming each dosage of those drug products in the official register of patents claiming approved pharmaceuticals (the "Orange Book"): U.S. Patent No. 6,096,341 ("the '341 patent") and U.S. Patent No. 6,143,327 ("the '327 patent"). *See* Orange Book at 81, 871, *available at* http://www.fda.gov/cder/orange/obannual.pdf (last visited December 27, 2006).

On September 21, 2004, Anchen filed the first ANDA seeking FDA approval to market generic bupropion in 150-mg and 300-mg dosages. Anchen's ANDA contained paragraph IV certifications asserting that neither of its bupropion products would infringe either of the above-listed patents. As a result, Anchen became eligible for 180-day exclusivity for sales of generic bupropion in those two dosages. 21 U.S.C. §§ 355(j)(5)(B)(iv).

On November 30, 2004, Impax filed an ANDA seeking FDA approval to market generic bupropion in 150-mg dosages. *See* Impax, *ANDA for Bupropion Hydrochloride Extended-release (XL) Tablets, 150 mg* (excerpt attached as Exh. 1). Like Anchen's ANDA, Impax's ANDA contained paragraph IV certifications asserting that its version of 150-mg bupropion would not infringe either the '327 or '341 patent, or that those patents were otherwise invalid or unenforceable. *Id*. at 16-18. On December 28, 2004, Impax submitted an amendment to its ANDA that would provide for a 300-mg generic product. *See* Impax, *ANDA for Bupropion Hydrochloride Extended-release (XL) Tablets, 150 mg—Addition of 300 mg Strength* (excerpt

attached as Exh. 2). That amendment included the requisite paragraph IV certifications asserting that Impax's proposed 300-mg dosage of bupropion would not infringe either the '327 or '341 patent, or that those patents were otherwise invalid or unenforceable. *Id*. at 1, 12-13.

In an attempt to forestall approval of generic bupropion drug products that would compete with Wellbutrin XL®, Biovail filed a Citizen Petition with FDA raising the same claims that it raises in this action. On December 14, 2006, FDA issued a detailed letter-decision denying the Petition and conclusively rejecting Biovail's claims as inconsistent with the text of the statutory scheme and its broader purposes. *See* FDA Citizen Petition Denial (the "CP Denial") (attached as Exh. 3), at 6-8. FDA then granted final approval to Anchen's 150-mg and 300-mg bupropion drug products, and Anchen triggered its statutory 180-day exclusivity period for 300-mg generic bupropion by commercially marketing its 300-mg generic bupropion product. *See* Declaration of David Marshall ("Marshall Declaration") (attached as Exh. 4), at ¶ 6. Pursuant to the terms of an agreement between Anchen, Teva and Impax, Anchen then "selectively waived" its exclusivity for 300-mg generic bupropion sales to Teva and Impax. *Id*. at ¶ 5. Together, these actions permitted FDA to grant final approval to Impax's 300-mg bupropion product, and FDA did so on December 15, 2006. *See* FDA Letter Decision (attached as Exh. 5).[1] In granting Impax's 300-mg ANDA, FDA affirmed that Impax's "drug is safe and

[1] For nearly a decade, FDA has honored selective waiver agreements between generic pharmaceutical manufacturers, *e.g.*, FDA Letter Decision Denying Citizen Petition No. 2004P-0227, July 2, 2004, at 4-5, and for just as long, courts have upheld them. *See, e.g*., *Boehringer Ingelheim Corp. v. Shalala*, 993 F. Supp. 1, 2 (D.D.C. 1997). Biovail does not challenge any aspect of the selective waiver at issue here.

effective for use" and is "bioequivalent" and "therapeutically equivalent" to the reference listed drug, Wellbutrin XL®. *Id.* at 1-2.[2]

As soon as FDA approved Impax's ANDA for 300-mg generic bupropion drug products, Impax began delivering its 300-mg bupropion drug products to Teva for immediate commercial marketing under the terms of the parties' strategic alliance agreement. Within hours, Teva began commercially marketing Impax's 300-mg bupropion to its major customers. *See* Marshall Declaration at ¶ 9. By December 16, 2006, Teva had distributed tens of millions of tablets of Impax's 300-mg bupropion drug product to its customers. These tablets are now being dispensed to patients, and Teva continues to sell Impax's 300-mg bupropion product to its customers. *Id*.

LEGAL STANDARD FOR INJUNCTIVE RELIEF

To demonstrate an entitlement to temporary injunctive relief a plaintiff must show that (1) there is a substantial likelihood of success on the merits; (2) the plaintiff would suffer irreparable injury if the requested injunction is denied; (3) an injunction will not substantially injure the opposing party or other third parties; and (4) the public interest will be furthered by the issuance of the injunction. *See Mova Pharm.*, 140 F.3d at 1066. District courts typically must "balance the strengths of the requesting party's arguments in each of the four required areas." *CityFed Fin. Corp. v. OTS*, 58 F.3d 738, 747 (D.C. Cir. 1995). However, where the movant demonstrates no likelihood of success on the merits, temporary injunctive relief may be denied without reaching the other factors. *Trudeau v. FTC*, 456 F.3d 178, 182 n.2 (D.C. Cir. 2006)

---

[2] Anchen has not yet commercially marketed its 150-mg generic bupropion drug product, and Impax has not yet sought final FDA approval for its 150-mg generic bupropion drug product.

(citing *Michigan State v. Miller*, 103 F.3d 1240, 1249 (6th Cir. 1997) (holding that a court may not issue a preliminary injunction where the plaintiff has no likelihood of success on the merits); *Transohio Sav. Bank v. Dir., Office of Thrift Supervision*, 967 F.2d 598, 614 (D.C. Cir. 1992) (affirming denial of preliminary injunction where the district court concluded that plaintiff had "no likelihood of success on the merits").

ARGUMENT

I. BIOVAIL HAS NO CHANCE OF SUCCESS ON THE MERITS.

Biovail essentially argues that this Court should take the extraordinary step of enjoining Anchen and Impax from marketing their approved, Wellbutrin XL®-equivalent generic bupropion drug products because FDA allegedly abused its discretion by not requiring an independent demonstration that the Anchen and Impax bupropion drug products were bioequivalent to two other drugs, Wellbutrin IR® and SR®. That is so, according to Biovail, because the labels for Biovail's Wellbutrin XL® drug products reference studies comparing those drug products to Wellbutrin IR® and SR® products, and neither Anchen nor Impax can truthfully include such comparisons on the labels for their respective bupropion products since neither the Anchen nor Impax generic bupropion drug products have been compared directly to the IR® and SR® products.[3] *See* Biovail Br. at 14-17.

FDA carefully considered and rejected each of Biovail's arguments, *see* CP Denial at 6-8, so Biovail must do more than quibble with FDA's expert analysis of the statutory and regulatory regime governing generic drug approvals in order to demonstrate a likelihood of success on this

[3] Biovail also argues that the label on the generic bupropion product is not "the same" as the label on Wellbutrin XL®. Biovail Br. at 15. This argument is factually incorrect – the generic labels do in fact contain the same statements as WELLBUTRIN XL® regarding bioequivalence between extended release bupropion, and standard-release and immediate-release bupropion.

argument. Instead, as Biovail acknowledges, it must demonstrate that the agency's actions were "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law." 5 U.S.C. § 706(2)(A); *see also Apotex*, 2006 WL 1030151, at *7. Under this highly deferential standard of review, this Court may not substitute its judgment for FDA's, and may set aside the agency's action only if no rational basis supports the agency's decision. *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971).

In this case, FDA's decision is entitled to an additional degree of deference, since that determination rests on the agency's interpretation of the statutory scheme it is charged with administering. Under the well-known framework of *Chevron, U.S.A. Inc. v. Natural Resources Defense Council*, 467 U.S. 837 (1984), this Court must first examine whether "Congress has spoken directly to the precise question at issue." *Chevron*, 467 U.S. at 842. If the statute leaves no room whatsoever for competing interpretations, "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, however, the statute is "silent or ambiguous" and reasonable minds could differ over the proper interpretation of the statutory scheme, this Court must defer to the agency's decision so long as it has chosen a reasonable interpretation. *Id.* at 843; *see also Zeneca, Inc. v. Shalala*, 213 F.3d 161, 168 (4th Cir. 2000) (holding that FDA's interpretations of its own regulations are entitled to "substantial deference").

Biovail has not remotely overcome the cascading layers of deference to which FDA's thorough and well-reasoned Citizen Petition Denial is entitled. As that decision explains (but Biovail fails to mention), the statute—by its plain terms—requires ***only*** that an ANDA include "information to show that the [generic] drug is bioequivalent ***to the listed drug***." 21 U.S.C. § 355(j)(2)(A)(iv) (emphasis added); *see also* CP Denial at 6-7 ("To obtain approval, an ANDA

applicant relies upon the Agency's finding of safety and effectiveness ***for the RLD***" (emphasis added) (citing *Zeneca v. Shalala*, 213 F.3d 161, 163 (4th Cir. 2000))). Indeed, the statute expressly ***forbids*** FDA from "requir[ing] that an [ANDA] contain information in addition to that required by [this] clause." 21 U.S.C. § 355(j)(2)(A).

As a result, FDA's regulations implement the statutory scheme in a consistent and straightforward manner, by requiring each ANDA applicant to "refer ***to a listed drug***" and include "the name ***of the listed drug***, including its dosage form and strength." 21 C.F.R. § 314.94(a)(3) (emphasis added). And FDA's regulatory scheme strictly limits all comparative requirements for the proposed generic drug—***including comparative bioequivalence requirements***—to the reference listed drug identified in the generic manufacturer's ANDA:

- *Conditions of use*: "[T]he conditions of use prescribed, recommended, or suggested in the labeling proposed for the [generic] drug product have been previously approved ***for the reference listed drug***." 21 C.F.R. § 314.94(a)(4) (emphasis added);

- *Active ingredients*: "[T]he active ingredient is the same as that of ***the reference … listed drug***." 21 C.F.R. § 314.94(a)(5) (emphasis added);

- *Route of administration, dosage form, and strength*: "[T]he route of administration, dosage form, and strength of the [generic] drug product are the same as those ***of the reference listed drug***…." 21 C.F.R. § 314.94(a)(6) (emphasis added);

  and, most important,

- *Bioequivalence*: "[T]he [generic] drug product is bioequivalent ***to the reference listed drug upon which the applicant relies***." 21 C.F.R. § 314.94(a)(7) (emphasis added).

The key point, then, is straightforward: The sole reference listed drugs for the Anchen and Impax generic bupropion drug products are Wellbutrin XL® in 150-mg and 300-mg dosages—***not*** Wellbutrin SR® or Wellbutrin IR®. By the plain terms of the statute (which, to reiterate, strictly limits required bioequivalence testing to the reference listed drug), and under

FDA's longstanding regulations (which have never been challenged and likewise limit all requisite comparative testing to the reference listed drug), it thus would have been unlawful for FDA to require Anchen and Impax to demonstrate the bioequivalence of their respective bupropion drug products to any other product (including Wellbutrin SR® or Wellbutrin IR®). As a result, FDA did not remotely abuse its discretion when it declined to require Anchen and Impax to independently demonstrate that their proposed bupropion drug products were bioequivalent to the ***non-reference*** Wellbutrin SR® and IR® products. In short, Anchen and Impax demonstrated the bioequivalence of their respective bupropion products to the reference listed drug, and FDA was therefore obligated to approve the Anchen and Impax drug products for commercial marketing. Biovail's argument would impose on ANDA applicants additional requirements that have not been approved by Congress or FDA, in clear violation of the text and the purpose of the statute. *See* 21 U.S.C. § 355(j)(2)(A); *see also* CP Denial at 6 n.24 ("[T]o require the ANDA applicants, as you request, to conduct all the clinical studies necessary to demonstrate safety and efficacy and, in this case equivalence studies, would vitiate the purpose of the Hatch-Waxman amendments.").

Biovail's only response is that FDA's decision nonetheless conflicts with the "statutory requirement that the generic product's label be the same as that of the innovator." Biovail Br. at 13. But Biovail offers no basis for thinking that Congress intended to shoehorn additional bioequivalence testing requirements through the labeling requirement. Indeed, under elementary principles of statutory interpretation, quite the opposite should be inferred from the statute. *See, e.g., North Am. Catholic Educ. Programming Found., Inc. v. FCC*, 437 F.3d 1206, 1209 (D.C. Cir. 2006) ("'It is a commonplace of statutory construction that the specific governs the general.'" (quoting *Morales v. Trans World Airlines, Inc.*, 504 U.S. 374, 384 (1992) (alteration

omitted))). Here, Congress has spoken to the specific issue implicated by Biovail's labeling claim—whether an ANDA applicant must demonstrate bioequivalence to a non-reference drug product in order to be approved—and there is no basis for interpreting the general labeling requirement to impose additional testing requirements not specifically provided in the bioequivalence subsection of the statutory scheme.

That general presumption is even more forceful here. Unlike the bioequivalence requirement, which is not subject to a single statutory or regulatory exception, Congress has created numerous exceptions to the labeling requirement. Those exceptions include situations where two products have a different route of administration, dosage form, or strength, and situations where the products are manufactured or marketed by different companies. *See* 21 U.S.C. § 355(j)(2)(A)(v). And FDA has long interpreted the labeling provision to authorize additional variances in cases where there are "differences [with respect to] expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act." 21 C.F.R. § 314.94(a)(8)(iv). Congress has never overridden FDA's interpretation of the statutory exceptions nor limited FDA's authority to supplement the statute. In contrast, Congress has expressly forbidden FDA from imposing any additional bioequivalence testing requirements on ANDA filers, demonstrating that Congress considers the bioequivalence provisions to be far less malleable than the labeling requirements. *See*, *e.g.*, H.R. Rep. 98-857(I), at 22, *reprinted in* 1984 U.S.C.C.A.N. 2647, 2655 ("The Committee recognizes that the proposed labeling for the generic drug ***may not be exactly the same*** [as that of the listed drug]." (emphasis added)). Biovail's rigid interpretation of the labeling requirement, which privileges the latter over the former, is

completely undermined by the text of the statute and should be rejected. As FDA thus reasonably concluded, "[o]nce an ANDA applicant has established that its generic bupropion … tablets are … bioequivalent to Wellbutrin XL, the Wellbutrin XL labeling, including equivalence and seizure information, would be applicable to the generic extended-release product." CP Denial at 7.

Finally, even if both the bioequivalence and labeling provisions were equally general in nature, and even if it there were no textual basis for deeming the bioequivalence provisions which sit at the core of the entire statutory regime to be any more significant than the statute's exception-riddled labeling requirements, Biovail still could not prevail on the merits of its challenge. Under those circumstances, Biovail at best would have demonstrated that the bioequivalence and labeling provisions might be in tension under the unique facts of this case—and thus that the statute does not speak clearly to the issue raised in Biovail's TRO. In those circumstances, of course, FDA would be entitled to full deference under *Chevron*—and Biovail has not articulated any sound basis for concluding that the agency acted arbitrarily, capriciously, or in clear violation of law when it concluded that the intervenors' respective drug products were therapeutically equivalent and that the respective product labels were thus sufficiently similar to warrant approval. Again, in reaching that conclusion, the agency carefully observed that the statute and regulations require only that a generic drug demonstrate bioequivalence with the reference listed drug, and it explained that the purpose of demonstrating bioequivalence is to show that the two drugs are "therapeutically equivalent" and to "ensure that the two drugs will be substitutable for one another." CP Denial at 7. It noted that there was no need to require the intervenors to demonstrate independent bioequivalence with the non-reference Wellbutrin SR and IR products, since they were not seeking to attain substitutability with those products. *Id.*

And after carefully considering the safety and efficacy of the Anchen and Impax products, the agency concluded that those products were fully safe for public consumption:

> Generic bupropion … tablets that are bioequivalent and pharmaceutically equivalent to the RLD are considered to be therapeutically equivalent and thus can be substituted for Wellbutrin XL. These two drugs would be expected to have the same climincal effect and safety profile when administered to patients under the conditions for use prescribed, recommended, or suggested in the labeling. ***You [Biovail] have not submitted any data or information to suggest otherwise***.

CP Denial at 7 (emphasis added).

More than a year after filing its Citizen Petition, Biovail still has not presented any evidence that undermines FDA's expert scientific determination,[4] much less evidence sufficient to authorize this Court to set aside that judgment and effectively remove generic bupropion drug products from the market. *See, e.g.*, *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995) ("[C]ourts give a high level of deference to an agency's evaluations of scientific data within its area of expertise."); *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) (FDA's "judgment as to what is required to ascertain the safety and efficacy of drugs falls squarely into the ambit of the FDA's expertise and merits deference."). Biovail thus has no chance of success on the merits, and its motion should be denied in its entirety.

---

[4] Indeed, Biovail's entire attempt to undermine FDA's expert judgment boils down to a ***hypothetical*** under which its own XL® product varies dramatically from the SR® and IR® products. Biovail Br. at 16. In addition to citing no evidence for the figures it employs, Biovail's hypothetical is based on a fundamentally flawed statistical methodology. It is elementary that one cannot combine data from two statistical samples drawn from two different populations—but that is precisely what Biovail's hypothetical purports to do. Thus, not only does Biovail attack an expert agency's reasoned scientific judgment with no more than an unsubstantiated hypothetical, but it does so with a hypothetical that defies basic statistical principles.

II. BIOVAIL HAS NOT DEMONSTRATED THAT IT WILL SUFFER IRREPARABLE HARM FROM THE DENIAL OF INJUNCTIVE RELIEF, THAT THE BALANCE OF HARDSHIPS FAVORS ENTRY OF INJUNCTIVE RELIEF, OR THAT THE PUBLIC INTEREST FAVORS ENTRY OF INJUNCTIVE RELIEF.

Were there any doubt as to the merits, Biovail has not come close to sustaining its burden of showing that it will be irreparably injured in the absence of temporary injunctive relief, that such hardships would outweigh those that entry of an injunction would impose on Teva and Impax, or that injunctive relief would further the public interest. To the contrary, each of those factors weighs in favor of denying the requested relief.

A. Biovail Has Not Demonstrated Irreparable Harm.

In an effort to demonstrate that it will be irreparably harmed unless this Court enjoins Teva's continued marketing of Impax's already-approved ANDA for generic 300-mg bupropion drug product, Biovail repackages the same claims it made the last time it sought a TRO from this Court—and which both this Court and the District of Maryland have already rejected across the board. *See Biovail Corp. v. FDA*, 448 F. Supp. 2d 154, 164-65 (D.D.C. 2006); Transcript of Hearing on Motion for a Temporary Restraining Order, Dec. 21, 2006 ("Hearing Trans.") (attached as Exh. 6). Biovail thus asserts it will suffer "customer loss, potential harm to relationships with customers, reputational damage, and non-recoverable monetary loss" because generic bupropion products might diminish Biovail's market share. Biovail Br. at 17-18. These arguments are the same as those raised before both this Court and the court in Maryland, and they fare no better here. As Judge Titus stated in denying Biovail's irreparable harm argument from the bench, "In this case, the harm that is alleged . . . is purely economic and is [of] a nature that [could be remedied if Biovail prevails in its patent infringement lawsuit]." Hearing Trans. at 92-93. And this Court likewise considered and rejected these same arguments in its prior decision:

> The plaintiff alleges that if non-bioequivalent generic versions reach the market and cause patients treated with bupropion to suffer from grand mal seizures, Wellbutrin XL's reputation would suffer. The plaintiff asserts that generic drugs, once approved, quickly saturate the market and, when those generic drugs are unsafe, produce a devastating effect on those with rights to the innovator drug….
>
> It is well established that economic loss is insufficient to demonstrate irreparable injury. The plaintiff's claims of potential harm to its business reputation are, at their core, arguments that it will suffer economic harm. The plaintiff argues that the introduction of dangerous generic versions of Wellbutrin XL to the market will "reduce the value" of Wellbutrin XL, will cause physicians to "try competitive products," and will damage Wellbutrin XL's market share. But, the fact that the plaintiff will face competition in the market and may lose profits if the defendant approves generic Wellbutrin XL is insufficient to establish irreparable harm.
>
> Similarly deficient to a showing of irreparable injury is the plaintiff's claim that its reputation will suffer if the generic drugs cause grand mal seizures. The plaintiff argues that it will suffer "inevitable and irreparable harm" if a generic form of Wellbutrin XL has a higher risk than the original of serious side effects. According to the plaintiff, the negative impact of an increase in bupropion-related seizures would affect "not only the manufacturer of the dispensed generic product, but will inevitably reach Wellbutrin XL as well." Absent evidence that the generic drug pending approval will actually cause harmful health effects, however, these allegations fail to meet the requisite standard.

Biovail Corp., 448 F. Supp. 2d at 164-65 (internal citations omitted); *see also Wisc. Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir.1985); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 221 (D.D.C. 1996); *Mead Johnson Pharm. Group v. Bowen*, 655 F. Supp. 53 (D.D.C. 1986).

One further point bears mention here. Despite Biovail's assertion in this litigation that the effects of FDA approval would be "devastating" to its market share, Biovail Br. at 25, it has publicly taken precisely the opposite position. Just a few months ago, Biovail CEO Douglas Squires told participants at an investor conference that entry of a generic version of Wellbutrin XL "is ***not*** a mortal or life-threatening situation for" Biovail. *See* B. Erman, *Biovail Shifts Gears to Thwart Generics*, The Ottawa Citizen (Aug. 11, 2006) (emphasis added). Mr. Squires has also told analysts that Biovail has $571 million in cash reserves and plans to replace any lost revenue

from its bupropion drug products by exploiting other opportunities. *See* Final Transcript – Q2 2006 Biovail Corporation Earnings Conference Call (attached as Exh. 7), at 13; *see also* Biovail CIBC World Markets Institutional Investor Conference Presentation (Oct. 5, 2006) (attached as Exh. 8), at 32 (stating Biovail has over $600 million in cash on hand and up to $400 million in revolving term credit). And Biovail has informed the public in its SEC filings that in the event of a generic launch, GSK maintains the right to launch a so-called "authorized generic," which would be manufactured and supplied by Biovail and would compete with other approved generic drugs. *See* Biovail Corp., U.S. Securities and Exchange Comm'n Form 6-K (June 30, 2006) (attached as Exh. 9), at 24.

Under these circumstances, then, it is particularly hard to credit Biovail's assertions that it will suffer "irreparable" and "devastating" harms from the continued marketing of generic bupropion drug products pending resolution of this case on the merits. This Court has rejected those arguments; the U.S. District Court for the District of Maryland has rejected those arguments; and until Biovail filed its latest briefs in this matter, Biovail itself rejected those arguments. The motion should be denied.

B. The Balance Of Hardships Favors Teva and Impax.

Whatever the nature of the hardship Biovail has identified (and without regard to the fact that it is illusory), it cannot demonstrate that such hardship significantly outweighs the harm that entry of an injunction would impose on Teva and Impax. After all, to the extent any parties have demonstrated they will suffer irreparable harm from the entry of the requested injunction, they are Teva and Impax. The 180-day period of marketing exclusivity was triggered on December 14, 2006, when Anchen effectuated the first sale of its 300-mg bupropion product and selectively waived its exclusivity to Impax, *see* Marshall Declaration at ¶¶ 6, 11, and pursuant to the parties'

agreement, Anchen will be paid significant sums for the right to its exclusivity. *Id*. at ¶ 5. There is no way to stop the 180-day clock now it has started ticking.

The consequences of an injunction thus would be severe: because the price of generic drug products drops significantly at the conclusion of an exclusivity period, it is impossible for a manufacturer to recoup revenues from sales it would have made during a period of marketing exclusivity after full market competition is introduced. *See* Marshall Declaration at ¶ 11. As a result, Teva stands to forever lose millions of dollars even from a temporary interruption of its ongoing sales of Impax's generic 300-mg bupropion drug product. *Id*. at ¶ 11. It thus is little wonder that courts have repeatedly held that the first generic entrant's loss of market exclusivity constitutes an irreparable injury sufficient to bar a competitor from securing temporary injunctive relief after the first generic filer has entered the market. *See Sandoz*, 439 F. Supp. 2d at 32 ("Given that Teva began distributing Ivax's generic simvastatin product on June 23, 2006, entry of an injunction would deprive Ivax of the exclusivity to which it is entitled and millions of dollars a day. 'Once the statutory entitlement has been lost, it cannot be recaptured.'" (quoting *Apotex*, 2006 WL 1030151, at *17)); *see also Mylan Pharms.*, 81 F. Supp. 2d at 48 ("[I]t would be inequitable to punish Geneva for justifiably relying on FDA.").

Moreover, entry of the requested injunction would preclude Teva from fulfilling the contracts it has negotiated with major bupropion purchasers, Marshall Declaration at ¶ 10, and which it has begun to fulfill. *Id*. at ¶ 9. That would not only undermine Teva's ability to negotiate further contracts for the supply of bupropion, but would severely undermine Teva's goodwill and impair its future access to customers. *Id*. at ¶ 10. Those impacts would be especially severe if the delay from an injunction were to deprive Teva of its ability to market Impax's product at any point prior to the conclusion of the 180-day exclusivity period. As the

Marshall declaration explains—and as the case law repeatedly has recognized, *see, e.g.*, *Sandoz*, 439 F. Supp. 2d at 32-33—the principal benefit of the exclusivity period is the "head-start" it provides generic pioneers in order to reward them for undertaking the risks of challenging vulnerable patents. *See* Marshall Decl. at ¶ 12. That head-start allows "first entrants to secure distribution channels and access to customers, enter into long-term sales agreements, increase sales across all product lines, and retain greater market share in the long term." *Id*. Should this Court enter injunctive relief that persists through the 180-day exclusivity period, Teva and Impax will lose the ability to take advantage of these key opportunities, effectively depriving them of any reward for the significant risks they have undertaken in order to bring a safe and affordable generic alternative to the market. Loss of that statutory entitlement and its accompanying rewards is irreparable and warrants the denial of interim injunctive relief. *See, e.g.*, *Apotex*, 2006 WL 1030151, at *17.

And that is not all. In order to prepare for the launch of Impax's generic 300-mg bupropion drug product, both Teva and Impax have made substantial investments in producing enough generic bupropion to satisfy the enormous market demand for this blockbuster drug. *See* Marshall Declaration at ¶ 8; Declaration of Charles V. Hildenbrand ("Hildenbrand Declaration") (attached as Exh. 10), at ¶ 9. By late November 2006, Impax thus had produced and packaged more than 68 million doses of 300-mg generic bupropion tablets on an accelerated basis. *Id*.

Like Teva, Impax would suffer a variety of other irreparable harms in the event temporary injunctive relief is entered. From roughly mid-summer until now, Impax has been operating its plants at maximum capacity. *Id*. at ¶ 10. Nonetheless, it has not been able to keep up with full consumer demand for its entire line of pharmaceutical products. Impax has therefore re-prioritized its production schedule, and in anticipation that its 300-mg bupropion product

would launch this Fall, it either ceased or curtailed its production of several other products in its line. As a result, Impax has a backlog of customer orders for those other products. *Id.* A delay in the continued marketing of Impax's bupropion product would therefore jeopardize Impax's ability to recoup its production losses from its other product lines and will impair Impax's long-term goodwill with its existing customers. *Id.*

At the same time it shifted production priorities to expedite its production of generic bupropion, Impax made a number of personnel changes. Four scientists who typically devote substantial attention to developing improvements to Impax's existing products have been devoting their full attention to overseeing the migration of Impax's 300-mg generic bupropion product from research-and-development to final production. *Id.* at ¶ 11. And Impax has hired approximately 25 workers to manage the manufacturing and packaging of its generic bupropion product. *Id.* Should this Court temporarily enjoin the continued marketing of Impax's bupropion drug product, Impax may be forced to furlough those recent hires, and in the event the injunction lasts, expend additional resources to hire and retrain new employees. *Id.* at ¶¶ 11-12.

Given the substantial and irreparable hardships that an entry of temporary injunctive relief would impose on intervenor-defendants Teva and Impax, Biovail has not come close to sustaining its burden of demonstrating that the balance of harms support the entry of injunctive relief. Instead, it has shown at best that "the hardships [it] may suffer if the emergency injunctive relief is denied are equal to the hardships that Teva will suffer…. Either way, some party may face significant economic disadvantage." *Teva Pharms. USA, Inc.*, 404 F. Supp. 2d at 246. Biovail's motion should be denied.

C. The Public Interest Strongly Favors Denying The Requested Relief.

Last—but certainly not least—the requested injunction will severely harm the public interest by denying patients immediate access to generic 300-mg bupropion pending this Court's

resolution of proceedings. Prior to the granting of the ANDAs for generic bupropion, Biovail had a monopoly on the market for extended-release bupropion product. Sales for the 300-mg dosage exceed ***$ 970 million per year***. *See* Marshall Declaration at ¶ 3; Hildenbrand Declaration at ¶ 4. Vacating FDA approval and reinstating Biovail's monopoly would give Biovail a windfall of millions of dollars a day. More importantly, patients will indisputably be harmed by restricting access to generic bupropion, despite the clear purpose of the Hatch-Waxman Act, which is to "'get generic drugs into the hands of patients at reasonable prices—fast.'" *Andrx Pharms., Inc. v. Biovail Corp. Int'l*, 256 F.3d 799, 809 (D.C. Cir. 2001) (quoting *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991)).

For these reasons, Biovail's motion for temporary injunctive relief should be denied.[5]

CONCLUSION

For the foregoing reasons, intervenors Teva and Impax respectfully request that this Court deny in all respects Biovail's motion for a temporary restraining order and/or preliminary injunction. In the alternative, Teva and Impax request that Biovail be required to post a $25 million bond to cover losses from any delay in Teva's continued distribution of Impax's generic bupropion product.

---

[5] If the Court nonetheless enters an injunction, it should do so on the condition that Biovail post a substantial bond to guarantee that Teva and Impax will not be harmed. Indeed, this Court may not grant such relief without requiring Biovail to provide such a security. *See* Fed. R. Civ. P. 62(c).

Respectfully submitted,

/s/ Michael D. Shumsky

Jay P. Lefkowitz (D.C. Bar No. 449280)*
Michael D. Shumsky (D.C. Bar No. 495078)
KIRKLAND & ELLIS LLP
655 15th Street N.W., Suite 1200
Washington, DC 20005
(202) 879-5000

* Counsel of Record

Counsel for Intervenors-Defendants Teva Pharmaceuticals USA, Inc. and Impax Laboratories, Inc.

December 29, 2006

CERTIFICATE OF SERVICE

The undersigned certifies that on this 29th day of December 2006, a true and correct copy of the foregoing Opposition to Biovail's Motion for a Temporary Restraining Order and/or Preliminary Injunction, and the attachments thereto was served via email and ECF filing as follows:

James F. Segroves
PROSKAUER ROSE LLP
1001 Pennsylvania Avenue, NW
Suite 400 South
Washington, D.C. 20004-2533
jsegroves@proskauer.com

Ronald S. Rauchberg
Kevin J. Perra
PROSKAUER ROSE LLP
1585 Broadway
New York, NY 10036
rrauchberg@proskauer.com
kperra@proskauer.com

John B. Dubeck
KELLER AND HECKMAN LLP
1001 G Street, NW
Washington, D.C. 20001
dubeck@khlaw.com

Counsel for Plaintiff

Gerald Cooper Kell
U.S. Department of Justice
1331 Pennsylvania Avenue, NW
Suite 950 N
Washington, D.C. 20004
gerald.kell@usdoj.gov

Shoshana Hutchinson
U.S. Food and Drug Administration
Office of the General Counsel
5600 Fishers lane GCF-1
Rockville, MD 20857
shoshana.hutchinson@fda.hhs.gov

Counsel for Federal Defendants

Gordon A. Coffee
WINSTON & STRAWN LLP
1700 K Street, N.W.
Washington, D.C. 20006
gcoffee@winston.com

John E. Mooney
Donald J. Mizerk
WINSTON & STRAWN LLP
35 West Wacker Drive
Chicago, IL 60601
jmooney@winston.com
dmizerk@winston.com

Counsel for Intervenor-Defendant Anchen Pharmaceuticals, Inc.

/s/ Michael D. Shumsky
Michael D. Shumsky
Counsel for Intervenors-Defendants Teva Pharmaceuticals USA and Impax Laboratories