IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

BIOVAIL CORPORATION, *et al.*,	)
Plaintiffs,	)
v.	)
U.S. FOOD & DRUG ADMINISTRATION, *et al.*,	)
Defendants.	)

PLAINTIFFS' MOTION FOR A TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION

Plaintiffs Biovail Corporation and Biovail Laboratories International SRL (collectively, "Biovail") hereby 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' Motion for a Temporary Restraining Order and Preliminary Injunction, Plaintiffs ask this Court to compel Defendants U.S. Food and Drug Administration and Andrew C. von Eschenbach, M.D., Acting Commissioner of Food and Drugs, to act upon Biovail's Citizen Petition related to the criteria to be used in evaluating applications to market a generic version of WELLBUTRIN XL®, a prescription drug that is widely prescribed for the treatment of Major Depressive Disorder. Biovail also asks that FDA be required to rule on the Petition at least one calendar week prior to granting any application for approval of generic WELLBUTRIN XL®, so that if the Citizen Petition is denied there will be a meaningful opportunity to seek judicial review of the denial.

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 Rule

65.1(a) is attached as Exhibit 2. Defendants have not yet appeared in this action and thus have not designated counsel to represent them herein. As a result, plaintiffs have been unable to confer with opposing counsel in accordance with Local Civil Rule 7(m).

Dated: August 23, 2006

Respectfully submitted,

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[*] In accordance with Local Civil Rule 7(a), Plaintiff chiefly relies on those sources marked with an asterisk.

CONSTITUTIONAL PROVISIONS AND STATUTES

REGULATIONS

Plaintiffs Biovail Corporation and Biovail Laboratories International SRL (collectively "Biovail") submit this memorandum in support of their 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 Acting Commissioner of Food and Drugs (collectively, "FDA").

Biovail has filed a Citizen Petition with FDA that seeks to protect the public by ensuring that FDA applies appropriate standards when determining whether or not to approve an application to market a generic version of WELLBUTRIN XL®, a prescription drug product. FDA by regulation ordinarily has 180 days to determine the issues raised in a Citizen Petition—but more than 180 days have passed without any ruling from FDA on Biovail's petition. Biovail's Complaint asks for a writ of mandamus to compel FDA to perform its duty: rule on the Citizen Petition, one way or the other.

Biovail also asks that FDA be required to rule on the Petition at least one calendar week prior to granting any application for approval of generic WELLBUTRIN XL®, so that if the Citizen Petition is denied there will be a meaningful opportunity to seek judicial review of the denial. This motion for a preliminary injunction and temporary restraining order seeks to preserve the *status quo* by ordering FDA not to grant any such approval for generic WELLBUTRIN XL® without having decided Biovail's Citizen Petition at least one calendar week in advance.

PRELIMINARY STATEMENT

WELLBUTRIN XL® is manufactured for marketing in the United States by Biovail. Wellbutrin contains the active ingredient bupropion and is used in the treatment of Major Depressive Disorder and Seasonal Affective Disorder. Bupropion is associated with a dose-related risk of seizures—including *grand mal* seizures—which can be quite dangerous, even life-

threatening. The safety of WELLBUTRIN XL®, and its effective management of the risk of seizure, was proved to FDA by, among other things, demonstrating the bioequivalence of WELLBUTRIN XL® to earlier versions of Wellbutrin. The products were "bioequivalent" because, in general terms, they delivered equal amounts of bupropion over time to the patient's blood stream. The products also delivered equal amounts of bupropion metabolites—i.e., products created in the patient's body, by ordinary metabolic processes, from bupropion. Bioequivalence is extremely important here because the risk of seizure appears to be related to the amount of bupropion and/or the amounts of bupropion metabolites in a patient's blood stream. In other words, if a generic substitute delivers more bupropion or bupropion metabolites to the patient's system than have been delivered by Wellbutrin products in prior use, patients taking the generic substitute could face an increased risk of seizure.

Biovail's Citizen Petition (Perra Decl. Ex. B)[2] was filed in December 2005 and asked FDA, in addressing any applications for approval of generic WELLBUTRIN XL®, to employ specific criteria that are essential in determining whether or not the proposed generic versions are bioequivalent. In particular, the criteria proposed in Biovail's Petition sought to ensure that any generic version of WELLBUTRIN XL® did not pose an undue risk of *grand mal* seizure, thereby protecting both (1) the public from serious health risks; and (2) Biovail from suffering the inevitable and irreparable harm that would flow if a generic alternative had a higher risk than WELLBUTRIN XL® of a serious adverse event, such as *grand mal* seizures. The Citizen Petition also would ensure that FDA does not permit misleading labeling concerning the safety risks posed by any generic versions of WELLBUTRIN XL®.

[2] References to the "Perra Decl." are to the accompanying August 21, 2006 Declaration of Kevin J. Perra, a copy of which is attached as Exhibit 3.

Despite the importance of Biovail's Petition and the 180-day timetable in the applicable regulations, FDA has not acted on Biovail's Petition. Indeed, FDA has made a practice of refusing to decide Citizen Petitions within 180 days when the Petitions bear on the criteria that should be employed in reviewing proposed generic versions of prescription drugs. In those situations, FDA routinely ignores the applicable regulation and withholds its decisions on the Citizen Petitions until it releases its decisions approving the generic substitutes. In the last six years, FDA has *never* decided such a Citizen Petition prior to its decision to approve a generic drug. (Stearns Decl. ¶¶ 3-4 and Ex. A.)[3]

FDA's general practice of refusing to timely decide these Petitions, and in particular its failure to decide Biovail's Petition in a timely manner, is severely prejudicial because it deprives the courts of the opportunity to review FDA decisions on Citizen Petitions. When a generic drug is approved, the generic drug manufacturer usually is prepared immediately to fill the distribution pipeline with its product. (*See id.* ¶¶ 9-11.) An application for judicial review, even if filed scant days after the approval, will follow rather than precede the widespread distribution of the product. As a result, *before* a court can examine the matter, patients are exposed to whatever dangers the generic alternative may pose, thereby harming both the public and the reputation of the branded drug. The parties and a court, moreover, are forced to confront the issues on an expedited basis. That is exactly the danger threatened here, where, as we explain below, approval of a generic version of WELLBUTRIN XL® is imminent and the issues raised by the Citizen Petition are unresolved.

[3] References to the "Stearns Decl." are to the accompanying August 21, 2006 Declaration of Frederick A. Stearns, a copy of which is attached as Exhibit 4.

If FDA instead complied with its regulation and decided Citizen Petitions within 180 days, there would in the typical case be time to seek judicial review of the denial of a Petition *before* the potentially dangerous drug were distributed to the public. The FDA process and timing for the approval or disapproval of generic drugs would not be affected in the slightest; but Citizen Petitions would be decided in a timely manner and judicial review, when appropriate, would be available. That is all Biovail seeks here.

STATEMENT OF FACTS

Biovail's Prescription Drug WELLBUTRIN XL®

Biovail is a pharmaceutical company that develops, tests, registers, manufacturers and sells a variety of drugs. Among the drugs in which Biovail owns patent rights is the drug WELLBUTRIN XL®. 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"). MDD is a common and severe psychiatric disorder that has been ranked by the World Health Organization as one of the most serious disability afflictions, among heart disease, cancer and HIV/AIDS. More recently, WELLBUTRIN XL® was approved for the treatment of Seasonal Affective Disorder, which is a common and serious psychiatric disorder.

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, bupropion is associated with a dose-related risk of seizures. The risk of seizure appears to be related to the amount of bupropion and/or bupropion metabolites in a patient's blood stream. The risk of seizure is also related to patient factors, including the excessive use of alcohol. To reduce the risk of seizures, the WELLBUTRIN XL® labeling (*see* attachment to Perra Decl. Ex. B) recommends that the total daily dose of bupropion not exceed 450 mg/day and that the rate of dose incrementation be gradual. 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. Therefore, seizure potential may be directly related to a particular dosage form and its release rate in the presence of food and alcohol. Warnings and other information on the above issues are contained in the labeling that accompanies WELLBUTRIN XL®. (*See* attachment to Perra Decl. Ex. B.)

The Drug Approval Process For Innovator Drugs and Generic Drugs

Congress has delegated to FDA the authority to regulate drugs under the Federal Food, Drug, and Cosmetic Act, as amended, 21 U.S.C. § 321 *et seq.*, ("FDCA"). 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 Abbreviated New Drug Applications ("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, 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 filers of the ANDA. *See* 21 U.S.C. § 355. So long as that suit is viably pending in district court, it causes an automatic thirty-month ANDA approval moratorium under the FDCA. *Id*. During that time, with certain exceptions not relevant here, FDA 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 the 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. (Rowland

Decl. ¶ 9.)[4] This allows for virtually immediate entry into the market upon receiving FDA's final approval.

It is also not uncommon for those with rights to, and scientific knowledge about, an innovator drug to provide FDA with technical information during the ANDA review process to ensure an accurate determination of bioequivalence and compliance with other requirements. The process for submitting such information is by filing a "Citizen Petition" under 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.) In fact, in the last six years, FDA has never denied a Citizen Petition addressing the criteria to be used in passing on an ANDA prior to its decision to approve an ANDA. (*Id.*) And, in all but one case, FDA's decision on each drug application was rendered at the exact same time as its decision on a related Citizen Petition. (*Id.*) In the one remaining case, FDA's decision on the Citizen Petition was rendered after the decision on the drug application. (*Id.*)

FDA's regulations permit the Agency to make a "tentative response" to a Citizen Petition, but only if FDA is "unable" to render a decision within 180 days and provided that FDA notifies the petitioner why the agency was "unable" to make a "final response," i.e. finally approving or denying the petition in whole or part. 21 C.F.R. § 10.30(e)(2)(iii). In such a tentative response, the regulation provides that FDA may also inform the petitioner of when a

[4] References to the "Rowland Decl." are to the accompanying August 22, 2006 Declaration of Charles A. Rowland, Jr., a copy of which is attached as Exhibit 5.

final response may be issued and the likely nature of that response. *Id.*

ANDAs for Generic Versions of WELLBUTRIN XL® and Biovail's Citizen Petition

Although a number of companies have filed ANDAs for generic versions of WELLBUTRIN XL®, there is currently no approved generic version. The first such ANDA deemed by FDA acceptable for review was filed by Anchen Pharmaceuticals, Inc. ("Anchen"). 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. After diligently investigating the matter, Biovail filed a patent infringement suit against Anchen, thereby triggering the thirty-month statutory ANDA approval moratorium. *See Biovail Laboratories SRL v. Anchen Pharmaceuticals, 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.)

The Biovail Citizen Petition was filed December 20, 2005. (*See id.* Ex. B.) In its petition, Biovail requested that FDA apply certain criteria in the final approval process of any ANDA that would allow a generic version of WELLBUTRIN XL® to be marketed. Application of those criteria, Biovail asserted, was necessary to ensure protection against the aforesaid known and potentially serious risks relating to high levels of bupropion hydrochloride, especially seizures.

Biovail also pointed out that there are parts of the approved WELLBUTRIN XL® labeling that refer to specific test results and other scientific findings that are crucial to the safe and effective use of the product. (Perra Decl. Ex. B at 4-6.) Critical, in this regard, is that the applicable statutory provisions under which FDA has been empowered to approve generic drugs is the requirement that the labeling of the generic drug be identical to that of the innovator drug.

21 U.S.C. § 355(j)(2)(A)(v); *see also* 21 C.F.R. § 314.94(a)(8)(iv). The labeling of a drug, also known as the package insert, provides detailed information regarding the identity, composition, pharmacokinetics, metabolism, indications, contraindications, risks, side effects and other information important to safe use of the drug.

Here, for example, with respect to the risk of seizures, the approved labeling states that, as WELLBUTRIN XL® and the sustained release version of bupropion (known as WELLBUTRIN SR) "are bioequivalent to the immediate release formulation of bupropion" (known as WELLBUTRIN IR), the seizure incidence with WELLBUTRIN XL and WELLBUTRIN SR "may be similar" to that presented in the immediate release formulation of bupropion. Thus, as Biovail noted in its Petition, a proposed generic drug must satisfy the same condition—i.e., that the generic drug is bioequivalent to WELLBUTRIN IR and WELLBUTRIN SR—as well. Otherwise, a proposed generic would be unable truthfully to make the important statement relevant to safety in its label.

And, it would be one thing to allow a variation in labeling on a subject such as pharmacokinetics in which the fact that the studies were done on the branded product is generalized. It would be quite another matter to sanction a generalized label which would have the effect of making information relevant to a serious health risk like the incidence of seizure untrue. Even a generalized statement would be untrue unless FDA applies the criteria urged in Biovail's Citizen Petition.

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." FDA's notice of delay did not cite other priorities or give any other reason for its failure to act, nor did it give an estimate as to when a final response would be issued or the likely nature of such a response, as suggested in the underlying regulation. *See* 21 C.F.R. § 10.30(e)(2)(iii).

On June 29, 2006, Biovail sent a letter to FDA taking issue with FDA's statement that it could not take action on the Petition within 180 days. (*See* Perra Decl. Ex. D.) In that letter, Biovail requested that FDA immediately take and give it notice of final action forthwith, but in no case fewer than two business days prior to finally approving any ANDA for a generic version of WELLBUTRIN XL®. (*Id.*) As grounds for those requests, Biovail Corporation asserted that FDA had sufficient information to take final action on the Petition. Biovail also argued that the Agency's practice of delaying notice of its denial of such petitions to a time concurrent with (or even after) approving the ANDAs to which the petitions related impeded effective judicial review of that denial and otherwise harmed petitioners contrary to law. FDA has not responded to those requests and assertions.

Very recently, the court in the Biovail Infringement Case granted summary judgment in Anchen's favor on the issue of infringement. That decision, when entered as a judgment, will end the thirty-month moratorium referred to above and permit FDA to issue final approval of Anchen's ANDA. On August 17, 2006, Biovail filed a motion for reconsideration of the decision, and a hearing on the motion is scheduled for August 28, 2006. Thus, as early as August 28, 2006, the court in the Biovail Infringement Case could deny the motion for reconsideration and enter a final judgment, thereby clearing the way for FDA immediately to

issue final approval of a generic version of WELLBUTRIN XL®. As described below, this makes Biovail's motion all the more urgent, pressing and necessary.

LEGAL STANDARDS AND JURISDICTION

Jurisdiction and Right to Judicial Review

This Court has jurisdiction over the underlying action under the All Writs Act, 28 U.S.C. § 1651(a), the Administrative Procedure Act (the "APA"), 5 U.S.C. §§ 555(b) and (e), 702 and 706, the Fifth Amendment to the United States Constitution, and related case law.

The APA creates a right to judicial review for a person suffering a legal wrong from agency action. 5 U.S.C. § 702. The reviewing court must "compel agency action unlawfully withheld or unreasonably delayed" and "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." *Id.* § 706(1), (2). "Agency action" includes the failure to act. *Id.* § 551(13).

Here, the provisions of the APA also require the FDA to conclude "within a reasonable time" a matter presented to it and the Agency must do so with "due regard for the convenience and necessity" of the interested person presenting that matter. 5 U.S.C. § 555(b). FDA also is obligated to provide "prompt notice" of the denial in whole or in part of the petition of any interested person made in connection with any Agency proceeding. *Id.* § 555(e).

Further, the Fifth Amendment to the Constitution of the United States provides that no person may be deprived of life, liberty, or property without due process of law. The "fundamental requirement" of due process is the "opportunity to be heard at a meaningful time and in a meaningful manner." *Beverly Enterprises, Inc. v. Herman*, 130 F. Supp. 2d 1, 17 (D.D.C. 2000) (citing *Mathews v. Eldridge*, 424 U.S. 319, 333 (1976)). To establish an actionable due process claim, the plaintiff must show that "(1) it has a protected [property]

interest, (2) the government deprived it of this interest, and (3) the deprivation occurred without proper procedural protections." *PDK Labs Inc. v. Reno,* 134 F. Supp. 2d 24, 32 (D.D.C. 2001)l *see also Beverly Enterprises,* 130 F. Supp. 2d at 17 (citing *Propert v. District of Columbia,* 948 F.2d 1327, 1331 (D.C. Cir. 1991); *Soeken v. Herman,* 35 F. Supp. 2d 99, 104-05 (D.D.C. 1999)). The deprivation of a fundamental constitutional right such as due process, "for even minimal periods of time, unquestionably constitutes irreparable injury." *Elrod v. Burns,* 427 U.S. 347, 373 (1976) (applied to First Amendment right of association).

Standards for Granting Injunctive Relief

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); *Sea Containers, Ltd. v. Stena AB,* 890 F.2d 1205, 1208 (D.C. Cir. 1989); *Wash. Metro. Area Transit Comm'n v. Holiday Tours, Inc.* 559 F.2d 841, 943 (D.C. Cir. 1977); *Va. Petroleum Jobbers Ass'n v. Federal Power Comm'n,* 259 F.2d 921, 925 (D.C. Cir. 1958). 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).

ARGUMENT

FDA's failure to act on Biovail's Citizen Petition within the 180-day regulatory response deadline and the Agency's general practice of delaying action on such petitions violates the APA

and due process. Biovail seeks to enjoin FDA from issuing a final approval on an ANDA for a generic version of WELLBUTRIN XL® before the Agency acts on Biovail's Citizen Petition. Without such relief, both the public and Biovail are threatened with immediate and irreparable harm.

I. FDA HAS UNLAWFULLY FAILED TO ACT ON BIOVAIL'S CITIZEN PETITION

FDA's failure to act on Biovail's Citizen Petition "within a reasonable time" is a violation of the Agency's affirmative duty to act under the APA. 5 U.S.C. § 555(b), (e). Further, FDA's claim that it could not meet the 180-day regulatory response deadline and failure to provide Biovail with an estimate as to when a response would be issued was pretextual and therefore arbitrary, capricious, and an abuse of discretion. In the context of the ANDA approval process, which is conducted by experienced and knowledgeable officials, the issues raised in the Biovail Citizen Petition, even if complex, do not require extensive review and analysis that would preclude FDA from acting on the Petition within 180 days of its filing. For example, as is facially evident from Biovail's Citizen Petition (Perra Decl. Ex. B), Biovail did not ask FDA to conduct any new tests or experiments or to do any other significant scientific work. Thus, the notion that FDA could not address the substance of the petition within 180 days is simply not credible.

It is even less credible given FDA's demonstrable pattern of not deciding Citizen Petitions with respect to ANDAs until it approves ANDAs. (*See generally* Stearns Decl. and Ex. A thereto.) It cannot be mere coincidence that FDA is consistently unable to decide Citizen Petitions prior to the 180-day timetable, but is able to decide them at the exact moment it decides ANDAs. (*See Id.*) Rather, this demonstrates that FDA has made it a practice deliberately to hold off on deciding Citizen Petitions until the last possible moment, without regard to its obligation

to decide such petitions within 180 days unless it is "unable" to do so.

This practice is capricious and an abuse of discretion and one that poses a threat to public safety and harms the rights of those that submit Citizen Petitions. Here, for instance, by failing to take proper action on Biovail's Citizen Petition, FDA's inaction threatens to harm the public and Biovail in a number of ways. First, approval of drugs that are not shown to be bioequivalent to the innovator drug is a dangerous act that can damage the integrity of the generic drug industry while putting unsuspecting patients at risk. More specifically, any FDA approval of a generic version of WELLBUTRIN XL® that is not bioequivalent to the innovator drug will present a potential health risk to patients suffering from MDD who would use the generic. If such patients are harmed, by virtue of seizures or otherwise, Biovail and its WELLBUTRIN XL® product will be further harmed as health care professionals move patients to other depression therapies simply to avoid the uncertainty, confusion and negative associations that will ensue when a product claimed to be bioequivalent to WELLBUTRIN XL® does harm.

The express purpose of the Biovail Citizen Petition is to insure that the Agency applies proper criteria to verify that any generic version of WELLBUTRIN XL® is bioequivalent to the innovator drug and its predecessors, thereby minimizing risks that would be associated with the generic, avoiding the dangers of misleading labeling and protecting WELLBUTRIN XL® from the inevitable harm that would flow from being associated with a dangerous or defective generic product. All pertinent evidence must be considered during, not after, the ANDA approval process. While FDA may not ultimately agree that the suggested criteria should be applied, it must at least consider the issues raised by Biovail's Citizen Petition and take action on them prior to issuing final ANDA approval.

Were there to be a denial of the Biovail Citizen Petition, FDA also must give Biovail

reasonable notice of such action to allow Biovail a time to review the decision for lawfulness and to seek judicial review prior to it suffering irreparable competitive harm and the public being put at risk. FDA's practice of indefinitely delaying denials, or at least notice thereof, of Citizen Petitions seeking to influence the ANDA approval process until issuing final ANDA approval effectively denies any meaningful judicial review of those denials.

Specifically, the petitioner that has rights in innovator drugs is effectively deprived of its property interests without the due process of judicial review, if the petitioner believes that the Agency's approval was unlawful. The approved generic is almost immediately placed on the market and the harmed innovator cannot collect damages from either FDA or the competitor whose actions are officially approved. These "unreasonably delayed" actions on the Biovail Citizen Petition must therefore be "h[e]ld unlawful" and "set aside" as "contrary to constitutional right." 5 U.S.C. § 706(1), (2).

II. BIOVAIL IS SUBSTANTIALLY LIKELY TO SUCCEED ON THE MERITS

For the above-stated reasons, FDA has a clear duty to act within a reasonable time on the Biovail Citizen Petition and to give Biovail prompt notice of any denial in whole or in part. 5 U.S.C. § 555(b), (e). There has been no such action of which Biovail has received notice. FDA's unlawful inaction is unlawful action within the meaning of the APA. Biovail has a clear right to relief from such unlawfully withheld or unreasonably delayed action. *Id.* § 706(1), (2).

Biovail's complaint for injunctive and declaratory relief and for a Writ of Mandamus is likely to succeed under this Circuit's guidelines in *Telecommunications Research and Action Center v. FCC*, 750 F.2d 70, 80 (D.C. Cir. 1984) ("TRAC") and its progeny. The first TRAC guideline states that "the time agencies take to make decisions must be governed by a 'rule of reason.'" *Id.* (citations omitted). Guideline 2 provides that, "where Congress has provided a timetable or other indication of the speed with which it expects the agency to proceed in the

enabling statute, that statutory scheme may supply content for this rule of reason." *Id.* at 80. The regulatory timetable in 21 C.F.R. § 10.30(e)(2) for deciding the Biovail Citizen Petition is 180 days and is legally binding on FDA. FDA's practice of delaying decisions on Citizen Petitions relating to the ANDA process and the use of excuses to avoid complying with its regulatory deadline are plainly unreasonable. And, as stated above, the FDA's excuse for failing to meet that target is simply not plausible or credible.

The third *TRAC* guideline states that "delays that might be reasonable in the sphere of economic regulation are less tolerable when human health and welfare are at stake." *Id.* (citations omitted). The most serious health and safety issues, including life itself, are at stake in the Biovail Citizen Petition. If FDA denies that Citizen Petition and delays notice of the denial until it approves an ANDA for a generic version of WELLBUTRIN XL®, effective judicial review of how FDA decided those health and safety issues will be unnecessarily limited.

The fourth *TRAC* guideline provides that "the court should consider the effect of expediting delayed action on agency activities of a higher or competing priority." *Id.* Nothing in the record indicates that other responsibilities should receive a higher priority by those responsible for deciding the Biovail Citizen Petition. Significantly, FDA's tentative response to that Citizen Petition did not assert that the need to tend to other activities was the reason behind FDA's inability to meet its own 180-day deadline.

The fifth *TRAC* guideline provides that "the court should also take into account the nature and extent of the interests prejudiced by delay." *Id.* (citations omitted). A statement of the nature and extent of Biovail's prejudiced interests and, more profoundly, the public's interest, is described throughout this brief.

The sixth and final *TRAC* guideline states that "the court need not 'find any impropriety lurking behind agency lassitude in order to hold that agency action is 'unreasonably delayed."' *Id.* (quoting *Public Citizen Health Research Group v. FDA*, 740 F.2d 21, 34 (D.C. Cir. 1984)). The delay in this case is reason enough to grant the Writ.

III. BIOVAIL WILL SUFFER IRREPARABLE HARM WITHOUT 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. (Rowland Decl. at ¶¶ 3-6.) If FDA is permitted to simultaneously announce denial of Biovail's Citizen Petition and issue final approval of an ANDA for a generic version of WELLBUTRIN XL®, Biovail would be seriously harmed before judicial review of the denial could be accomplished.

Biovail's Citizen Petition (Perra Decl. Ex. B) lays out the danger that the public may be exposed to unacceptable increased risks of *grand mal* seizures unless FDA employs the criteria Biovail urges for assessing applications for approval of generic versions of WELLBUTRIN XL®. If a generic drug posing these serious risks reaches the market, the potential harm to Biovail is enormous. An increase in seizures in patients treated with bupropion will have impacts not limited to the manufacturer of the dispensed generic product, but will inevitably reach WELLBUTRIN XL® as well. (Rowland Decl. ¶ 7.) In many states, for example, prescriptions written for "WELLBUTRIN XL" will be filled with the generic and the consumer is not even informed that a pharmacy has provided a generic product rather than Biovial's product. (*Id.*) The association of "WELLBUTRIN" with "risk of seizure" in these

circumstances will be unavoidable, will tarnish Biovail's product, and will reduce the value of its immensely important product in a manner that can never be recompensed. (*Id.*)

Physicians too will inevitably be affected by the marketing of an unsafe generic version of WELLBUTRIN XL®. Some as a result will prescribe other bupropion products; some will be driven to try competitive products that do not contain bupropion. (Rowland Decl. ¶ 9.) There is no reason to expect that even the prompt removal of the unsafe product from the market will enable WELLBUTRIN XL® to regain its reputation and market share in full.

And, this Court has recognized how quickly generic drugs, once approved, saturate the marketplace, and how devastating 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.

If FDA does not act on Biovail's Citizen Petition and provide notice of that action prior to approving any ANDA for a generic version of WELLBUTRIN XL®, then subsequent judicial review of a denial of the Petition would follow rather than proceed harm to Biovail. The Citizen

Petition relates to the criteria that Biovail believes must be applied by FDA *before* approving the ANDA. If FDA agrees with the need to apply such criteria, it easily could—and should—approve the Petition and give notice to Biovail and others now.

If FDA denies the Biovail Citizen Petition in whole or in part, it should do so and give Biovail notice of doing so with sufficient time and explanation to allow Biovail to determine whether it should seek judicial review of such action as being unlawful. Once that ANDA is approved, the allegedly improperly approved generic drug could immediately be in distribution, a factor over which Biovail will have no realistic control. Biovail will have to challenge simultaneously *both* FDA's denial of its Petition and the Agency's approval of the ANDA. Moreover, Biovail would be forced to immediately seek and obtain from this Court a temporary restraining order ("TRO") against implementing FDA's final approval of the ANDA in question. Even if this difficult and unfair burden were overcome, it is unlikely that a TRO would take effect before Biovail suffered irreparable tarnishment to the reputation of the brand Wellbutrin XL®. It is also unlikely that a TRO would take effect before the distribution of the potentially dangerous generic version of WELLBUTRIN XL®. The only way such harm can be avoided in this case (and similar situations) is to require the FDA to comply with its regulation, and to decide Citizen Petitions prior to rendering its decision on ANDAs.

In addition to the economic injury that FDA would be inflicting on Biovail, denial of due process is in and of itself an irreparable harm. The deprivation of a constitutional right such as due process "for even minimal periods of time, unquestionably constitutes irreparable injury." *Elrod*, 427 U.S. at 373.

IV. THERE IS NO COGNIZABLE HARM TO OTHERS WITH A SUBSTANTIAL INTEREST

While Biovail readily recognizes the importance of the availability of generic drugs to the public, it is nonetheless entitled to due process and judicial review of FDA action that would have such significant and irreparable adverse effects on its business. On balance, the harm that may be suffered by other parties if a preliminary injunction is granted is nonexistent, or at least greatly outweighed by the irreparable harm that would be suffered by Biovail absent an injunction. FDA can suffer no cognizable harm as a result of an injunction imposed on account of its violation of its own regulations and due process.

Nor will any person that has submitted an ANDA clearly be harmed by the preliminary injunction requested here. Biovail seeks only that FDA act on its pending Citizen Petition and provide very short notice of that action prior to issuing final approval of any ANDA for a generic version of WELLBUTRIN XL®. Biovail does not ask that FDA be enjoined from approving any ANDA or from taking any particular action on the Biovail Citizen Petition. Even if approval of such an ANDA were delayed for awhile by granting an injunction, the delay at the most would be one week and any harm that would be caused by that delay would not rise to the level of the harm that would be caused by denying Biovail's administrative and constitutional law rights and potentially subjecting vulnerable members of the public to health risks.

V. THE PUBLIC INTEREST FAVORS GRANTING INJUNCTIVE RELIEF

Citizen Petitions often raise safety and efficacy issues concerning generic drugs. Biovail's Citizen Petition in particular suggests certain criteria that Biovail believes should be applied to any ANDA for a generic version of WELLBUTRIN XL®, and failure to do so may result in approval of a generic version of WELLBUTRIN XL® that is not bioequivalent to the innovator drug. Such approval would present potential health risks to patients suffering from

MDD and Seasonal Affective Disorder who use the generic, possibly including the aforementioned life-threatening risks associated with unintended delivery of an improper dose of bupropion. Forcing FDA to act on such Citizen Petitions and provide notice of such action prior to final approval of ANDAs helps to ensure that only safe and efficacious generic drugs are made available to the public and will contribute to public confidence in the Agency.

If FDA is permitted to prevent effective judicial review of denials of Citizen Petitions such as Biovail's, the bioequivalence determination of a potentially dangerous generic drug may not be challenged until after that drug has already been made available to the public. The public interest strongly favors abolishing FDA's practice of delaying action, or at least notice of action, on Citizen Petitions seeking to affect the ANDA approval process until after issuing final approval of ANDAs.

Further, injunctions can serve the public interest "by preserving the Plaintiffs' right to meaningful judicial review." *Ugine-Savoie Imphy v. United States*, 121 F. Supp. 2d 684, 690 (Ct. Int'l Trade 2000). The ultimate requirement of due process is "'that an individual be given an opportunity for a hearing *before* he is deprived of any significant property interest.'" *Cleveland Bd. of Educ. v. Loudermill*, 470 U.S. 532, 542 (1985) (quoting *Boddie v. Connecticut*, 401 U.S. 371, 379 (1971)).

If FDA approves an ANDA for a generic version of WELLBUTRIN XL® prior to denying and providing Biovail notice of denial of its Citizen Petition, Biovail will almost certainly be deprived of its property interest in WELLBUTRIN XL® without due process of law, including effective judicial review. Allowing FDA to so deny Biovail due process also runs afoul of the "strong public interest in meticulous compliance with law by public officials." *Fund for Animals, Inc. v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993).

CONCLUSION

For the reasons stated above, Biovail respectfully requests that the Court issue a temporary restraining order and preliminary injunction in the form submitted herewith.

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Respectfully submitted,

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