IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

BIOVAIL CORPORATION, and BIOVAIL LABORATORIES INTERNATIONAL, SRL, Plaintiffs, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, and ANDREW C. VON ESCHENBACH, M.D., in his official capacity as COMMISSIONER OF FOOD AND DRUGS, Defendants, and ANCHEN PHARMACEUTICALS, INC., Intervenor.	)	Civ. No. 06-1487 (RMU)

GOVERNMENT'S OPPOSITION TO PLAINTIFFS' SECOND MOTION FOR A TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION

INTRODUCTION

At issue in this case is the Food and Drug Administration's (FDA or agency) approval of generic versions of bupropion hydrochloride (HCl) extended-release tablets, an antidepressant.[1] Biovail Corporation manufactures the brand-name version of bupropion HCl extended-release tablets for GlaxoSmithKline (GSK), which markets the drug as Wellbutrin XL®. Anchen Pharmaceuticals, Inc., (Anchen) is the first manufacturer of a generic version of Wellbutrin XL.

Biovail is challenging the scientific basis of FDA's approval of abbreviated new drug applications (ANDAs) for generic versions of Wellbutrin XL. Its challenge is but one is a series of efforts by Biovail to inappropriately extend the market monopoly of Wellbutrin XL.[2] The agency's decision to approve ANDAs for generic bupropion HCl extended-release tablets falls squarely within FDA's scientific and technical expertise. Therefore, Biovail's attempt to reverse

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[1] The term "generic" is not defined in FDA's statute or regulations. It is used here to refer to drug products for which approval is sought under an abbreviated new drug application.

[2] Biovail challenges Anchen's generic version of Wellbutrin XL here because Anchen's application represents FDA's first approval of an ANDA for this product. Biovail's objection, however, is a general one relevant to FDA's position regarding the scientific support necessary for approval of any and all ANDAs for generic versions of Wellbutrin XL. Therefore, the case is not a challenge to Anchen's ANDA per se but to all similarly situated ANDAs. For ease of reference, however, our opposition refers to Anchen and its ANDA.

Regarding similarly situated ANDAs, this case is one of two actions that Biovail has filed against the federal defendants regarding bupropion HCl extended-release tablets. See infra p. 16 n. 21 (describing Biovail's action filed in the U.S. District Court for the District of Maryland alleging violations stemming from FDA's approval of Impax Laboratories, Inc.'s (Impax) ANDA for a generic version of Wellbutrin XL). As described in that action by the intervenors (Impax and Teva Pharmaceuticals USA, Inc. (Teva)) there, Impax and Teva have launched commercial marketing of their generic version of Wellbutrin XL. MD Intervenors' Opp. at 9-10. The marketing of their product was enabled by an agreement they entered into with Anchen, which has "selectively waived" marketing exclusivity of its product. The details of the agreement are not relevant to the government's position here. What is relevant is that the commercial marketing of a generic version of Wellbutrin XL is well underway.

FDA's decision(s) in order to preserve its own profits, while decreasing the availability of low cost, reliable, and safe pharmaceuticals, should be rejected.

Biovail argues that FDA has violated the unambiguous statutory requirement that the generic version of a drug have the same labeling as the brand-name drug. As a result, according to Biovail, the labeling on generic versions of Wellbutrin XL is inadequate to protect the public against the risks associated with the use of bupropion HCl extended-release tablets. In Biovail's view, FDA approved Anchen's product without assuring that it provides the same level of safety and effectiveness as the brand-name drug. These contentions are not well-grounded in fact or law and, thus, do not support the relief Biovail seeks.

Although Biovail frames its lawsuit as a challenge involving statutory interpretation, Biovail's dispute is with the scientific criteria FDA uses to determine whether generic bupropion HCl extended-release tablets are bioequivalent to Wellbutrin XL – one of the requirements for approval of a generic version of Wellbutrin XL. To obtain the relief its seeks, Biovail must establish a substantial likelihood that FDA's approval of Anchen's product must be set aside – a burden Biovail has manifestly failed to meet. Biovail offers no plausible justification to refute FDA's scientific conclusion that Anchen's application for a generic version of Wellbutrin XL meets the statutory requirements for approval. The record reflects that FDA engaged in reasoned decision-making and based its decision to approve generic bupropion HCl extended-release tablets after a careful, thorough review of the scientific and technical issues. The record provides clear and compelling grounds to reject Biovail's challenge to FDA's approval of generic competitors.[3]

[3] The administrative record in this matter, accompanied by an affidavit and certificate, is submitted along with this opposition as Attachments 1-13. See Fed. R Civ. P. 44.

Because Biovail is not likely to succeed on the merits of its case, it must present a substantial showing of irreparable harm from the denial of preliminary injunctive relief pending resolution of this action on the merits. It has not done so. By contrast, every day that the marketing of generic bupropion HCl extended-release tablets – whose performance FDA has found to be equivalent to Wellbutrin XL – is delayed, American consumers would be deprived of less expensive alternatives to the costly brand-name drugs, and FDA's mandate to approve generic products that meet the statutory requirements would be hampered. Because the alleged harm that Biovail will suffer if a preliminary injunction is not granted is less than what the public, FDA, and any party with an approved or pending ANDA for a generic version of Wellbutrin XL, will suffer if a preliminary injunction to block the marketing of a generic product is granted, the balance of harms does not weigh in Biovail's favor.

This case represents another instance in which a manufacturer of a brand-name drug, in fear of losing its lucrative hold on the market, has attempted to block generic competition by challenging the scientific basis upon which FDA has approved a generic drug. See Serono Labs., Inc. v. Shalala, 158 F.3d 1313, 1326 (D.C. Cir. 1998); Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212 (D.D.C. 1996); Fisons Corp. v. Shalala, 860 F. Supp. 859 (D.D.C. 1994); see also Schering Corp. v. FDA, 51 F.3d 390 (3d Cir. 1995); Somerset Pharmaceuticals, Inc. v. Shalala, 973 F. Supp. 443 (D. Del. 1997). In these cases, such challenges failed, as should this one. The courts' reviews of FDA's approval decisions have unequivocally held that scientific determinations as to the appropriate methodology required for approval of a generic drug fall squarely within the broad discretion of the agency, which Congress has determined is in the best position to make such highly technical scientific decisions. For the same reason, FDA's

approval of Anchen's ANDA should be upheld, and Biovail's motion for a preliminary injunction denied.

STATEMENT OF THE CASE

I. STATUTORY AND REGULATORY SCHEME

A. New Drug Applications And Abbreviated New Drug Applications

Under the Federal Food, Drug, and Cosmetic Act (FDCA), a pharmaceutical company seeking to market a "brand-name," "pioneer," or "innovator" drug must first obtain FDA approval by filing a new drug application (NDA) containing extensive scientific data demonstrating the safety and effectiveness of the drug. 21 U.S.C. § 355(a), (b). Congress amended the FDCA through the Drug Price Competition and Patent Term Restoration Act of 1984 (known as the "Hatch-Waxman Amendments"), codified at 21 U.S.C. § 355 and 35 U.S.C. §§ 156, 271, 282, in an effort to increase the availability of lower cost generic versions of approved brand-name drugs while at the same time encouraging innovation in drug development. 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, e.g., Tri-Bio Labs., Inc. v. United States, 836 F.2d 135, 139 (3d Cir. 1987). The Hatch-Waxman Amendments created Section 505(j) of the FDCA, 21 U.S.C. § 355(j), which permits a manufacturer to seek marketing approval of a generic drug through an ANDA.[4]

An ANDA applicant need not submit extensive clinical data to demonstrate the safety and effectiveness of its product, as is required for an NDA. Rather, under the Hatch-Waxman

[4] To compensate innovator drug manufacturers for the costs of demonstrating safety and effectiveness of new drug products and to encourage new drug research, the Hatch-Waxman Amendments provide for certain benefits, e.g., exclusive marketing rights, 30-month stays, and patent term extensions. 21 U.S.C. §§ 355(j)(5)(F), 355(j)(5)(B)(iii); 35 U.S.C. § 156.

Amendments, an ANDA relies on FDA's previous findings that the product approved under the NDA (the "reference listed drug"[5] (RLD)) is safe and effective. The ANDA approval process "'permits generic drug applications to piggy-back on clinical findings that [the] FDA has already embraced' in the NDA" and, thus, the ANDA applicant "need not duplicate the clinical safety studies that supported the pioneer drug's NDA." Zeneca, Inc. v. Shalala, 213 F.3d 161, 164 (4th Cir. 2000) (quoting In re Barr Laboratories, Inc., 930 F.2d 72, 73 (D.C. Cir. 1991)); Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1495 (D.C. Cir. 1996).

The scientific premise of the Hatch-Waxman Amendments is that a generic drug product that meets the approval requirements of 21 U.S.C. § 355(j) is as safe and effective as the RLD. Among other things, an ANDA generally must include information showing that the generic drug has the same active ingredient, conditions of use, dosage form, strength, and route of administration as the RLD.[6] Moreover, the ANDA must show that "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are []adequate to assure and preserve its identity, strength, quality, and purity."[7] The law further requires that the ANDA include information to show that the generic drug's labeling is the same as the labeling for the RLD (except for certain permissible differences).[8] In addition, the ANDA

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[5] "Listed drug" is a drug with an effective approval, which is evidenced by the drug's listing as such in the Approved Drug Products with Therapeutic Equivalence Evaluations 26th Ed., 2006 (the Orange Book) (available at http://www.fda.gov/cder/orange/obannual.pdf). 21 C.F.R. § 314.3(b). A reference listed drug is "the listed [i.e. approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application." 21 C.F.R. § 314.3(b).

[6] 21 U.S.C. § 355(j)(2)(A)(i)-(iii); 21 C.F.R. § 314.94(a).

[7] See 21 U.S.C. § 355(j)(4)(A); 21 C.F.R. § 314.94(a)(9).

[8] 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8).

must include information showing that the generic drug is "bioequivalent" to the RLD.[9] Failure to satisfy any one of the requirements is grounds for refusal to approve the ANDA.[10]

B. Bioequivalence And Therapeutic Equivalence

To reiterate, an ANDA applicant must provide information to show that its proposed generic product is bioequivalent to the RLD. If the generic drug demonstrates bioequivalence to the RLD, and the generic drug meets the other requirements for ANDA approval described above, the ANDA may be approved, and the generic drug and the RLD will be considered to be "therapeutic equivalents." Therapeutically equivalent products can be expected to have the same clinical effect and safety profile when administered under the conditions specified in the labeling. A therapeutically equivalent generic product is considered to be interchangeable with the brand-name drug. Orange Book at vi.

For drugs like bupropion that are absorbed into the bloodstream, a drug is considered to be bioequivalent to the RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient . . . ." 21 U.S.C. § 355(j)(8)(B)(i); see 21 C.F.R. §§ 320.1(e), 320.23(b). The purpose of a bioequivalence study of a generic drug is to show that the bioavailability of the proposed product (i.e., the rate and extent of absorption of the drug) is not significantly different from the bioavailability of the RLD. FDA regulations discuss

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[9] 21 U.S.C. § 355(j)(2)(A)(iv) (requiring "information to show that the new drug is bioequivalent to the listed drug"); 21 C.F.R. § 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the RLD upon which the applicant relies); see 21 C.F.R. § 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA).

[10] 21 U.S.C. § 355(j)(4); 21 C.F.R. § 314.127(a).

the types of evidence (e.g., in vivo and in vitro methods) required to establish bioequivalence. 21 C.F.R. § 320.24.

C. The "Same Labeling" Requirement

The statute provides that an "abbreviated application for a new drug shall contain . . . (v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug . . . except for changes required . . . because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. §§ 355(j)(2)(A)(v), 355(j)(4)(G); 21 C.F.R. §§ 314.127(a)(7), 314.94(a)(8)(iv).[11]

The labeling for an innovator drug generally includes, among other things, information on clinical and preclinical studies conducted on the innovator product. 21 C.F.R. §§ 201.56, 201.57. Because the generic drug is required to have the same labeling as the RLD, the generic drug's labeling generally contains the same substantive study descriptions, summaries of data, findings, and conclusions as the labeling for the RLD. As a result – and also because the ANDA

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[11] The regulation setting forth the required content for ANDAs provides examples of permissible labeling differences:

> Labeling . . . proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in 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 [now section 505(j)(5)(F)].

21 C.F.R. § 314.94(a)(8)(iv) (emphasis added).

applicant relies on FDA's previous findings for the innovator drug – the generic drug's labeling will include information on scientific studies that were *conducted on the RLD*.[12] Cf. SmithKline Beecham Consumer Healthcare, L.P. v. Watson Pharm., Inc., 211 F.3d 21, 26 (2d Cir. 2000) (noting that the Hatch-Waxman Amendments reflect the view that clinical retesting of generic drugs is "unnecessary and wasteful . . . as well as unethical") (internal quotations omitted); see also id. at 25 (holding that the Hatch-Waxman Amendments require generic drugs to use the same labeling as the innovator drug even if that labeling has been copyrighted).

II. FACTUAL BACKGROUND

A. NDA For Wellbutrin XL

On August 28, 2003, Wellbutrin XL was approved as an extended-release formulation under NDA 21-515 and is available in 150- and 300-mg tablets for once-daily administration. Wellbutrin XL is approved for the treatment of major depressive disorder and for the prevention of seasonal major depressive episodes in patients with a diagnosis of seasonal affective disorder.

FDA's approval of the NDA for Wellbutrin XL was based in part on what Biovail refers to as bioequivalence studies, which have a purpose different from the bioequivalence studies that are conducted for generic drug approval. The types of studies to which Biovail refers are informally called "line extensions" because they are done to support certain changes in a drug product, e.g., formulation changes, that result in a "line" of products. The Wellbutrin XL labeling reflects the findings from line extension studies – a showing of bioequivalence between

[12] When a generic drug's labeling describes those scientific studies, the drug product studied may be identified by its established (chemical) name, rather than its brand-name. Replacing the RLD's brand name with the drug's established name – e.g., replacing Wellbutrin XL with bupropion HCl extended-release tablets – is a permissible difference in generic drug labeling. See 21 C.F.R. § 314.94(a)(8).

Wellbutrin XL and the other product formulations, i.e., the sustained-release (Wellbutrin SR) and immediate-release (Wellbutrin IR) formulations.[13] See Pls. Mem. at 8-9.

B. Anchen's ANDA For A Generic Version Of Wellbutrin XL

Anchen submitted ANDA 77-284 for a generic version of Wellbutrin XL on September 21, 2004, which received a tentative approval on November 14, 2005.[14] FDA approved Anchen's application on December 14, 2006.[15]

To be approved, Anchen's product had to meet all requirements under 21 U.S.C. § 355(j), including showing that it is bioequivalent to Wellbutrin XL and that it has the same labeling as the RLD. Based on its review of Anchen's ANDA, FDA determined that Anchen's generic bupropion HCl extended-release tablets and Wellbutrin XL are bioequivalent and have the same labeling (with permissible differences). Anchen's ANDA also met the other statutory requirements for approval. As a result, Anchen's approved product and Wellbutrin XL are therapeutic equivalents and can be expected to have the same clinical effect and safety profile when administered under the conditions specified in the labeling. Therefore, Anchen's product is considered to be interchangeable with Wellbutrin XL.

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[13] Wellbutrin was first approved as an immediate-release tablet (for dosing three times a day) on December 30, 1985, (NDA 18-644) and was subsequently approved in a sustained-release formulation (for dosing twice a day) on October 4, 1996 (NDA 20-358). Although Wellbutrin SR is categorized as a type of extended-release product, it is clearly distinct from Wellbutrin XL. For clarity, the term "extended-release" will not be used in this brief to refer to the sustained-release formulation. When referring specifically to a sustained-release formulation, we will use the term "sustained-release."

[14] On December 21, 2004, Biovail instituted legal proceedings for patent infringement and has appealed its loss on summary judgment. Biovail Labs., Inc., v. Anchen Pharm., Inc., No. 06-1641, Fed. Cir. (appeal docketed Sept. 25, 2006).

[15] On December 15, 2006, Impax received approval for its ANDA for a generic version of Wellbutrin XL.

C. Biovail's Citizen Petition

On December 20, 2005, Biovail submitted a citizen petition (Petition) to FDA concerning approval standards for ANDAs for generic versions of Wellbutrin XL. Biovail's Petition asked the agency to require any ANDA for generic bupropion HCl extended-release tablets to satisfy the following criteria to support a determination that the generic extended-release product is bioequivalent to Wellbutrin XL:

(1) demonstrate that the generic extended-release product is also bioequivalent to Wellbutrin IR and Wellbutrin SR;

(2) calculate bioequivalence based on the parent drug – bupropion HCl – plus the parent drug's three metabolites;[16]

(3) use multiple-dose studies, rather than single-dose studies, to demonstrate that the generic extended-release product is bioequivalent to Wellbutrin IR and Wellbutrin SR; and

(4) conduct in-vitro tests on the generic formulation to show that alcohol does not cause a substantial difference in the product's dose-release profile, i.e., "dose dumping."

Biovail noted that, under the FDCA, the labeling for generic bupropion HCl extended-release tablets must be the same – with certain exceptions – as the labeling for Wellbutrin XL. Petition at 3. According to Biovail, unless Biovail's proposed criteria are satisfied, "there can be no assurance" that the approved labeling for Wellbutrin XL, which includes test results and warnings about potentially serious risks such as seizure, "are adequate to ensure that generic versions are as safe and effective as the innovator product." Petition at 1 (Attachments 4, 4b, 4c).

[16] A "metabolite" is a chemical produced in the body following the absorption and processing of a parent chemical.

On June 7, 2006, FDA issued a tentative response to Biovail's Petition in accordance with its regulations,[17] explaining that FDA had been unable to reach a decision to date because the Petition "raises complex issues requiring extensive review and analysis by Agency officials." (Attachment 11). Subsequently, Biovail submitted a letter to FDA, dated June 29, 2006, (Letter) requesting that FDA take final action on the Petition no fewer than two business days before giving final approval to any ANDA for generic bupropion HCl extended-release tablets. In the Letter, Biovail threatened that, if the agency did not indicate by July 14, 2006, its intent to respond to the Petition before taking action on any relevant ANDAs, "Biovail will consider itself free to pursue appropriate judicial relief." Letter at 1 (Attachment 12).

On August 23, 2006, Biovail filed a Motion for a Temporary Restraining Order (TRO) with this Court alleging that FDA violated the Administrative Procedure Act (APA) and Biovail's right to due process by failing to substantively respond to the Petition within 180 days. Biovail requested that this Court compel the agency to act on the Petition at least one week before approving any ANDA for a generic version of Wellbutrin XL. This Court denied the motion on August 25, 2006. Biovail Corp. v. FDA, Civ. No. 06-1487 (RMU), 2006 U.S. Dist. LEXIS 62920 (D.D.C. Sept. 6, 2006).

In denying the motion, this Court found that Biovail did not make a sufficient showing of irreparable harm to support its TRO request. Id. at *24. Further, this Court found that Biovail did not demonstrate a substantial likelihood of success on the merits of its claims. This Court recognized that "the public also has an interest in receiving generic competition to brand-name

[17] See 21 C.F.R. § 10.30(e)(2) (requiring the agency to respond to petitions within 180 days of receipt by either approving or denying the petition or providing a tentative response).

drugs as soon as is possible" and stated that Biovail "has not established, or even alleged, that the pending ANDA represents a drug that is unsafe." Id. at *31 (internal quotations omitted).

D. FDA's Response To Biovail's Petition

On December 14, 2006, after careful consideration of the issues, FDA denied most of Biovail's Petition. FDA also denied Biovail's Letter, stating that the requested stay in approving ANDAs is unwarranted because Biovail failed to demonstrate public policy grounds for the stay and any delay is outweighed by public health interests. FDA's Response to the Petition (Petition Resp.) at 15. (Attachment 13). FDA also disagreed with Biovail's assertion, as did this Court, that due process requires FDA to give Biovail two days' notice before approving such ANDAs. Id. at 16-18.

In denying the Petition in part, FDA responded as follows. First, FDA stated that, to obtain approval, an ANDA applicant relies on the agency's finding of safety and effectiveness for the RLD. FDA explained that, to rely on this finding, the ANDA applicant must demonstrate that its generic drug is bioequivalent to the RLD, which in this case is Wellbutrin XL,[18] and meets all other requirements for ANDA approval, including appropriate labeling. Once these requirements are met, the generic drug can be expected to be as safe and effective as the innovator drug. FDA further explained that, once an ANDA applicant establishes that its

[18] FDA agreed with Biovail that, in assessing the bioequivalence of generic bupropion HCl extended-release tablets to Wellbutrin XL, ANDA applicants should conduct a "fed" bioequivalence study (drug administered shortly after a meal), in addition to a "fasted" study (drug administered under fasting conditions), to demonstrate the absence of a "food effect" on the release of the active ingredient in the generic product. Petition Resp. at 8; see FDA' s guidance for industry, Food-Effect Bioavailability and Fed Bioequivalence Studies (Dec. 2002) (Food Effect Guidance) at 4 (recommending that ANDA applicants conduct fasting and fed bioequivalence studies for all orally administered modified-release drug products (such as extended-release products)) (available at http://www.fda.gov/cder/guidance/5194fnl.htm).

bupropion HCl extended-release tablets are bioequivalent to Wellbutrin XL and meet all the other requirements for ANDA approval, the Wellbutrin XL labeling, including equivalence and seizure information, are applicable to the generic extended-release product. Petition Resp. at 6-7. FDA also stated that an ANDA applicant is not required to independently demonstrate bioequivalence of its proposed product to Wellbutrin IR or Wellbutrin SR because neither one is (or could be) the RLD in any ANDA application for generic bupropion HCl extended-release tablets (i.e, generic versions of Wellbutrin XL). See id.

Second, FDA stated that, in comparing generic bupropion HCl extended-release tablets to Wellbutrin XL for the purpose of demonstrating bioequivalence, it is necessary to measure certain, but not all, of the three metabolites proposed by Biovail. In applying current recommendations found in FDA's guidance for industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (March 2003) (BA/BE Guidance) (available at http://www.fda.gov/cder/guidance/5356fnl.htm), the agency concluded that only one metabolite – hydroxybupropion – based on its relative potency and exposure compared to the other two metabolites (threohydrobupropion and erythrohydrobupropion), contributes meaningfully to the safety and/or efficacy of the drug product and meets the other factor described therein.[19] Petition Resp. at 9-11. Therefore, FDA expects an ANDA applicant for generic bupropion HCl extended-release tablets to measure the parent drug and the

[19] The BA/BE Guidance generally recommends measurement of only the parent drug, rather than the metabolite, for bioequivalence studies and also describes two situations when it may be appropriate to measure metabolites. BA/BE Guidance at 18. FDA determined that one of the situations – when a metabolite may be formed as a result of gut wall or other presystemic metabolism and the metabolite contributes meaningfully to safety and/or efficacy – applies to Wellbutrin XL. FDA found that this situation is relevant to the metabolite hydroxybupropion only. Petition Resp. at 10.

metabolite hydroxybupropion when evaluating bioequivalence.[20] FDA concluded that the parent drug and hydroxybupropion provide a scientifically reasonable and reliable indicator of the drug's activity. Petition Resp. at 11.

Third, FDA stated that a single-dose, not a multiple-dose, study is the preferred approach to demonstrating bioequivalence for generic drugs because single-dose studies are more sensitive at detecting small differences in the rate and extent of drug absorption. Petition Resp. at 12. Nevertheless, FDA concluded that, because an ANDA applicant is not required to demonstrate bioequivalence of its generic version of Wellbutrin XL to the IR and SR formulations of Wellbutrin, Biovail's argument that such evaluations should be conducted using multiple-dose studies for those formulations is irrelevant. Id.

Finally, Biovail's request that the agency require ANDA applicants to provide in vitro data demonstrating the absence of dose-dumping if the extended-release formulation is consumed with alcohol is moot. The agency has asked ANDA applicants to submit data from in vitro dissolution studies using various concentrations of ethanol (alcohol) to evaluate the possible effect of alcohol. FDA stated that it considers the results of the in vitro data submitted by the ANDA applicants when determining whether to approve each ANDA. Petition Resp. at 13.

E. Biovail's Second Application For Emergency Relief

[20] FDA denied Biovail's request that ANDA applicants be required to employ statistical criteria to calculate bioequivalence parameters for metabolites, noting that the BA/BE Guidance currently recommends that metabolite data should be used to provide supportive evidence of comparable therapeutic outcome and that only the parent drug should be analyzed using specified bioequivalence statistical criteria. Petition Resp. at 11; see BA/BE Guidance at 18.

On December 14, 2006, FDA approved, pursuant to 21 U.S.C. § 355(j), bupropion HCl extended-release tablets manufactured by Anchen because the agency determined that Anchen's generic product met the statutory and regulatory requirements for approval. FDA found this drug product to be therapeutically equivalent to Biovail's Wellbutrin XL. FDA's approval of Anchen's ANDA represents the first generic competitor to Biovail's Wellbutrin XL.

On December 18, 2006, Biovail filed a motion for leave to file an amended complaint in this suit, seeking injunctive, declaratory, and mandamus relief against FDA. Biovail requests this Court to declare that FDA was arbitrary and capricious for denying its Petition and for approving Anchen's ANDA and any other ANDA for a generic version of Wellbutrin XL. Biovail also requests this Court to require FDA to (i) suspend or withdraw the approval of Anchen's ANDA (and any other approved ANDA for the same product), and (ii) grant Biovail's Petition. Finally, Biovail seeks an injunction (preliminary and permanent) to prevent FDA from approving ANDAs for bupropion HCl extended-release tablets until the applicants demonstrate that they have met the conditions of approval set forth by Biovail.

The same day, Biovail filed a motion for a temporary restraining order and preliminary injunction, alleging that FDA's denial of its Petition and approval of Anchen's ANDA were improper.[21] Biovail asserts that, because the Wellbutrin XL labeling states that the innovator product has been demonstrated to be bioequivalent to the Wellbutrin SR and Wellbutrin IR

[21] Biovail also filed a motion for a temporary restraining order and preliminary injunction, challenging FDA's approval on December 15, 2006, of Impax's ANDA and alleging that, pursuant to the FDCA, Biovail's pending patent infringement suit against Impax should have stayed the approval of Impax's 300 mg strength product. Biovail Corp., et al., v. FDA, et al., Civ. No. 8:06-cv-03355 (RWT), (D. Md.) (filed Dec. 18, 2006). On December 21, after oral argument on the motion, the court denied Biovail's request for emergency relief. (Docket No. 13).

product formulations, an ANDA for a generic version of Wellbutrin XL must also contain information demonstrating bioequivalence between the proposed generic and the Wellbutrin SR and IR formulations. Pls. Mem. at 14-15. Biovail claims that, if the generic version has not been tested to demonstrate bioequivalence to these other formulations, the generic extended-release product cannot legitimately use the same labeling that is used for Wellbutrin XL.[22] Biovail concludes that, if the Wellbutrin XL labeling approved by FDA is used on Anchen's product, "the public will be deceived as to the health risks associated with the product." Id. at 4, 15-16.

Biovail states that the Wellbutrin XL labeling provides not only that Wellbutrin XL has been shown to be bioequivalent to Wellbutrin IR and Wellbutrin SR, but that the risk of seizure associated with Wellbutrin XL is based on clinical trials conducted on those formulations. According to Biovail, any ANDA applicant, therefore, has to conduct bioequivalence studies between its product and the immediate- and sustained-release formulations in order to (i) ensure that the seizure risk information on the Wellbutrin XL labeling is applicable to the generic extended-release product, and (ii) permit the ANDA applicant to label its product with the seizure risk information from the Wellbutrin XL labeling. In Biovail's view:

> In order to legitimately have the same labeling as that used by Wellbutrin XL® as required by the FDCA, Anchen (or any other ANDA applicant) must first demonstrate bioequivalency not only to Wellbutrin XL®, but also to the sustained-release and immediate-release versions of bupropion. Unless such data are presented, the generic labeling would be inherently

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[22] At other times in its brief, Biovail asserts that, because "FDA *did not* require Anchen (or any other ANDA applicant) to have the same labeling as Wellbutrin XL®," the labeling on the generic product(s) is "in clear violation of the FDCA." Pls. Mem. at 4 (emphasis added); see also id. at 11, 15. Although, in these instances, Biovail claims that the labeling on Anchen's product is not the same, it never points to any differences in the labeling. Of course, it could not, as FDA approved Anchen's ANDA with the same labeling (with permissible exceptions) as the labeling for Wellbutrin XL.

> false and misleading with respect to the applicability of the seizure risk information presented in the labeling.

Pls. Mem. at 15.

Biovail's assertions are wrong. FDA determined that Anchen (i) demonstrated that its generic bupropion HCl extended-release tablets are bioequivalent to the RLD, Wellbutrin XL, (ii) met the other statutory requirements for approval, (iii) may rely on the agency's finding of safety and effectiveness for the RLD, which finding is embodied in the labeling of Wellbutrin XL, and (iv) can (and must) use the labeling for the RLD, with permissible differences. Despite FDA's conclusions, which are based on a thorough review of the information in Anchen's ANDA and – more importantly to Biovail's challenge – a complete assessment of the issues raised in Biovail's Petition, Biovail now seeks emergency relief staying the effectiveness of Anchen's and any other prior approval, and preventing any new approval, of generic versions of Wellbutrin XL. Biovail insists that its own criteria for bioequivalence should replace the agency's scientific expertise on the matter. Biovail's attempt to usurp FDA's authority should not be tolerated, and its motion for preliminary relief should be denied.

ARGUMENT

A preliminary injunction is an extraordinary remedy not to be granted lightly. Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 215 (D.D.C. 1996). As the Supreme Court has said, "It frequently is observed that a preliminary injunction is an extraordinary and drastic remedy, one that should not be granted unless the movant, by a clear showing, carries the burden of persuasion." Mazurek v. Armstrong, 520 U.S. 968, 972 (1997) (internal quotation omitted). 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. Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1066 (D.C. Cir. 1998); CityFed Fin. Corp. v. Office of Thrift Supervision, 58 F.3d 738, 746 (D.C. Cir. 1995); see also Washington Metro. Area Transit Comm'n v. Holiday Tours, Inc., 559 F.2d 841, 843-44 (D.C. Cir. 1977) ("Holiday Tours"). The Court must balance the four factors in deciding whether to grant the injunctive relief. Mova, 140 F.3d at 1066. Although the factors are balanced on a sliding scale, without a "'substantial indication'" of likely success on the merits, "'there would be no justification for the court's intrusion into the ordinary processes of administration and judicial review.'" American Bankers Ass'n v. Nat'l Credit Union Admin., 38 F. Supp. 2d 114, 140 (D.D.C. 1999) (quoting Holiday Tours, 559 F.2d at 843); see Serono Labs., Inc. v. Shalala, 158 F.3d 1313, 1326 (D.C. Cir. 1998).

I. BIOVAIL HAS NOT SHOWN A LIKELIHOOD OF SUCCESS ON THE MERITS

A. FDA's Administrative Decision Is Entitled To Deference

Biovail's likelihood of success on the merits of its claim must be considered in light of the applicable standard of review. 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). Indeed, "'there is a presumption in favor of the validity of the administrative action.'" Bristol-Myers, 923 F. Supp. at 216 (quoting Ethicon, Inc. v. FDA, 762 F. Supp. 382, 386 (D.D.C. 1991)). The reviewing court must consider whether the agency's decision was based upon consideration of the relevant factors and whether there has been a clear error of judgment. Overton Park, 401 U.S. at 416. However, "under this narrow scope of review, '[t]he 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). In applying the arbitrary and capricious standard, the court reviews the administrative record assembled by the agency and does not undertake its own fact finding. See, e.g., Camp v. Pitts, 411 U.S. 138, 142 (1973).

When, as here, an agency's decision is based on evaluation of scientific information within the agency's area of technical expertise, its decisions are traditionally accorded great deference. Southwestern Pennsylvania Growth Alliance v. Browner, 121 F.3d 106, 117 (3d Cir. 1997); Bristol-Myers, 923 F. Supp. at 216 (citing Federal Power Comm'n v. Florida Power & Light Co., 404 U.S. 453, 463 (1972)). Courts "review scientific judgments of the agency 'not as the chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality.'" Troy Corp. v. Browner, 120 F.3d 277, 283 (D.C. Cir. 1997) (quoting Ethyl Corp. v. EPA, 541 F.2d 1, 36 (D.C. Cir. 1976)); see also International Fabricare Inst. v. EPA, 972 F.2d 384, 389 (D.C. Cir. 1992) ("The rationale for deference is particularly strong when [the agency] is evaluating scientific data within its technical expertise."). Affording the highest level of deference to an agency's scientific judgments is particularly apt when the judgment relates to a choice of an appropriate testing methodology. See Solite Corp. v. EPA, 952 F.2d 473, 489-90 (D.C. Cir. 1991); see also National Ass'n of Metal Finishers v. EPA, 719 F.2d 624, 657 (3d Cir. 1983) ("the choice of scientific data and statistical methodology to be used is best left to the sound discretion of the [agency]").

Such deference has repeatedly been applied in cases under the FDCA. See, e.g., Serono Labs., 158 F.3d at 1320-21 (in innovator's challenge to ANDA approval on whether the active ingredient in the generic was the same, the court held that "FDA's determination of 'sameness'

for purposes of the Act rests on the 'agency's evaluations of scientific data within its area of expertise,' and hence is entitled to a 'high level of deference' from this court") (quoting in part A.L. Pharma, Inc. v. Shalala, 62 F.3d 1484, 1490 (D.C. Cir. 1995)); Henley v. FDA, 77 F.3d 616, 621 (2d Cir. 1996) ("FDA possesses the requisite know-how to conduct such [scientific] analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug . . . . We therefore defer to its reasonable findings."); Tri-Bio Laboratories, Inc. v. United States, 836 F.2d 135, 142 (3d Cir. 1987) ("in evaluating scientific evidence in the drug field, the FDA possesses an expertise entitled to respectful consideration by this court"), cert. denied, 488 U.S. 818 (1988).

This deference is especially apparent in the context of bioequivalence determinations. In Bristol-Myers, the company sought a preliminary injunction against FDA's approval of a generic competitor. Bristol-Myers argued that FDA had impermissibly utilized in vitro testing to determine the bioequivalence of the generic product. 923 F. Supp. at 216. The court denied the preliminary injunction, explaining that the "case involves the agency's scientific judgments concerning what testing methods are needed to establish bioequivalence" and that FDA "has wide discretion to determine how the bioequivalence requirement is met." Id. at 218. Where FDA had examined all relevant data and articulated a satisfactory explanation for its action, the court concluded that the "dispute is fundamentally a scientific one over which court lacks expertise and FDA is expert." Id. at 219-20.

There are several other examples of FDA's bioequivalence determinations receiving deference from the courts. See, e.g., Fisons Corp. v. Shalala, 860 F. Supp. 859, 866-67 (D.D.C. 1994) (denying Fisons' request for a preliminary injunction against approval of generic competitors, recognizing that "the factual determination of how bioequivalence is determined

properly rests within FDA's discretion"); Schering Corp. v. FDA, 51 F.3d 390, 399 (3d Cir. 1995) (recognizing that, in selecting methods of determining bioequivalence for non-systemically effective generic drugs, FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us"); Somerset Pharmaceuticals, Inc. v. Shalala, 973 F. Supp. 443, 453 (D. Del. 1997) (denying Somerset's motion for preliminary injunction because the "determination of which method is the most 'accurate, sensitive, and reproducible' for measuring bioequivalence is a matter of scientific judgment, falling squarely with the FDA's discretion").[23]

B. FDA's Decision Regarding The Scientific Information Necessary To Support A Demonstration Of Bioequivalence Between A Generic Version Of Wellbutrin XL, Including Anchen's, And The Brand-Name Drug Is Not Arbitrary And Capricious

The record reflects FDA's reasoned decision-making in rejecting Biovail's argument that ANDA applicants must meet criteria in addition to the requirements set forth by FDA to demonstrate that a generic version of Wellbutrin XL is bioequivalent to Wellbutrin XL, the RLD. In relying on its scientific and technical expertise, the agency acted reasonably when it used its long-standing, well-established, and scientifically based bioequivalence criteria to approve Anchen's ANDA. Biovail has failed to show that FDA was arbitrary and capricious in

[23] See also Berlex Labs., Inc. v. FDA, 942 F. Supp. 19, 25 (D. D.C. 1996) (upholding FDA's decision to permit Biogen to show that its product, which had not been clinically tested, was "comparable" to Berlex's product, which had been clinically tested, because such scientific judgment within the agency's discretion); Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1499-1500 (D.C. Cir. 1996) (rejecting claim that, because the statute requires generic drugs to have the "same" labeling, FDA could not approve generic drugs with labeling that omitted certain uses that were on the innovator drugs' labeling, and holding that FDA's determination that generic products did not have to have identical labeling when labeling was protected by exclusivity was permissible).

reaching its decision on the requirements necessary to demonstrate bioequivalence for generic versions of Wellbutrin XL or in applying that decision to Anchen's ANDA.

As Congress has set forth in the FDCA, 21 U.S.C. § 355(j), a generic product can be expected to be as safe and effective as the RLD if all of the requirements for ANDA approval are met. The ANDA applicant need not duplicate extensive clinical studies to demonstrate safety and effectiveness. Rather, the generic drug relies on FDA's finding of safety and effectiveness for the RLD, which FDA has already approved. For an ANDA applicant to rely on FDA's previous determination of safety and effectiveness, its application must, among other things, include information to show that the generic drug (i) has the same active ingredient, conditions of use, dosage form, strength, and route of administration as the RLD, and (ii) is bioequivalent to, and has the same labeling as, the RLD. See 21 U.S.C. § 355(j)(2)(A); 21 C.F.R. § 314.94(a). Meeting the approval criteria means that the generic drug can be expected to provide the same level of safety and effectiveness as – and as a general matter can be substituted for – the innovator product. This is the "bedrock principle" of the Hatch-Waxman framework.

As previously explained, FDA approved Anchen's ANDA because it met all of the statutory requirements for approval. Anchen's bupropion HCl extended-release tablets have the same active ingredient, conditions of use, dosage form, strength, and route of administration as the RLD, Wellbutrin XL. In addition, Anchen's product is bioequivalent to Wellbutrin XL, and has the same labeling (except for certain permissible differences) as Wellbutrin XL. Thus, FDA has determined that Anchen's product can be expected to have the same clinical effect and safety profile as the brand-name drug and can be substituted for it – the precise result that Biovail hopes to reverse.

In this case, there is no dispute that Wellbutrin XL and Anchen's drug product have the same active ingredient, conditions of use, dosage form, strength, and route of administration. Further, Biovail does not challenge FDA's review of the bioequivalence data – or any other data – contained in Anchen's ANDA. The only issue here is whether the bioequivalence requirements set forth in FDA's response to Biovail's Petition, and applied in the approval of Anchen's ANDA, are adequate. As described in the Petition Response, pursuant to FDA's statute and regulations, the bioequivalence data necessary to support ANDA approval must show that the proposed generic is bioequivalent to the RLD. Biovail argues that that is insufficient.

Biovail incorrectly asserts that ANDA applicants for bupropion HCl extended-release tablets have to show that their products are bioequivalent not only to the RLD, but to other formulations of bupropion HCl – Wellbutrin SR and Wellbutrin IR – as well. Pls. Mem. at 15. This is simply not so. According to Biovail, unless generic competitors fulfill the additional criteria it has proposed, generic extended-release products cannot be expected to be as safe and effective as Wellbutrin XL. Again, Biovail is wrong.

Wellbutrin XL's labeling states that Wellbutrin XL is bioequivalent to both the IR and SR formulations of bupropion HCl and that the seizure risk information for Wellbutrin XL is based on the seizure risk data for the other formulations (i.e., Wellbutrin risks may be similar).[24] In Biovail's view, such labeling statements have created new bioequivalence requirements for generic versions of the drug. See Pls. Mem at 14-15. Its argument rests on the proposition that

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[24] The labeling states that the seizure risks for Wellbutrin XL® were "not formally evaluated in clinical trials" and that the risks for Wellbutrin XL "may be similar to that presented below for the immediate-release and sustained-release formulations of bupropion." Pls. Mem. at 9; Petition at 5. The labeling also states that "both Wellbutrin XL and the sustained-release formulation of bupropion (Wellbutrin SR) are bioequivalent to the immediate-release formulation." Petition at 5.

the seizure risk information in Wellbutrin XL's labeling may be inaccurate as applied to the generic drug, unless the ANDA applicant conducts studies that Biovail believes will independently confirm the applicability to the generic drug of the Wellbutrin XL's labeling on seizure risk. In fact, Biovail suggests that, if the generic extended-release product does not meet these additional criteria but, nevertheless, uses the labeling approved for Wellbutrin XL (a statutory requirement), that labeling, when used for the generic drug, would be false and misleading (a statutory violation). Id. at 15. This argument does not withstand scrutiny, however.

Biovail flips the ANDA approval process on its head when it suggests that comparative bioequivalence information for other formulations that is included in the RLD's labeling establishes new bioequivalence requirements for ANDA applicants seeking FDA approval for generic versions of Wellbutrin XL. Instead, the statute requires the proposed generic product to demonstrate bioequivalence with respect to the RLD, with which it shares, among other things, its active ingredient and dosage form. See 21 U.S.C. § 355(j)(2)(A)(iv). The applicability of risk and other information in the RLD's labeling to the generic drug follows, as a matter of science, once the ANDA applicant has established bioequivalence and met the other requirements for ANDA approval. Wellbutrin XL's substantive risk information is applicable to Anchen's product without requiring Anchen to conduct the additional bioequivalence studies Biovail proposes.[25] Although Biovail derides Anchen's "attempt[] to piggy-back on Biovail's

[25] In seeking preliminary relief, Biovail's argument focuses on demonstrating bioequivalence to formulations other than Wellbutrin XL. However, because Biovail's amended complaint refers, albeit cursorily, to two other proposed criteria, which were raised in the Petition, we mention those criteria here. According to the amended complaint, FDA abused its discretion by not requiring ANDA applicants to: (a) demonstrate bioequivalence with respect to all three metabolites; and (b) submit data from bioequivalence trials at steady-state. See

determination" that Wellbutrin XL has the same seizure risk as the SR and IR formulations "without doing the requisite research and analysis" (Pls. Mem. at 15), this "piggy-backing" is exactly what Hatch-Waxman contemplates. See, e.g., Zeneca, 213 F.3d at 164; In re Barr Laboratories, 930 F.2d at 73; see also Bristol-Myers, 91 F.3d at 1495.

. To require Anchen to duplicate the findings in the innovator labeling would be contrary to law and the underlying purpose of Hatch-Waxman Amendments.

Biovail's point that FDA, in other instances, required ANDA applicants to conduct additional testing is unavailing. See Pls. Mem. at 16-17. Biovail cites to FDA's Food Effect Guidance, see supra at 13 n.18, to support its contention that FDA can require an ANDA applicant to provide "additional data to make the labeling accurate." Pls. Mem. at 16. FDA has the discretion to require certain studies under circumstances when it believes such studies are warranted. FDA also has the discretion to decline to ask for additional studies unless it has determined that they are necessary.[26] Cf. 21 C.F.R. § 320.25(a) ("no unnecessary human research should be done").

Amended Cmplt. ¶ 32. FDA previously considered and, for the reasons explained in its Petition Response, rejected these claims. See supra at 13-14. Biovail's motion for preliminary relief fails to advance any supporting arguments. It also bears noting that neither Biovail's Petition nor its amended complaint takes issue with FDA's BA/BE Guidance that describes the current method for determining which metabolite(s) to examine in demonstrating bioequivalence or with FDA's finding that the metabolite hydroxybupropion meets the factors set forth therein.

[26] Even if relevant here, the Food Effect Guidance and the "sprinkle study" referenced therein, support the agency's position, not Biovail's. A "sprinkle study" is done in very specific circumstances to demonstrate that both the generic drug and the RLD perform the same when sprinkled on soft foods, such as applesauce. Food Effect Guidance at 9. In such circumstances, the ANDA applicant will demonstrate (as the statute requires) bioequivalence by comparing the generic drug product to the RLD.

Furthermore, Anchen's product labeling is truthful and not misleading. Cf. Dr. Reddy's Labs., Inc., v. Thompson, 302 F. Supp.2d 340, 363 (D. N.J. 2003) (stating that FDA has the scientific expertise to assess proposed labeling and is entitled to deference); Henley, 77 F.3d at 620-21 (same). The generic product's labeling does not state that Anchen has independently demonstrated bioequivalence of its extended-release formulation with the immediate-release and sustained-release formulations. See Pls. Mem. at 15. Rather, the labeling for Anchen's product states that bupropion hydrochloride extended-release tablets (XL) are bioequivalent to both the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion.[27] The labeling also includes the same substantive dose-related seizure risk information as is presented in Wellbutrin XL's labeling. Anchen's product, therefore, is appropriately labeled and meets the statutory "same labeling" requirement.

Biovail's point that FDA "requested" or "required" Wellbutrin XL's NDA to contain certain information is immaterial and irrelevant. See Pls. Mem. at 8 (asserting that FDA requested Biovail to examine three metabolites of bupropion), 10 (stating that FDA required Biovail to demonstrate that Wellbutrin XL was bioequivalent to the IR and SR formulations), 11 (same). In presenting its position, Biovail fails to recognize an important distinction. The bioequivalence information used in approving an innovator drug such as Wellbutrin XL fulfills a function different from bioequivalence studies conducted for purposes of generic drug approval. In approving an NDA, FDA makes a *finding of safety and effectiveness*, 21 U.S.C. § 355(c)(1),

[27] This statement is based on the studies conducted to support the approval of the RLD, Wellbutrin XL. In light of the design of the ANDA approval process – to allow ANDA applicants to "piggy-back" on the innovator's findings – the labeling for generic drugs generally includes information on scientific studies conducted not on the generic product, but on the RLD. Replacing the trade name of the RLD with the chemical name for generic drug labeling is one of the permissible labeling differences and is established practice.

(d); when approving an ANDA, FDA determines that a generic drug meets certain approval criteria set out in 21 U.S.C. § 355(j), which permits the generic product to *rely on the finding of safety and effectiveness made for the RLD.*

In this case, the safety and effectiveness finding for the Wellbutrin XL on which the ANDA applicant is entitled to rely is based, in part, on certain bioequivalence information used by the innovator to obtain approval for its Wellbutrin XL formulation. Wellbutrin XL was not approved based on clinical trials demonstrating the safety and effectiveness of the XL product itself. Pls. Mem. at 8. Rather, Wellbutrin XL received FDA approval based on other data, including bioequivalence comparisons between Wellbutrin XL and other (already approved) formulations of the drug. See supra at 9. It simply does not follow, however, that determining bioequivalence between a generic drug and its RLD must be based on the same quantum and type of evidence used to support approval of the RLD; nor does it follow that the bioequivalence criteria for generic drugs must vary depending upon the type of evidence submitted to support approval of the RLD.

Biovail seeks to have FDA require ANDA applicants to meet the proposed additional criteria because Biovail claims the criteria are necessary to protect patients from potentially serious risks (as disclosed in Wellbutrin XL labeling) that may be associated with bupropion HCl extended-release tablets. See Pls. Mem. at 15-16, 19-20. Biovail's concern that there are safety issues with generic versions of Wellbutrin XL that are unique to the generic drug is baseless. The seizure risks are inherent in the drug product (i.e., bupropion HCl) itself – whether the innovator or generic version – and are adequately addressed in the bioequivalence requirements FDA has adopted for the generic products. FDA is as mindful of the safety-related issues in approving the ANDA for the generic product as it was in approving the NDA for Wellbutrin

XL.[28] Because the generic drug labeling includes the same substantive warnings and dose-related seizure risk information as is found in the RLD labeling for Wellbutrin XL, health care providers are aware of the risks associated with the product, regardless of whether the product is the innovator or generic version.

The additional studies Biovail would require from ANDA applicants are not necessary. Biovail has provided neither FDA nor this Court with evidence that FDA's decision regarding the scientific information necessary to support a demonstration of bioequivalence between generic versions of Wellbutrin XL, including Anchen's, and the brand-name drug is inadequate. Biovail's attempt to have FDA create requirements that are neither statutorily mandated nor scientifically necessary should be rejected. Furthermore, in Serono, the court held that a finding that the movant is not likely to succeed on the merits "effectively decides the preliminary injunction issue" because the other injunction factors "either are a wash or are inextricably linked to the merits." 158 F.3d at 1326. The same holds true in this case.

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[28] In a last-ditch effort to call into question the safety of generic versions of Wellbutrin XL, Biovail submits the Silverstone declaration and accompanying attachments. Pls. Mem. at 6 n.6, 19-20 and n.14; Exh. 4 to Pls. Mem. Biovail claims that the Silverstone declaration and attachments demonstrate the need to ensure bioequivalence of generic Wellbutrin XL to other formulations of bupropion. However, those documents are not part of the administrative record and, therefore, deserve no consideration. Under the APA, review of FDA's decision is limited to the record compiled by the agency. Biovail could have submitted the information in the Silverstone declaration to FDA when its Petition was under review. It did not, and should not be permitted to do an end-run around the agency's administrative process.

Even if the Silverstone declaration were to be considered, it does little to advance Biovail's position. For example, the one paragraph in the declaration to which Biovail cites in regard to other bupropion formulations fails to offer any support for its conclusory statement therein. See Silverstone Decl. ¶ 9 (proposing, without explanation, that "[u]nless bioequivalence is established with regard to the previous bupropion formulations, there is no linkage between the risk of seizure for a generic formulation and the label statement regarding the incidence of seizure").

II. BIOVAIL HAS FAILED TO SHOW THAT IT WILL SUFFER IRREPARABLE HARM ABSENT PRELIMINARY INJUNCTIVE RELIEF

Biovail has failed to demonstrate that it will suffer irreparable harm if the court does not grant the preliminary relief it seeks. Courts insist that only irreparable harm justifies the issuance of a preliminary injunction. Indeed, "[t]he 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).

"Irreparability of injury is a very high standard." Bristol-Myers, 923 F. Supp at 220 (internal quotations omitted). The injury alleged must be certain, great, actual, and imminent, Wisconsin Gas Co. v. FERC, 758 F.2d 669, 674 (D.C. Cir. 1985), and it must be "'more than simply irretrievable; it must also be serious in terms of its effect on the plaintiff.'" Mylan v. Thompson, 139 F. Supp. 2d 1, 27 (D.D.C.) ("Mylan (buspirone)") (quoting Gulf Oil Corp. v. Dept. of Energy, 514 F. Supp. 1019, 1026 (D.D.C. 1981)), rev'd other grounds, 268 F.3d 1323 (Fed. Cir. 2001). Because Biovail is not likely to succeed on the merits, Biovail "would have to make a very substantial showing of severe irreparable injury" to prevail on its motion. National Pharm. Alliance v. Henney, 47 F. Supp. 2d 37, 41 (D.D.C. 1999).

It is well settled that mere economic loss in and of itself does not constitute irreparable harm. Wisconsin Gas, 758 F.2d at 674; Mylan Pharm., Inc. v. Shalala, 81 F. Supp. 2d 30, 42 (D.D.C. 2000) ("Mylan (terazosin)"); Bristol-Myers, 923 F. Supp. at 220. "'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)). Even irrecoverable economic loss does not rise to the level of irreparable harm unless the financial injury is "serious in terms of its effect on the plaintiff."

Gulf Oil, 514 F. Supp. at 1026; see also Experience Works, Inc., 267 F. Supp. 2d at 96 ($21.1 million reduction in funding is 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"); Mylan (terazosin), 81 F. Supp. 2d at 42-43.

Notwithstanding this well-established standard, Biovail's claimed financial loss, as well as its claim of intangible losses, are speculative and merely forms of economic loss that do not meet the high standards set forth above. Specifically, Biovail projects that its sales revenue from Wellbutrin XL is about $33.6 million per month, suggesting that, "shortly after announcement of a generic version being approved," the company will lose about one to two month's worth of that revenue. Howling Decl. at ¶ 18 (attached to Pls. Mem. as Exh. 3). Biovail also asserts that, "at the midpoint of total revenue guidance . . . for 2006," the sale of "Wellbutrin XL® constitutes approximately 42% of Biovail's sales." Howling Decl. at ¶ 6; Pls. Mem. at 17. Biovail fails to demonstrate, however, that the loss of such revenue would have any materially significant impact on its business. Nor could it.

It is evident from publicly available sources that Biovail has anticipated the introduction of generic competitors of Wellbutrin XL and planned for the impact on its revenue. Biovail reported in a recent financial update that its "overall revenue guidance for 2007," which is an estimated $800 million to $850 million, is based on the "assumption that a generic formulation of Wellbutrin XL® is launched in the U.S. on January 1, 2007." Biovail Provides Financial

Update, 2007 Guidance, Toronto (Business Wire), Dec. 6, 2006.[29] An amount of $800 million or more in total revenue hardly gives the appearance of a company facing severe irreparable injury.

Further, Biovail has provided *no* evidence that diminished sales of Wellbutrin XL will severely compromise its continued viability. Biovail's size is not trivial – it "operates facilities in Barbados, Canada, the United States, Ireland, and Puerto Rico" with "approximately 1,750 employees worldwide." Biovail's 2005 Annual Report at i. Nor is it a one-product company. Cf. Bracco Diagnostics, Inc. v. Shalala, 963 F. Supp. 20, 29 (D.D.C. 1997) (recognizing injury to one-product line company). According to Biovail, it promotes and distributes a variety of products in the United States and Canada. Biovail's 2005 Annual Report at 31 (providing a table "summarizing Biovail's commercial product line").

Biovail's attempt to meet the irreparable harm standard is further weakened by statements in its Form 6-K for the quarterly period ending June 30, 2006, filed with the Securities and Exchange Commission:

> In the event of generic competition, GSK may launch an authorized generic version of Wellbutrin XL® for distribution in the U.S. Under the terms of the Wellbutrin XL® agreement, [Biovail] will be the exclusive manufacturer and supplier to GSK of such an authorized generic. [Biovail's] supply price to GSK for Wellbutrin XL® generic product will be fixed each year based on contractually agreed prices. This supply price will be substantially lower than the tiered supply price that [Biovail] currently receives on sales of Wellbutrin XL® brand product.

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[29] See also Biovail's 2005 Annual Report at 44 ("A number of companies are seeking FDA approval for generic versions of Wellbutrin XL®. As a result, a generic version of Wellbutrin XL® could be launched in 2007 or sooner, at which point *we would anticipate* losing a substantial portion of the pre-genericization revenue from Wellbutrin XL® product sales within a short period of time.") (emphasis added); id. at 100-101 (noting that four manufacturers have filed ANDAs for a generic version of Wellbutrin XL).

Id. at 24. Thus, Biovail stands to profit by supplying an "authorized generic" version of Wellbutrin XL.

Biovail suggests that its losses are per se irreparable because they are unrecoverable from the government.[30] Pls. Mem. at 18. The two cases that Biovail cites, however, do not support that proposition in the absence of extraordinary circumstances. See Express One Int'l, Inc. v. U.S. Postal Serv., 814 F. Supp. 87, 91 (D.D.C. 1992) (finding that, without preliminary injunctive relief, movant would face "significant lay-off, capital, and facility costs inherent in closing down and restarting a major transportation network"); Hoffman-Laroche, Inc. v. Califano, 453 F. Supp. 900, 901 (D.D.C. 1978) (noting that movant's sales accounted for 99% of all sales of the drug at issue).

Allegations of lost sales are a far cry from the required demonstration of a "serious" and "irretrievable" loss that "would significantly damage its business above and beyond a simple diminution in profits." Mylan (buspirone), 139 F. Supp. 2d at 27 (also noting that the "D.C. Circuit is hesitant to award injunctive relief based purely on loss opportunities and market share"); Mylan (terazosin), 81 F. Supp. 2d at 42. Biovail relies on CollaGenex Pharm., Inc. v. Thompson, Civ. No. 03-1405 (RMC), 2003 WL 21697344 (D.D.C.), which is easily distinguishable. There, plaintiff was a small company that received its only significant revenue from sales of the drug subject to the litigation. Id. at *3. The court found that, without preliminary relief, the innovator's "continued viability would be at issue." Id. at *10.

Regarding other potential injuries, Biovail's arguments about the harm to its reputation and marketing relationships that will follow from an alleged "potentially unsafe generic version"

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[30] We note that Biovail would have the opportunity to recover damages (although not against the government) if it ultimately prevails in its patent infringement suit against Anchen.

of Wellbutrin XL presume that FDA has not complied with the statutory and regulatory requirements when approving ANDAs for a generic version of Wellbutrin XL. See Howling Decl. at ¶¶ 5, 12, 19-21. Biovail has offered no persuasive evidence to show that a generic version of Wellbutrin XL will have a safety profile different from Wellbutrin XL – and FDA's determination that the generic version of Wellbutrin XL is bioequivalent to Wellbutrin XL is directly contrary. Moreover, Biovail's speculation of reputational marketplace injury does not meet the standard of irreparable harm. This argument has been specifically rejected in the drug approval context. See Bristol-Myers, 923 F.Supp. at 221 (rejecting company's allegation that its reputation would suffer if a generic were approved, noting that there was nothing in the record to support such a claim); Somerset, 973 F. Supp. at 455 (rejecting company's claim that its reputation would be harmed if patients were injured by generic products, noting that company had "offered little more than a bare assertion" in support of this claim).

Biovail has not demonstrated any irreparable injury sufficient to justify entry of the emergency relief it seeks. Biovail has also failed to demonstrate that it is likely to succeed on the merits, for all of the reasons stated in Section I, supra. In sum, Biovail has failed to demonstrate that this case warrants the grant of the extraordinary remedy of a preliminary injunction.

III. FDA WILL BE HARMED IF BIOVAIL'S REQUEST FOR RELIEF IS GRANTED

Biovail has also failed to show that any harm it may suffer in the absence of injunctive relief outweighs the potential harm to FDA. 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. FDA must implement the Hatch-Waxman Amendments to make lower cost drugs available to the public when those drugs are

found to meet the requirements for approval. See In re Barr Laboratories, Inc., 930 F.2d 72, 76 (D.C. Cir. 1991) ("Congress sought to get generic drugs into the hands of patients at reasonable prices – fast."). As such, FDA's interest coincides with the public interest. Serono Labs,158 F.3d at 1326 (determining that the public interest is "inextricably linked" to Congress's purpose in passing the Hatch-Waxman Amendments); Mylan (terazosin), 81 F. Supp. 2d at 41-45.

Biovail argues that FDA will suffer no harm if a preliminary injunction issues because the injunction would maintain the status quo. Pls. Mem. at 20-21. Biovail ignores, however, that the agency has already determined pursuant to its statutory authority that generic versions of Wellbutrin XL meets the statutory requirements for approval. A preliminary injunction therefore would not simply maintain the status quo of *unapproved* ANDAs, but would thwart Congress's generic drug approval scheme and FDA's lawful implementation of that scheme by forcing FDA to suspend its approval of *approved* ANDAs. FDA and the public, therefore, would be considerably harmed if this Court were to grant a preliminary injunction. For these reasons, the balance of harms do not tilt in Biovail's favor.

IV. THE PUBLIC INTEREST WEIGHS AGAINST BIOVAIL'S REQUEST FOR INJUNCTIVE RELIEF

As noted, the public benefits from the increased competition incident to FDA's approval of a generic version of Wellbutrin XL. Biovail cannot show that the public interest would be served by delaying approval for the generic extended-release product. Such a stay would cause consumers to suffer because Biovail's monopoly and the accompanying price structure for its innovator drug would continue. See Boehringer Ingelheim Corp. v. Shalala, 993 F. Supp. 1, 3 (D.D.C. 1997) ("there is the public interest in receiving generic competition to brand-name drugs as soon as is possible"); see also Apotex, Inc. v. FDA, 2006 U.S. Dist. LEXIS 20894 *60 (public

interest is not served by injunction that "would effectively constitute a constructive extension of the brand manufacturer's patent").

As explained above, Biovail's contention that the failure to grant injunctive relief will put the public health at risk is baseless. After full consideration of Biovail's arguments in its Petition, FDA has determined that none of Biovail's arguments has merit or otherwise justifies any stay of approval of ANDAs for generic bupropion HCl extended-release tablets. The public interest, therefore, weighs against Biovail's claim for injunctive relief.

CONCLUSION

For the reasons above, Biovail's motion for a preliminary injunction should be denied.

Respectfully submitted,

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