**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

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| BIOVAIL CORPORATION, *et al.*, | ) | |
| Plaintiffs, | ) | |
| v. | ) | Civil Action No. 06-1487 (RMU) |
| U.S. FOOD & DRUG ADMINISTRATION, *et al.*, | ) | |
| Defendants, | ) | |
| and | ) | |
| ANCHEN PHARMACEUTICALS, INC., | ) | |
| Intervenor. | ) | |

**PLAINTIFFS' SECOND MOTION FOR A TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION**

Plaintiffs Biovail Corporation and Biovail Laboratories International SRL (collectively, "Biovail") respectfully move this Court for a temporary restraining order and preliminary injunction. As set forth more fully in the attached Memorandum of Points and Authorities in Support of Plaintiffs' Second Motion for a Temporary Restraining Order and Preliminary Injunction, Plaintiffs ask this Court to issue an order temporarily enjoining and restraining Defendants from approving any Abbreviated New Drug Application ("ANDA") for generic WELLBUTRIN XL®, as well as staying the effectiveness of any such prior approvals.

In accordance with Local Civil Rule 7(c), a proposed order granting the relief requested herein is attached as Exhibit 1. A Certificate Pursuant to Fed. R. Civ. P. 65(b)(2) and Local Civil Rule 65.1(a) is attached as Exhibit 2. In accordance with Local Civil Rule 7(m), early on the morning of December 18, 2006, counsel for Biovail attempted to speak via telephone with

counsel for Defendants and Intervenor. After leaving voicemail messages for counsel, the undersigned notified counsel via electronic mail of Biovail's intent to file the instant motion on an expedited basis. As of the time of filing, however, counsel have not indicated whether they oppose Biovail's request.

Dated: December 18, 2006

Respectfully submitted,

By: */s/ James F. Segroves*

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| BIOVAIL CORPORATION, *et al.*,<br><br>Plaintiffs,<br><br>v.<br><br>U.S. FOOD & DRUG ADMINISTRATION, *et al.*,<br><br>Defendants,<br><br>and<br><br>ANCHEN PHARMACEUTICALS, INC.,<br><br>Intervenor. | Civil Action No. 06-1487 (RMU) |

**MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF PLAINTIFFS' SECOND MOTION FOR A TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION**

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## INTRODUCTION

Plaintiffs Biovail Corporation and Biovail Laboratories International SRL (collectively "Biovail") submit this memorandum in support of their second motion for a preliminary injunction and temporary restraining order against the U.S. Food and Drug Administration and Andrew C. von Eschenbach, M.D., in his official capacity as Commissioner of Food and Drugs (collectively, "FDA").

Biovail manufactures for marketing in the United States the prescription drug WELLBUTRIN XL®, which is used by millions of patients for the treatment of Major Depressive Disorder and Seasonal Affective Disorder. On December 14, 2006, FDA approved an Abbreviated New Drug Application ("ANDA") filed by Anchen Pharmaceuticals, Inc. ("Anchen") for a generic formulation of WELLBUTRIN XL®, paving the way for Anchen to immediately market and sell the generic drug. On that same day, FDA denied a Citizen Petition filed by Biovail almost one year earlier, in which Biovail urged FDA to apply certain standards designed to protect the public when determining whether or not to approve any ANDA for generic WELLBUTRIN XL®.

FDA's approval of Anchen's ANDA for generic WELLBUTRIN XL® and the concurrent denial of Biovail's Citizen Petition cannot be reconciled with the unambiguous language of the Food, Drug and Cosmetic Act ("FDCA"), nor can it be squared with FDA's responsibility to ensure that generic drugs provide the same level of safety and efficacy as the innovator drug. Biovail therefore asks that this Court preserve the status quo and issue an order temporarily enjoining and restraining FDA from approving any ANDA for generic WELLBUTRIN XL®, as well as staying the effectiveness of any such prior approvals, until this Court has had the opportunity to consider Biovail's contentions on their merits.

## PROCEDURAL BACKGROUND

On August 23, 2006, Biovail initiated this action seeking to compel FDA to rule on Biovail's Citizen Petition at least one calendar week prior to granting any ANDA for generic WELLBUTRIN XL®, thus providing Biovail with an adequate opportunity to seek judicial review if the Citizen Petition was denied by FDA. That same day, Biovail moved for a temporary restraining order and preliminary injunction, warning that FDA's course of practice was to deny Citizen Petitions on the same date that it announced approval of ANDAs. Biovail contended that this practice not only violated the Administrative Procedure Act ("APA") and pertinent regulations, but that it also denied an opportunity for meaningful and timely judicial review of FDA's denial of Citizens Petitions. Indeed, Biovail urged, FDA's practice of denying Citizen Petitions on the same date that it granted an ANDA all but guaranteed that challenged products—including those, like here, raising serious safety issues—would reach the public before judicial review of the applicable FDA decision. Notwithstanding these issues, the Court denied the requested provisional relief on August 25, 2006. *See Biovail Corp. v. FDA*, 448 F. Supp. 2d 154 (D.D.C. 2006).

Subsequent factual developments (*i.e.*, FDA's denial of Biovail's Citizen Petition and the agency's concurrent decision to approve Anchen's ANDA) have resurrected the need for Biovail to seek immediate injunctive relief from this Court.[1]

## PRELIMINARY STATEMENT

The bedrock principle behind the statutory and regulatory generic drug approval system is the assurance that a generic drug will provide the same level of safety and efficacy as the

[1] Immediately preceding the filing of the instant motion, Biovail filed a Motion for Leave to File an Amended and Supplemented Complaint for Injunctive and Declaratory Relief and Writ of Mandamus, which accounts for these factual developments.

innovator drug. To that end, the FDCA mandates that the generic drug be bioequivalent to, and have the same labeling as, the innovator drug. These fundamental requirements are critical in allowing physicians, pharmacies and patients to prescribe, dispense and consume generic drugs without having to carefully study and compare the products and their labeling to determine if there are any important differences in safety and efficacy between the generic and brand name drugs.

These principles are of the utmost importance here, because the active ingredient in WELLBUTRIN XL®—bupropion—is associated with a dose-related risk of seizures, including serious seizures that can be dangerous, even life-threatening. The safety of WELLBUTRIN XL®, and its effective management of the risk of seizures, was proved to FDA by (among other things) demonstrating the bioequivalence of WELLBUTRIN XL® to earlier formulations of bupropion. These earlier formulations, known as WELLBUTRIN (for immediate release) and WELLBUTRIN SR (for sustained release), had been the subject of clinical trials and were proven to be safe. As a result of Biovail's demonstration of equivalence, the labeling for WELLBUTRIN XL® accurately states that the product has been shown to be bioequivalent to the immediate-release and sustained-release formulations of bupropion and that, as a result, the risk of seizure may be the same.

In its Citizen Petition, Biovail reminded FDA of the unambiguous statutory requirement that the generic drug have "the same" labeling as the innovator drug. 21 U.S.C. § 355(j)(2)(A)(v) (requiring that an ANDA contain "information to show that the labeling proposed for the [generic] drug *is the same* as the labeling approved for the [innovator] drug") (emphasis added). However, in rejecting Biovail's Citizen Petition and granting Anchen's

ANDA, FDA did not require Anchen (or any other ANDA applicant) to have the same labeling as WELLBUTRIN XL®.

This Court should stay the effectiveness of FDA's decisions to prevent the distribution of a generic product whose label is in clear violation of the FDCA. Without such relief, the statutory scheme governing the approval of generic drugs will be severely undermined, the public will be deceived as to the health risks associated with the product, and Biovail and its WELLBUTRIN XL® product will suffer serious and irreparable harm.

## STATEMENT OF FACTS

### A. The Drug Approval Process For Innovator Drugs and Generic Drugs

Congress has delegated to FDA the authority to regulate drugs within certain statutory parameters. Under the FDCA, any person seeking to market a new innovator drug must file and obtain FDA approval of a New Drug Application ("NDA") for the innovator drug. This often is a costly and intensive process that includes the submission of safety and effectiveness data, among other things.

In 1984, the "Hatch-Waxman Amendments" modified the FDCA to allow companies to file ANDAs for generic forms of FDA-approved innovator drugs (such as WELLBUTRIN XL®). *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355(j)). Under the Hatch-Waxman Amendments, a generic version of an innovator drug may be approved under an ANDA that relies upon the findings of safety and effectiveness for the innovator drug. *Id.* However, because a generic is

marketed as a substitute for the innovator drug, FDA may not approve an ANDA unless the applicant proves that its generic version is bioequivalent to the innovator drug. Generally speaking, a generic drug is bioequivalent to the innovator drug if tests prove that the generic behaves in the same manner as the innovator drug when ingested by a patient according to the conditions of use that appear in the labeling accompanying the innovator drug, including directions for use, warnings, test reports, and other information that may be of use to prescribing medical care providers and patients.

Under the Hatch-Waxman Amendments, the ANDA approval is stayed for up to thirty months when those with patent rights in the innovator drug bring a timely patent infringement suit against the ANDA applicant. *See* 21 U.S.C. § 355. So long as that suit is viably pending in federal district court, it causes an automatic thirty-month ANDA approval moratorium under the FDCA. *Id*. During that time, FDA generally may not grant final approval to the ANDA for the generic drug in question. *Id*. That moratorium is lifted if a district court finally decides the case against the patent holder. *Id*.

While such infringement suits are pending, it has been FDA's practice to grant a "tentative approval" of the first-filed ANDA for a generic version of the innovator drug. Tentative approval means that FDA has tentatively decided that the drug product is approvable but for the thirty-month moratorium. It is common for a company that has received a tentative approval of its ANDA, and that is prepared to manufacture and distribute the generic substitute, to begin manufacturing operations by the time final approval draws near. (Howling Decl. ¶ 15.)[4] This allows for virtually immediate entry into the market upon receiving FDA's final approval.

[4] References to the "Howling Decl." are to the accompanying December 17, 2006 Declaration of Kenneth G. Howling, a copy of which is attached as Exhibit 3.

FDA regulations permit the filing of a "Citizen Petition" by which those with rights to or knowledge about an innovator drug call to the FDA's attention information to ensure an accurate determination of bioequivalence and compliance with other requirements. *See* 21 C.F.R. §§ 10.20, 10.25, and 10.30. Under those regulations, FDA must consider and take action on the petition within 180 days of filing unless "unable" to do so. 21 C.F.R. § 10.30(e)(2). However, FDA has developed a practice of indefinitely delaying action, or at least notice of any action, on such Citizen Petitions until or after the agency has already granted final approval to the subject ANDA. (*See generally* Stearns Decl. and Ex. A thereto.)[5]

**B. Biovail's Prescription Drug WELLBUTRIN XL®**

Biovail is a pharmaceutical company that develops, tests, registers, manufacturers and sells a variety of drugs. (Howling Decl. ¶ 2.) Among the drugs in which Biovail owns patent rights is the drug WELLBUTRIN XL®. (*Id.* ¶ 3.) WELLBUTRIN XL® is an FDA-approved "innovator" prescription drug (sometimes referred to as a "pioneer," "brand-name," or "branded" drug) that is widely prescribed for, among other things, the treatment of Major Depressive Disorder ("MDD"). (Silverstone Decl. ¶ 8.)[6] MDD is a common and severe psychiatric disorder that, according to the World Health Organization, is one of the most serious disability afflictions, among heart disease, cancer and HIV/AIDS. (*Id.* ¶ 13.) More recently, WELLBUTRIN XL® was approved for the treatment of Seasonal Affective Disorder, which is a common and serious psychiatric disorder. (Howling Decl. ¶ 3.)

[5] References to the "Stearns Decl." are to the August 21, 2006 Declaration of Frederick A. Stearns, a copy of which was attached as Exhibit 4 to Plaintiffs' first motion for preliminary injunctive relief.

[6] References to the "Silverstone Decl." are to the accompanying December 17, 2006 Declaration of Peter H. Silverstone, M.D., a copy of which is attached as Exhibit 4.

Chemically, WELLBUTRIN XL® is bupropion hydrochloride in extended-release tablet form for once-a-day administration. WELLBUTRIN XL® is sold in 150 and 300 milligram ("mg") strengths. The usual target dose is 300 mg once a day with a maximum dose of 450 mg per day. The drug was designed to facilitate the treatment of patients who were taking bupropion in immediate-release 100 mg form three times a day or sustained-release 150 mg bupropion twice a day. Taking medication once a day, rather than more frequently, is more convenient for the patient and is also medically beneficial because it generally leads to better patient compliance with prescribed dosages.

Although WELLBUTRIN XL® has proven safe and effective, its active ingredient—bupropion—is associated with a dose-related risk of seizures. (*See* Silverstone Decl. ¶¶ 20-21.) The risk of seizure appears to be related to the amount of bupropion in a patient's blood stream. (*See id.* ¶ 24.) Further, bupropion is extensively metabolized (*i.e.*, broken down in the body), resulting in the circulation in the bloodstream of "active metabolites." (*Id.* ¶ 23.) These active metabolites contribute to both the activity and toxicity of bupropion formulations. (*Id.*)

The risk of seizure is also related to patient factors, including the use of alcohol. (*Id.* ¶ 8.) To reduce the risk of seizures, WELLBUTRIN XL®'s labeling recommends that the total daily dose of bupropion not exceed 450 mg/day and that the rate of dose incrementation be carefully monitored. (*See* Perra Decl. Ex. B.)[7] Variability in the bupropion release rate and/or "dose dumping" in the presence of food or alcohol may have an effect similar to rapid dose incrementation. (*See id.*) "Dose dumping" refers to the rapid release of the active ingredient from an extended-release product into the blood stream. *See* FDA, *Mitigating the Risks of*

[7] References to the "Perra Declaration" are to the August 21, 2006 Declaration of Kevin J. Perra, a copy of which was attached as Exhibit 3 to Plaintiffs' first motion for preliminary injunctive relief.

*Ethanol Induced Dose Dumping from Oral Sustained/Controlled Release Dosage Forms* 1 (Oct. 2005).[8]

Hence, the risk of seizures is related to a particular dosage form, its release rate and performance characteristics in the presence of food and alcohol. As a result, warnings and other information on the above issues are contained in the labeling that accompanies WELLBUTRIN XL®. (*See* Perra Decl. Ex. B.)

### C. The Bioequivalence of WELLBUTRIN XL® To Prior Formulations of Bupropion

When FDA approved WELLBUTRIN XL®, it did so on Biovail's showing that WELLBUTRIN XL® was bioequivalent to the immediate-release and sustained-release formulations of bupropion, known respectively as WELLBUTRIN and WELLBUTRIN SR. In showing bioequivalence, Biovail demonstrated not only equivalence of the bupropion in WELLBUTRIN XL® to the prior two formulations, but also equivalence of the three "metabolites" formed when the bupropion in each of the three products is metabolized.

Biovail did so at the request of FDA, which suggests FDA was concerned about the effect of both bupropion and its metabolites on the incidence of seizure. As a result of Biovail's equivalence data—and FDA's acceptance of it—the labeling for WELLBUTRIN XL® truthfully and accurately states that:

> *In a study comparing 14-day dosing with WELLBUTRIN XL Tablets 300 mg once daily to the immediate-release formulation of bupropion* at 100 mg 3 times daily, equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the 3 metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion). *Additionally, in a study comparing 14-day dosing with WELLBUTRIN XL*

[8] Available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4187B1_01_08-Alcohol-Induced.pdf.

> *Tablets 300 mg once daily to the sustained-release formulation of bupropion* at 150 mg 2 times daily, equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the 3 metabolites.

(*Id*. (emphasis added).)

Since FDA's approval of WELLBUTRIN XL® was based on its bioequivalence to the immediate-release and sustained-release bupropion formulations, the seizure risks for WELLBUTRIN XL® was not formally evaluated in clinical trials. Instead, Biovail was permitted to rely on the clinical trials for the prior formulations of this drug—*i.e.*, the immediate-release and sustained-release formulations of bupropion—and the demonstration that WELLBUTRIN XL® was bioequivalent to those prior formulations. Thus, on the important issue of risk of seizure, the label truthfully and accurately states that, while the "seizure incidence with WELLBUTRIN XL . . . [was not] formally evaluated in clinic trials, [it] may be similar to that presented below for the *immediate-release and sustained-release formulations of bupropion*." (*Id*. (emphasis added).)

**D. Anchen's ANDAs and Biovail's Citizen Petition**

After filing the ANDA, and in accordance with the FDCA, Anchen certified to FDA and notified Biovail that its generic formulation and its marketing would not infringe Biovail's patent rights. Biovail subsequently filed a patent infringement suit against Anchen, thereby triggering the thirty-month statutory ANDA approval moratorium. *See Biovail Labs. SRL v. Anchen Pharm., Inc.*, No. 8:04-CV-01468-JVS-RC (C.D. Cal.) (the "Biovail Infringement Case"). Unable to issue a final approval of the Anchen ANDA, FDA granted it a "tentative approval" on November 14, 2005. (*See* Perra Decl. Ex. A.)

After FDA granted tentative approval of Anchen's ANDA, Biovail filed a Citizen Petition on December 20, 2005. (*See id*. Ex. B.) In its petition, Biovail reminded FDA of the

FDCA's requirement that any generic version of WELLBUTRIN XL® have the same labeling as WELLBUTRIN XL®. In addition, Biovail urged FDA to apply certain criteria in the final approval process of any ANDA that would allow a generic version of WELLBUTRIN XL® to be marketed. Most notably, Biovail urged FDA to require any ANDA to demonstrate—as FDA had required of Biovail—that the generic version of WELLBUTRIN XL® was bioequivalent to WELLBUTRIN and WELLBUTRIN SR, and that it was bioequivalent with respect to both bupropion and bupropion-metabolites. Application of those criteria, Biovail asserted, was necessary to ensure protection against the known and potentially serious risks relating to high levels of bupropion, especially seizures. Such criteria were also necessary, Biovail asserted, to ensure that the labeling of any generic drug would be the same as the labeling for WELLBUTRIN XL® *and* truthful with respect to the issues of bioequivalence to prior formulations and risk of seizure.

In a June 7, 2006 notice, FDA stated that it would be unable to decide the Biovail Citizen Petition within the 180-day regulatory response deadline and indefinitely delayed such action. (*See* Perra Decl. Ex. C.) This tentative response (called an "interim response" in the notice) stated without further explanation that, "FDA has been unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis by Agency officials." (*See id.*)

As noted above, on August 23, 2006, Biovail initiated the instant case seeking to compel FDA to rule on the Citizen Petition at least one calendar week prior to granting any application for approval of generic WELLBUTRIN XL®, so that there would be adequate opportunity for judicial review of the Citizen Petition (if the Citizen Petition were denied by FDA). On August

25, 2006, this Court denied Biovail's request for provisional relief. *See Biovail*, 448 F. Supp. 2d 154.

### E. FDA Denies Biovail's Citizen Petition and Concurrently Approves Anchen's ANDA

Just as Biovail had feared, on December 14, 2006, FDA—consistent with its past practice—issued a denial of Biovail's Citizen Petition on the same day that it granted Anchen's ANDA for generic WELLBUTRIN XL®. (*See* Segroves Decl. Ex. A and B.)[9] In denying Biovail's Citizen Petition and granting Anchen's ANDA, FDA did not require Anchen to have the same labeling as WELLBUTRIN XL®.[10] The agency also refused to require Anchen (or any other ANDA applicant) to demonstrate bioequivalence of the applicant's product to either WELLBUTRIN and WELLBUTRIN SR, as it had required Biovail to do. Moreover, FDA did not require Anchen (or any other ANDA applicant) to demonstrate equivalence at the metabolite level with respect to all three metabolites, as it also had required Biovail to do.

Biovail's Amended and Supplemented Complaint challenges the FDA decisions on the ground that they are arbitrary, capricious, and an abuse of discretion, or otherwise not in accordance with law. This motion seeks to preserve the status quo until the Court has had an opportunity to review the FDA decisions and to consider Biovail's contentions on the merits. More specifically, Biovail asks for provisional relief to preclude the FDA decisions from going into effect until this Court conducts a review of the FDA decisions and adjudicates Biovail's Amended and Supplemented Complaint.

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[9] References to the "Segroves Decl." are to the December 18, 2006 Declaration of James F. Segroves, a copy of which is attached as Exhibit 5.

[10] The date of FDA's denial is typed. On most FDA correspondence, however, the date is stamped. The logical inference is that the response to the Citizen Petition was prepared in advance of December 14 with the intention of withholding it until the ANDA could be approved. Such actions are consistent with FDA's practice of timing petition responses in order to deprive petitioners of meaningful judicial review.

## ARGUMENT

Preliminary injunctive relief is available in this Circuit when a plaintiff demonstrates that: (1) there is a substantial likelihood of success on the merits of the underlying case; (2) irreparable injury will result in the absence of the requested relief; (3) other interested parties will not suffer substantial harm if preliminary relief is granted; and (4) the public interest will be furthered by the injunction. *Nat'l Treasury Employees Union v. United States*, 927 F.2d 1253, 1254 (D.C. Cir. 1991) (citation omitted). These factors provide a balancing test and "must be viewed as a continuum, with more of one factor compensating for less of another." *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27 (D.D.C. 1997). Indeed, "[injunctive relief] may be granted with either a high probability of success and some injury, or *vice versa*." *Cuomo v. U.S. Nuclear Regulatory Comm'n,* 772 F.2d 972, 974 (D.C. Cir. 1985).

### I. BIOVAIL IS LIKELY TO SUCCEED ON THE MERITS

The APA provides that a reviewing court must "hold unlawful and set aside agency action . . . found to be arbitrary, capricious, and an abuse of discretion, or otherwise not in accordance with law" or that is "contrary to constitutional right." 5 U.S.C. § 706(1), (2). In so doing, the reviewing court "must consider whether the [agency] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971).

In reviewing FDA's interpretation of the FDCA, this Court applies the two-step analysis enunciated by the Supreme Court in *Chevron, U.S.A. Inc. v. Natural Resources Defense Council*, 467 U.S. 837 (1984). *Ranbaxy Labs. Ltd. v. Leavitt*, --- F.3d ---, No. 06-5154, 2006 WL 3289050, at *8 (D.C. Cir. Nov. 14, 2006). First, the Court asks whether "Congress has directly spoken to the precise question at issue." *Chevron*, 467 U.S. at 842. "If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the

unambiguously expressed intent of Congress." *Id.* at 842-43. Only if the statute is "silent or ambiguous with respect to the specific issue" will the Court inquire as to whether the agency's interpretation is "based on a permissible construction of the statute." *Id.* at 843.

The abbreviated generic drug approval system hinges upon the assurance that a generic drug will provide the same level of safety and efficacy as the innovator drug. This concept has received significant public attention in the last few years through efforts by all levels of government to promote the use of generic drugs. Such promotion of generic drugs is designed to reinforce the message that consumers can rely on generic drugs to provide the same performance as the innovators they copy. This confidence is only justified, however, to the extent that the generic has been shown to deliver the active ingredient in a way that does not raise potential issues concerning its safety.

For these reasons, the applicable statute and regulations preclude FDA from approving an ANDA for generic drugs unless the agency determines (among other things) that: (1) the proposed generic drug is bioequivalent to the innovator product it seeks to copy (the "reference listed drug" or "RLD"); and (2) that the proposed generic drug can legitimately use a label that is "the same" as the label for the RLD (other than changes required because the drugs are produced by different manufacturers). 21 U.S.C. § 355(j)(2)(A)(iv)-(v).

Here, FDA's decisions denying Biovail's Citizen Petition and approving Anchen's ANDA clearly violate the unambiguous statutory requirement that the generic product's label be the same as that of the innovator.

### A. Anchen's Generic Drug Must Have "The Same" Labeling As WELLBUTRIN XL®

The FDCA mandates that the generic drug have "the same" labeling as the RLD's labeling. 21 U.S.C. § 355(j)(2)(A)(v). More specifically, the statute requires that an ANDA contain:

> information to show that the labeling proposed for the [generic] drug *is the same* as the labeling approved for the [innovator drug] except for changes required . . . because the new drug and the listed drug are produced or distributed by different manufacturers.

*Id.* (emphasis added); *see also* 21 C.F.R. § 314.94(a)(8)(iv). This requirement underpins the whole concept of generic drugs, in that it allows physicians, pharmacies and patients to prescribe, dispense, and consume generic drugs without having to carefully study and compare the labeling to determine if there are any important differences in safety and efficacy with the brand name version. As such, "the same" labeling requirement goes to the very essence of what it means to be a generic drug. The labeling provision must also be read in conjunction with another provision of the FDCA stating that a drug is "misbranded" if "its labeling is false or misleading in *any particular*." 21 U.S.C. § 352(a) (emphasis added).

### B. The Labeling For Brand Name WELLBUTRIN XL® Accurately Discloses That The Risks of Seizure May Be Similar To That For Prior Formulations of Bupropion

As discussed in detail above, the approved labeling for WELLBUTRIN XL® discloses all of the seizure-related risks, and refers to specific test results or other scientific findings that are crucial to the safe and effective use of the product. In particular, the WELLBUTRIN XL® labeling accurately states that the product has been shown to be bioequivalent to the immediate-release and sustained-release formulations of bupropion, and therefore, the risk of seizure may be similar to those drugs.

### C. The Anchen Product's Label is Not the Same As WELLBUTRIN XL®

Although Anchen (or any other ANDA applicant) is required by federal law to use "the same" labeling as WELLBUTRIN XL®, it does not do so. The Anchen product's labeling does not state that Anchen's product has demonstrated bioequivalency with the immediate-release and sustained-release formulations of bupropion.

In essence, Anchen is attempting to piggyback on Biovail's determination that *Biovail's* extended-release product has the same seizure risk as the sustained-release and immediate-release formulation—but without doing the requisite research and analysis to demonstrate whether this is, in fact, true with respect to Anchen's product. 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 false and misleading with respect to the applicability of the seizure risk information presented in the labeling.

The potential for the Anchen product to have greater or different safety risks than WELLBUTRIN XL® cannot be understated. According to FDA's own guidelines**,** there should not be more than a 5% chance that a given generic drug is not "truly equivalent" to the reference drug. *See* FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* ix (26th ed. 2006).[11] To minimize the potential for variations, bioequivelancy must be shown by comparing the proposed generic to a single reference drug. The risks for such potential variations are significant here.

[11] Available at http://www.fda.gov/cder/orange/obannual.pdf.

To illustrate, assume that there is a 4% chance that a given brand name WELLBUTRIN XL® tablet is not truly equivalent with the sustained-release or immediate-release forms of bupropion (which falls within FDA's 5% guidelines). Assume further that there is a 4% chance that a given Anchen generic tablet is not truly equivalent with WELLBUTRIN XL® (again, falling within the 5% guideline). While each individual comparison falls within the 5% guideline, there may be a greater than 5% chance that each Anchen tablet is not truly equivalent to the sustained-release and immediate-release forms—and these are the formulations to which the Anchen product compares itself and claims to have a similar seizure risk. Thus, Anchen's labeling is not only false and misleading—indeed, "misbranded "under the relevant statutory provision (*see* 21 U.S.C. § 352(a))—but it has the potential to understate the important medical risks with its product.

Requiring additional testing before allowing a manufacturer to make a statement in a label is a concept familiar to FDA. For example, the agency's *Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies* (Dec. 2002)[12] recognizes that, in some circumstances, the ANDA must include additional data to make labeling accurate. In order for the label of a branded drug to indicate that the drug can be taken by sprinkling it on soft foods (so it can be swallowed without chewing), page nine of this guidance states that the drug manufacturer should conduct testing and present data comparing administration by sprinkling it on a soft food (like applesauce) versus administration in intact form.

Significantly, the guidance goes on to state that, in order for an ANDA to be approved for the generic version of such a drug, the generic manufacturer must also perform a similar test in order to ensure that its labeling would also be accurate. Here, that means that Anchen (and any

[12] Available at http://www.fda.gov/CDER/guidance/5194fnl.htm.

other party submitting an ANDA for generic WELLBUTRIN XL®) must make the same showing—namely, demonstrating bioequivalence to WELLBUTRIN and WELLBUTRIN SR—that Biovail made to ensure that the labeling is accurate.

In sum, Anchen (or any other ANDA applicant) should not be permitted to market a generic version of WELLBUTRIN XL® that so blatantly runs afoul of the FDCA's unambiguous requirement that the generic's labeling be the same as that of the innovator, and the FDA's decisions leading to a contrary result should be set aside.

## II. BIOVAIL WILL SUFFER IRREPARABLE HARM ABSENT INJUNCTIVE RELIEF

Biovail has a significant property interest in WELLBUTRIN XL® that it acquired by making substantial human resource and financial investments. WELLBUTRIN XL® is widely known to doctors and patients as being safe and effective in treating MDD, and accounts for a substantial portion of Biovail's revenue. (Howling Decl. at ¶¶ 6-7.) The sale of WELLBUTRIN XL® constitutes approximately 42% of Biovail's sales and more than 75% of Biovail's total profits. (*Id.*)

The customer loss, potential harm to relationships with customers, reputational damage and non-recoverable monetary loss that Biovail will suffer from FDA's improper approval of ANDAs for generic WELLBUTRIN XL® all constitute irreparable harm. *See Morgan Stanley DW, Inc. v. Rothe*, 150 F. Supp. 2d 67, 77 (D.D.C. 2001) (finding that loss of customers and the potential damaging of relationships with customers constitutes irreparable harm); *Express One Int'l, Inc. v. U.S. Postal Serv.*, 814 F. Supp. 87, 91 (D.D.C. 1992) (granting injunctive relief after finding plaintiff faced non-recoverable monetary losses); *Honeywell, Inc. v. Consumer Prod. Safety Comm'n*, 582 F. Supp. 1072, 1078 (D.D.C. 1984) (concluding that injury to goodwill, reputation and competitive position constitute irreparable harm).

This Court has recognized how quickly generic drugs, once approved, saturate the marketplace, and how devastating the effect that final approval of ANDAs can be to those possessing rights in an innovator drug:

> [Plaintiff] cites industry publications to demonstrate that generic Prozac achieved 59% market penetration of total prescriptions for one dosage strength and 70% of new prescriptions for another dosage strength within one month of launch. Within two weeks of availability of a generic version of Astra's drug Zestril, Merck-Medico mail order pharmacy apparently achieved 91% generic conversion. Megestrol is said to have achieved 75% market share within six months. . . .

*CollaGenex Pharm., Inc. v. Thompson*, No. Civ. A. 03-1405 (RMC), 2003 WL 21697344, at *10 (D.D.C. Aug. 26, 2003) (granting preliminary injunction to innovator manufacturer). As this Court recognized on the same page of that decision:

> It is not at all difficult to foresee that [Plaintiff]'s market position would collapse as soon as one or more generic drugs became available. [Plaintiff] would lose its head start in the market and its continued viability would be at issue. It could never recoup from FDA any losses that would occur . . . . These are the kinds of circumstances in which irreparable harm has been found.

*Id*. This type of economic harm—unrecoverable because FDA is immune from suit for damages for its action here under the Federal Tort Claims Act (*see Berkowitz v. United States*, 486 U.S. 531, 535 (1988))—is therefore irrefutably irreparable. *Express One*, 814 F. Supp. at 91; *Hoffman-Laroche, Inc. v. Califano*, 453 F. Supp. 900, 903 (D.D.C. 1978) (noting that "[i]f the order goes into effect, plaintiff will suffer loss of sales and good will for which it would have no right of recourse, and thus its injury will be irreparable").[13]

[13] In similar cases where courts have found FDA action did not give rise to irreparable injury, the total impact of the agency action on the companies' sales was dramatically smaller. *See Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 220 (D.D.C. 1996) (finding in discussion of irreparable harm that the sales of the plaintiff's drugs that would be subject to competition from FDA-approved generic constituted only **0.7%** of the Plaintiff's total sales); *Sandoz, Inc. v. FDA*, Civ. Action No. 06-1134, 2006 U.S. Dist. LEXIS 46672, at *12 (D.D.C. July 12, 2006) (denying injunctive relief to a generic drug manufacturer, noting in discussion of irreparable harm that the company's claimed losses constituted less than **1 percent** of the company's sales from generic drugs).

(continued)

This motion, and Biovail's Citizen Petition, lay out the danger that the public will be exposed to false and misleading labeling on a drug that has the significant adverse side-effect of causing *grand mal* seizures unless FDA employs the criteria Biovail urges for assessing applications for approval of generic versions of WELLBUTRIN XL®. As explained in the Silverstone Declaration, given the unique nature of bupropion, it is very important for patient wellbeing and safety to ensure that any generic version of Wellbutrin XL® is truly "equivalent" to currently available versions as must be claimed in the labeling that will accompany the generic version. (*See* Silverstone Decl. ¶ 9.) If not, there is a significant risk of inadvertent under-dosing, which may significantly increase the risk of a clinical relapse, or inadvertent over-dosing, which may significantly increase the risk of developing seizures. (*Id.*)

This is not mere speculation. Congress knew full well that the accurate labeling of generics was vitally important to ensuring their safety. Like the posting of a speed limit sign designed to prevent auto accidents known to be caused by excess speed, Congress used unambiguous language to reflect its intent that a generic drug not be marketed until proven safe by requiring that an ANDA contain "information to show that the labeling proposed for the [generic] drug is *the same* as the labeling approved for the [innovator] drug . . . ." 21 U.S.C. § 355(j)(2)(A)(v) (emphasis added). "The same" does not mean "similar," "resembling" or "approximating." It means "identical." Anchen's generic version of WELLBUTRIN XL® (or that of any other ANDA applicant) cannot satisfy this unambiguous standard because FDA did not require applicants to demonstrate bioequivalence with the immediate-release and sustained-release formulations of bupropion. As a result, Anchen's generic version of WELLBUTRIN

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These cases have no bearing where, as here, the drug at issue is responsible for over **42%** of sales and more than **75%** of Biovail's total profits. (Howling Decl. ¶¶ 6-7.)

XL® (or that of any other ANDA applicant) have not been proven safe, thereby presenting a threat to public safety.[14]

## III. THE BALANCE OF HARMS AND THE PUBLIC INTEREST COUNSEL IN FAVOR OF GRANTING PRELIMINARY INJUNCTIVE RELIEF

### A. The Harm to Biovail Outweighs Any Harm To Anchen or Any Other ANDA Applicant

The harm that may be suffered by other parties if a preliminary injunction is granted is greatly outweighed by the irreparable harm that would be suffered by Biovail if an injunction is not issued.

FDA can suffer no cognizable harm as a result of an injunction imposed on account of its violation of applicable regulations and its own abuse of discretion.

Any potential harm to Anchen or any other ANDA applicant is easily outweighed by the harm to Biovail if provisional relief is not granted. Investments in developing a generic version will not be "lost" if provisional relief is granted. These investments will be lost *only* if the applicants cannot adequately demonstrate bioequivalence and develop a label that is truthful and accurate. In that case, however, applicants have no right to FDA approval no matter how much they have invested. On the other hand, if applicants such as Anchen are ultimately able to demonstrate that their products are bioequivalent and that they can legitimately use the same

[14] Biovail recognizes that in its September 6, 2006 Memorandum Opinion, this Court discounted Biovail's concerns regarding the public health risk created by the marketing of a generic version of WELLBUTRIN XL® improperly found to be bioequivalent to the pioneer. Biovail nonetheless believes that the danger is real and directs the Court's attention to the Silverstone Declaration's discussion of the risks involved. For example, when equivalence is not properly determined, and does not exist, between forms of bupropion that are currently being used and a proposed generic, there is a significant risk that patients will be harmed by taking the proposed generic through either inadvertent under-dosing, which may significantly increase the risk of a clinical relapse, or inadvertent over-dosing, which may significantly increase the risk of developing seizures. (Silverstone Decl. ¶ 9.) In the case of WELLBUTRIN XL®, this risk has been amplified by FDA's recent approval of a generic version of WELLBUTRIN XL® with label language specifically related to the risk of seizures that is not accurate with respect to the generic (*i.e.*, the generic was not found to be bioequivalent to prior versions of bupropion, as was WELLBUTRIN XL®). (*Id.*)

label as the branded product, then applicants would have lost none of their investment as a result of a preliminary injunction. The only arguable loss would be a brief delay in recovering their investment, while the status quo is preserved so that the Court can address Biovail's claims on their merits. In any event, an applicant's claimed investment in developing a generic version pales in comparison to the expense that was incurred in conducting extensive clinical trials and to demonstrate bioequivalence with the immediate-release and sustained-release formulations of bupropion.[15]

### B. The Public Interest In Buying A Safe And Effective Product Outweighs Any Interest in Cheaper Drugs

The cornerstone of Biovail's Amended and Supplemented Complaint is that the Anchen labeling and that of any other applicant whose ANDA has been approved are false and misleading with respect to the product's health risks and that the generic products have not been shown to have the same risk of seizure as WELLBUTRIN XL®. The Court can face no greater public interest than protecting the public from misleading labeling and a pharmaceutical product that potentially endangers the public health and safety.

Indeed, FDA's decisions present potential health risks to patients suffering from MDD and Seasonal Affective Disorder who purchase the generic product, possibly including *life-threatening risks* associated with unintended delivery of an improper dose of bupropion. The public interest is clearly served by maintaining the status quo until the Court has had an

[15] Further, in considering whether a preliminary injunction should be issued, it is significant that all of the concerns that Biovail has raised about the adequacy of an ANDA for generic WELLBUTRIN XL® could have been resolved long before an actual threat to the public health arose. Had FDA responded promptly to Biovail's Citizen Petition, Biovail could have considered FDA's response, evaluated its adequacy and, if necessary, filed suit. The Court would then have had ample time to consider these issues upon a fully developed record months before any generic product was actually sold. Now, as a result of FDA's substantial delay, the Court cannot do so. FDA should not be rewarded for its own delay. It should not be permitted to use its own dilatory conduct to defeat meaningful judicial review, now that it has finally issued a decision on Biovail's Citizen Petition.

opportunity to ensure that only a safe and efficacious product is made available to the public.

Neither FDA, Anchen nor any other ANDA applicant can be heard to contend that a preliminary injunction is not in the public interest because it would deprive consumers of access to a cheaper form of bupropion. That is precisely why the Hatch-Waxman Act requires that every generic drug must be demonstrated to be "bioequivalent" to a previously approved reference drug *before* it can be approved for sale to the public, 21 U.S.C. § 355(j)(2)(A)(iv), and that it have labeling that is the same *and* truthful, *id.* §§ 352(a), 355(j)(2)(A)(v). The public interest in cheaper drugs is, of course, outweighed by the significant public health risks in allowing a potentially unsafe and mislabeled product to enter the marketplace.

## CONCLUSION

For the reasons stated above, Biovail respectfully requests that this Court issue an order temporarily enjoining and restraining FDA from approving any ANDAs for generic WELLBUTRIN XL®, as well as staying the effectiveness of any such prior approvals, until this Court has had the opportunity to consider Biovail's contentions on their merits.

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Respectfully submitted,

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