IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

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

REPLY IN SUPPORT OF PLAINTIFFS' SECOND MOTION FOR A TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION

Plaintiffs Biovail Corporation and Biovail Laboratories International SRL (collectively, "Biovail") respectfully submit this reply brief in support of their second motion for a temporary restraining order and preliminary injunction.

INTRODUCTION

The federal Food, Drug and Cosmetic Act ("FDCA") allows generic drug companies such as Intervenors[1] here to rely on the research and testing performed for a branded drug, but it also requires (with certain limited exceptions not applicable here) a generic product to use the same label as a branded drug. The same-label requirement is a crucial part of the statutory

[1] The term "Intervenors" refers to Anchen Pharmaceuticals, Inc. ("Anchen"); Teva Pharmaceuticals USA, Inc. ("Teva"); and Impax Laboratories, Inc. ("Impax"), all of whom have been granted leave to intervene in this case.

scheme, and is essential to allow fulfillment of the statutory purpose of free substitution of generic equivalents for their branded counterparts. Physicians, pharmacists and patients familiar with the brand label could not safely substitute the generic for the brand without the assurance that the information about safety, efficacy, dosages, warnings, etc., on the generic product's label was "the same."

Nothing in this statutory scheme, however, permits a generic drug to be released on the market with a label that is not truthful and accurate. Quite the contrary, understanding the statutory scheme underscores the importance of truthful labeling—the health and safety of the patient population depends upon it. Yet Defendant U.S. Food and Drug Administration's ("FDA") recent approval of generic versions of WELLBUTRIN XL® has authorized a dangerously false label. Specifically, FDA has approved a label which falsely implies that studies have been conducted on the generic versions of WELLBUTRIN XL® demonstrating that the risk of seizures associated with those products is similar to the risks associated with earlier immediate-release and sustained-release formulations of WELLBUTRIN. In fact, it is admitted here that such studies have not been conducted. This stated basis for concluding that the risk of seizure is acceptably low for these generic products does not in fact exist.

FDA does not have statutory power to override the statutory requirement that labels be "the same," or that they be truthful. Nothing about FDA's expertise allows it to decide that a label claiming a non-existent basis for safety is acceptable. FDA has clearly exceeded its powers in an area where no deference is due it and its action should be preliminarily enjoined by this Court.

When it submitted its moving papers, Biovail had not yet seen the actual label approved by FDA for generic WELLBUTRIN XL®. The opposition papers include a copy of the FDA-

approved label which—on its face—demonstrates why Biovail should prevail on its injunction application. As shown below, FDA has wrongfully authorized generic drugs to enter the market with a label that falsely and misleadingly implies that the generic product has been tested for the risk of seizure in ways that it indisputably has not. This approval violates the clear statutory prohibition against misbranding of drug products. Accordingly, and because of the substantial risk of irreparable harm that FDA's violation of these unambiguous statutory provisions has caused to both Biovail and to the public, Biovail is entitled to preliminary injunctive relief.

PRELIMINARY STATEMENT

The opposition papers submitted by FDA and by Intervenors misstate the basis of Biovail's motion, arguing that Biovail has not established arguments Biovail never made in the first place.[2] Biovail's motion does not question FDA's scientific expertise, nor does it ask this Court to be the "chemist, biologist, or statistician that [it is] qualified neither by training nor experience to be . . . ." *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976). Nor does Biovail seek to undermine the bioequivalence standards contemplated by the Hatch-Waxman Amendments to the FDCA. Instead, Biovail asks this Court to enforce simple, unambiguous statutory requirements concerning labeling that FDA has chosen to ignore in its haste to bring generic versions of WELLBUTRIN XL® onto the market.

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[2] As a threshold matter, FDA's and Intervenors' argument that Biovail is seeking to relitigate issues that have already been decided is completely without merit. The issues raised by Biovail's second motion for injunctive relief are distinct from the legal issues raised by its first such motion, the latter of which challenged FDA's historical practice—since confirmed by the agency's conduct — of denying citizen petitions on the same day that it grants the ANDAs to which those petitions relate thereby often frustrating petitioners' ability to obtain meaningful judicial review. Biovail's recent litigation against FDA in the U.S. District Court for the District of Maryland also involved different issues than those presented here. In that suit, Biovail challenges FDA's decision to allow Impax to manufacture a generic version of WELLBUTRIN XL® during the pendency of patent infringement litigation against Impax. *See* 21 U.S.C. § 355(j)(5)(B)(iv) (requiring that FDA delay action on an ANDA for thirty months if the applicant has been sued for patent infringement).

Congress forbids drugs to be released on the market unless and until FDA has ensured that their labeling—including statements regarding risks and contraindications—is truthful and accurate. Further, in the case of generic drugs (which their manufacturers seek to market as substitutes for the reference listed drug ("RLD") they seek to copy), Congress requires that the labeling must be "the same" as the RLD. Taken together, these requirements reflect a core purpose of the statutory scheme: FDA, in approving a generic drug, is *not* making new findings of safety and efficacy, but is merely determining that the generic drug is bioequivalent to the RLD, and thus uses the RLD's approved label. The "same labeling" requirement provides physicians and patients the comfort that they may use the generic and RLD drugs interchangeably for their treatment needs, without imposing on the public the burden of independently analyzing the differences in the two drugs and determining whether such differences require different treatment.

Here, however, FDA has approved a label that, in providing warnings about the incidence of seizure, states there have been studies of the generic version of WELLBUTRIN XL® that have demonstrated its bioequivalence to the immediate- and sustained-release formulations of the drug. *It is undisputed that this statement is false.* There have been no such studies. WELLBUTRIN XL® has undergone such studies, and so states on the label—but the generic versions have not. Yet a patient or physician receiving the generic product will reasonably understand the FDA-approved label to mean that the product in the generic bottle has been studied for incidence of seizure. Because it has not (and because the studies conducted on WELLBUTRIN XL® cannot simply be transferred over to the generic product), the label at issue is not only not "the same," but is dangerously misleading.

FDA and Intervenors have taken the position that, because the generic versions have demonstrated bioequivalence to WELLBUTRIN XL®, the generic label can falsely claim to have been tested for bioequivalence as compared to other drugs merely because WELLBUTRIN XL® was the subject of such studies. But establishing bioequivalence does not permit a generic manufacturer to ignore the unambiguous statutory requirement that its label be "the same" as the market its innovator drug. More fundamentally, it does not permit the generic manufacturer to market its drug with a label that violates that statutory requirement that a drug's label be truthful and accurate.

In the end, FDA's scientific expertise does not allow the agency to choose between those statutory requirements it deems worth obeying and those it believes it can disregard on the ostensible basis that it is seeking to promote competition.[3]

ARGUMENT

I. THE FDA-APPROVED LABEL FOR GENERIC VERSIONS OF WELLBUTRIN XL® IS FALSE AND MISLEADING

A. The FDCA Prohibits False or Misleading Labeling

The FDCA states that a drug is "misbranded" if "its labeling is false or misleading in any particular." 21 U.S.C. § 352(a). "[I]n determining whether the labeling . . . is misleading there shall be taken into account . . . representations made *or suggested* by statement, word, design,

[3] FDA and Intervenors characterize Biovail's sole motivation for the present litigation, and for its submission of a Citizen Petition, as a method to improperly extend the company's lawful exclusive rights over the manufacture of extended-release bupropion tablets. The fact is, however, that FDA agreed with certain safety concerns raised in Biovail's Citizen Petition, which caused the agency to require the submission of additional scientific data from ANDA applicants seeking to market a generic version of WELLBUTRIN XL®. *See* FDA Opp'n at 13 n.18 (admitting that FDA agreed with Biovail's concern that in assessing the bioequivalence of generic bupropion extended-release tablets to WELLBUTRIN XL®, ANDA applicants should be required to conduct a "fed" bioequivalence study in addition to a "fasted" study in order to demonstrate the absence of a "food effect" on the release of bupropion in the generic version); Segroves Decl. Ex. A at 19 (Dec. 14, 2006 FDA Response to Citizen Petition granting Biovail petition in part, and requiring ANDA applicants, among other things, to measure the metabolite hydroxybupropion in their bioequivalence studies).

device, or any combination thereof . . . ." *Id.* § 321(n) (emphasis added). In the case of generic versions of RLDs already on the market, the Abbreviated New Drug Application ("ANDA") for the generic must show both that the drug itself is "bioequivalent to the [RLD]," *id.* § 355(j)(2)(A)(iv), and that the "labeling proposed for the new drug is *the same* as the labeling approved for the [RLD]," *id.* § 355(j)(2)(A)(v) (emphasis added). The "same labeling" requirement is not merely a technicality. As FDA has recognized, because patients and physicians often use RLDs and generic versions interchangeably, it is critically important that the drugs—including the representations, warnings and contraindications reflected on the labeling—actually *be* interchangeable. To allow variations in the labeling subjects patients to unnecessary risks. *See* 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992) ("FDA believes that a generic drug product approved on the basis of studies conducted on the listed drug and whose labeling is inconsistent with the listed drug's labeling might not be considered safe and effective for use under the conditions prescribed, suggested, or recommended in the listed drug's labeling.") Thus, FDA cannot approve an ANDA unless the proposed label is (1) "the same" as that of the RLD *and* (2) truthful and accurate.

B. The Label Approved by FDA Is False and Misleading

Despite the unambiguous statutory requirement prohibiting false or misleading labeling, FDA and Intervenors ask this Court to rule that an ANDA may be approved with a label that is, in fact, false and misleading with respect to the generic drug's properties related to the drug's potential risks. Specifically, FDA and Intervenors ask this Court to rule that the FDA-approved label for generic versions of WELLBUTRIN XL® contains only "permissible differences" from WELLBUTRIN XL®'s label, and that it therefore qualifies as accurate. But the generic label is not accurate; it contains assertions that are false and misleading as applied to that drug.

Most critically, WELLBUTRIN XL®'s label accurately states the following with respect to the drug's bioequivalency to previous versions of the drug:

> Although there are no independent trials demonstrating the antidepressant effectiveness of WELLBUTRIN XL, studies have demonstrated similar bioavailability of WELLBUTRIN XL to both the bioavailability under steady-state conditions, i.e., WELLBUTRIN XL 300 mg once daily was shown to have bioavailability that was similar to that of 100 mg 3 times daily of the immediate-release formulation of bupropion and to that of 150 mg 2 times daily of the sustained-release formulation of bupropion, with regard to both peak plasma concentration and extent of absorption, for parent drug and metabolites.
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> . . .
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> *As WELLBUTRIN XL is bioequivalent to both the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion, the seizure incidence with WELLBUTRIN XL, while not formally evaluated in clinical trials, may be similar to* that presented below for *the immediate-release and sustained-release formulations of bupropion.*

Perra Decl. Ex. B at 5, 8 (emphasis added).[4] In other words, WELLBUTRIN XL®'s label explains that the pills in the WELLBUTRIN XL® bottle have been shown by studies to have a similar bioequivalence to the two previous formulations of the drug, and, as a result, accurately inform patients and physicians that the pills in the WELLBUTRIN XL® bottle may have a seizure incidence similar to that found with the two previous formulations.

The FDA-approved label for generic versions of WELLBUTRIN XL® merely replaces "WELLBUTRIN XL" with "bupropion hydrochloride extended-release tablets (XL)," thus falsely implying to the reader that the pills in the generic drug's bottle have been studied and may be compared to seizure incidence similar to that in previous formulations:

> Although there are no independent trials demonstrating the antidepressant effectiveness of bupropion hydrochloride extended-release tablets (XL), studies have demonstrated similar bioavailability of bupropion hydrochloride extended-

[4] 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.

> release tablets (XL) to both the immediate-release formulation and to the sustained-release formulations of bupropion under steady-state conditions, i.e., bupropion hydrochloride extended-release tablets (XL) 300 mg once daily was shown to have bioavailability that was similar to that of 100 mg 3 times daily of the immediate-release formulation of bupropion and to that of 150 mg 2 times daily of the sustained-release formulation of bupropion, with regard to both peak plasma concentration and extent of absorption, for parent drug and metabolites.
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> . . .
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> *As bupropion hydrochloride extended-release tablets (XL) are bioequivalent to both the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion, the seizure incidence with bupropion hydrochloride extended-release tablets (XL), while not formally evaluated in clinical trials, may be similar to* that presented below for *the immediate-release and sustained-release formulations of bupropion.*

Rurka Decl. Ex. 9 at 4, 7 (emphasis added).[5]

This statement, as applied to the generic drug, is false and misleading. The pills in the generic's bottle are *not* bioequivalent to the immediate- and sustained-release formulations of bupropion and have *not* been shown to have a similar bioavailability to the immediate- and sustained-release formulations of bupropion. By implying that the pills in the generic bottle will have a similar antidepressant effect and may have a similar risk of seizure as earlier formulations of WELLBUTRIN XL®, without any studies to confirm that fact, the labeling approved by FDA for the generic violates the misbranding prohibition of 21 U.S.C. § 352(a).[6]

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[5] References to the "Rurka Declaration" are to the December 28, 2006 Declaration of Maureen L. Rurka, a copy of which was attached as an exhibit to Anchen's opposition.

[6] Nor would the false and misleading nature of the label be cured were FDA to require the generic drug to refer to WELLBUTRIN XL®, rather than the generic name of the drug, on the label. The reasonable implication would remain the same—and would remain inaccurate: the reader would understand that the pills in the generic's bottle had been studied against earlier versions of WELLBUTRIN's drug with respect to risk of seizure. It is undisputed that the generic drug has not been so studied, and thus, the label would remain misleading and in violation of the statute even if revised to be technically accurate. Rather, in order to meet the statutory requirements of truthfulness and accuracy, the generic label would have to disclose that it had been found to be bioequivalent, within acceptable variance ranges, to WELLBUTRIN XL®, that WELLBUTRIN XL® had been studied and found to meet bioequivalence standards with respect to earlier formulations, and thus, seizure incidences under WELLBUTRIN XL® may be similar to earlier formulations; however, no conclusions could be drawn with respect to the generic drug's bioequivalency to earlier formulations, and thus no conclusions could be drawn regarding its

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In sum, because FDA's decision violates the plain meaning of the FDCA prohibiting false or misleading labeling, this Court "must give effect to the unambiguously expressed intent of Congress" and set aside the agency's decision as arbitrary, capricious and otherwise not in accordance with law. *See Chevron, U.S.A. Inc. v. Natural Res. Def. Council*, 467 U.S. 837, 842-43 (1984); *see also Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120, 125 (D.C. Cir. 2006) (rejecting FDA interpretation of FDCA under *Chevron* step-one).

II. FDA'S AND INTERVENORS' ARGUMENTS ABOUT BIOEQUIVALENCY DO NOT CURE THE FALSE AND MISLEADING LABELING

FDA and Intervenors contend that the label of the generic drug is not false and misleading because the generic drug has been demonstrated to be bioequivalent to WELLBUTRIN XL®. They argue that such bioequivalence entitles the generic drug to rely on WELLBUTRIN XL®'s own bioequivalence studies. They conclude by accusing Biovail of "flip[ping] the ANDA approval process on its head," FDA Opp'n at 25, and of attempting to "shoehorn additional bioequivalence testing requirements through the labeling requirement," Teva Opp'n at 14. But it is FDA and Intervenors, not Biovail, whose arguments would violate statutory and agency requirements of bioequivalence, and permit the release of drugs onto the market with unsubstantiated, and inaccurate, safety warnings.

As explained in Biovail's moving papers (at p. 15)—and not challenged by any of the opposition papers—a finding of "bioequivalence" is permitted with up to a 5% chance of variation between the two drugs. Thus, a bioequivalence between Drug A and Drug B, and a bioequivalence between Drug B and Drug C, does not establish that Drugs A and C are

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risk of seizure incidences. Clearly, such a label would not meet the "sameness" requirement and would be unacceptable, and FDA would have abused its discretion in permitting a drug on the market that disclosed this lack of studies. FDA and Intervenors should not be permitted to approve this drug merely by crafting the label in a vague and misleading manner so as to avoid making the drug's untested nature explicit.

bioequivalent to each other. Accordingly, the label of the generic drug, implying that its generic formulation has been shown in studies to be bioequivalent to earlier formulations, is false and misleading.

Further, this risk of variation could cause significant harm to the public. FDA has promulgated specific parameters for a finding of bioequivalence between two drug products, which take into account the potential for variables and differences in, for example, the absorption rate of the active ingredient of the drug into the bloodstream on an hour-by-hour basis. A generic drug may be found to be bioequivalent to a branded drug where certain patients may show absorption rates of as low as 85% that of the branded drug, or, alternatively, as high as 125% of the branded drug, provided that the average rate falls within permissible parameters. *See* FDA, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations* 23 (Mar. 2003) (noting that "[u]nless otherwise indicated by a specific guidance, this guidance recommends that the traditional [bioequivalency] limit of 80 to 125 percent for non-narrow therapeutic range drugs remain unchanged for the bioavailability measures . . . of narrow therapeutic range drugs").[7]

Here, WELLBUTRIN XL® has established through studies bioavailability and bioequivalence with respect to seizure incidence to the earlier formulations. In other words, WELLBUTRIN XL®'s absorption rates fell within this acceptable range. If, for example, WELLBUTRIN XL®'s rates fell at the high end of the parameter as compared to earlier formulations (though still within a range FDA has determined acceptable), and the generic bupropion drug falls within the high range of the parameter as compared to WELLBUTRIN

[7] Available at http://www.fda.gov/cder/guidance/5356fnl.pdf.

XL®, it is possible that the generic version is *not* bioequivalent to earlier formulations, and indeed, could deliver significantly more of the active ingredient to a patient—outside acceptable FDA parameters. Given that the drug carries a risk of seizures within FDA-acceptable parameters, the danger from allowing potential over-dosing is not immaterial. Conversely, if both bioequivalence studies are at the low end, the risk of under-dosing becomes significantly greater and a patient would not be receiving appropriate treatment.

Biovail does not ask this Court to impose a requirement that all generic drugs undergo the identical safety and efficacy testing that an innovator drug has undergone in order to be approved, and FDA's argument to the contrary is a straw man that should be disregarded.[8] Rather, Biovail's argument is limited to the unique situation here, where the innovator drug itself was compelled to undergo certain bioequivalence studies in order to establish its safety and efficacy and the label refers to those studies to inform the doctor and patient about health risks associated with that drug. Those studies do not necessarily transfer to any other bioequivalent products, and FDA is not permitted to approve labels which imply that they do.

By approving a label for the generic drug which implies that it has undergone studies of bioequivalence with regard to seizure risk when it has not, based solely on the fact that the generic drug is bioequivalent to a branded drug which has undergone such studies, FDA has implicitly read the truthful-labeling requirement out of the FDCA. Put differently, FDA's approval is tantamount to a statutory reading that a finding of bioequivalence overrides the requirement that a label be truthful and accurate. This reading violates a cardinal principle of

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[8] Nor does Biovail's motion challenge FDA's conclusion that certain generic drugs are bioequivalent to WELLBUTRIN XL®. Thus, Intervenors' reliance on case law deferring to FDA's expertise in determining the appropriate testing to determine bioequivalence, *see, e.g., Serono Labs. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212 (D.D.C. 1996), is misplaced.

statutory construction. A statute must be read so as to give effect to every clause and word. *Williams v. Taylor*, 529 U.S. 362, 364 (2000); *see also Nutritional Health Alliance v. FDA*, 318 F.3d 92, 105 (2d Cir. 2003) (finding that FDA's construction of statutory provisions impermissibly relied on piecemeal construction and failed to give meaning to other important terms). The arguments by FDA and Intervenors, therefore, must fail.

III. THE NARROW STATUTORY EXCEPTIONS TO THE "SAME-LABELING" REQUIREMENT DO NOT ALLOW APPROVAL OF THE FALSE AND MISLEADING LABEL AT ISSUE HERE

Nor can FDA and Intervenors rely on the argument that the generic label merely reflects "permissible" differences permitted by the narrow statutory exceptions to the "same-labeling" requirement of 21 U.S.C. § 355(j)(2)(A)(v). Neither exception authorizes the approval of a false or misleading label. Rather, the existence of these exceptions supports the reasonable inference that no other exceptions are permissible.

First, differences in labeling are allowed when an applicant wants to submit an ANDA for a new drug that has a different active ingredient or whose route of administration, dosage form or strength differ from that of the RLD. 21 U.S.C. § 355(j)(2)(A)(v); *see also id.* § 355(j)(2)(C). Neither FDA nor Intervenors argue that the first exception applies to the instant case.

The second exception to the same-labeling requirement allows for nonsubstantive changes made necessary "because the new drug and the listed drug are produced or distributed by different manufacturers." *Id.* § 355(j)(2)(A)(v). FDA and Intervenors apparently believe that the false and misleading generic label may be approved under this exception. FDA and Intervenors are incorrect.

The central (and fundamentally flawed) thesis of FDA's argument is relegated to a footnote in its opposition. According to FDA: "When a generic drug's labeling describes . . .

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." FDA Opp'n at 9 n.12.

Where, as here, the RLD has met certain safety and efficacy requirements by demonstrating comparative bioequivalence to other formulations rather than through independent testing of the RLD, permitting FDA to allow, as a "permissible difference," labeling for the generic product that substitutes the name of the generic for the name of the RLD in alleging that such bioequivalence had been established violates the plain language, purpose and intent of the "same labeling" requirement. FDA may not use its regulations regarding ANDA labeling to make additional safety and efficacy findings—much less to permit the labeling on a generic drug to assert safety tests have been conducted which have not in fact been conducted. This interpretation is well beyond the scope of FDA's authority with respect to approving ANDA labeling. *See* 21 U.S.C. § 355(j)(4)(G).

Indeed, both Congress and FDA have recognized that this statutory exception is substantially more narrow than FDA and Intervenors now seek to claim. The House of Representatives committee responsible for creating the same-labeling requirement explained:

> For example, the name and address of the manufacturers would vary as might the expiration dates for the two products. Another example is that one color is used in the coating of the listed drug and another color is used in that of the generic drug. The FDA might require the listed drug maker to specify the color in its label. The generic manufacturer, which has used a different color, would have to specify a different color in its label.

H.R. Rep. No. 98-857, pt. I, at 22 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647, 2655. The Committee Report shows no intent to permit substantive changes to the label, such as assertions regarding what sort of bioequivalence testing and studies have actually been done. Similarly,

when FDA first promulgated its regulation interpreting the FDCA's same-labeling requirement, FDA recognized that the requirement's two statutory exceptions were to be narrowly construed. *See* 54 Fed. Reg. 28,872, 28,878 (July 10, 1989) ("FDA emphasizes that the exceptions to the requirement of 'same labeling' are limited."); *id.* at 28,884 ("FDA emphasizes that the exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited.").[9]

FDA has recognized that the same-labeling requirement was not a procedural technicality, stating, "Because an ANDA must have labeling that is the same as the [RLD], FDA believes that a generic drug product approved on the basis of studies conducted on the listed drug and whose labeling is inconsistent with the listed drug's labeling might not be considered safe and effective for use under the conditions prescribed, suggested, or recommended in the listed drug's labeling." 57 Fed. Reg. at 17,961. FDA went so far as to reject comments suggesting that the same-labeling requirement should be relaxed to allow for the inclusion of *additional* warnings or safety-related information. *See id.* The agency did so on the basis that "[c]onsistent labeling [would] assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart." *Id.*

Thus, the purpose of the same-labeling requirement is not furthered (to the contrary, it is violated) by the approval of this false and misleading generic label. If, as FDA contemplates, this label assures physicians, health professionals and consumers that the generic version of

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[9] Moreover, as Teva concedes, it is an elementary principle of statutory construction that such specific exceptions preclude an inference of more general exceptions. *See* Teva Opp'n at 14 (citing *North Am. Catholic Educ. Programming Found., Inc v. FCC*, 437 F.3d 1206, 1209 (D.C. Cir. 2006)). Thus, that the FDCA contemplates a difference in labeling to, for example, reflect a different tablet color for generic and innovator drugs, supports the inference that more fundamental differences, such as different assertions regarding the types of studies that have been done on the generic and innovator drugs, are neither contemplated by nor permitted by the statute.

WELLBUTRIN XL® is as safe and effective as WELLBUTRIN XL®, it does so under false pretenses, and creates unnecessary risks for those physicians, health professionals and consumers.

IV. BIOVAIL HAS SATISFIED THE OTHER ELEMENTS FOR PRELIMINARY INJUNCTIVE RELIEF

In approving ANDAs for generic versions of WELLBUTRIN XL® whose labels are false and misleading, FDA has violated the plain meaning of the FDCA. *See* 21 U.S.C. § 352(a). Biovail therefore possesses a "particularly strong" likelihood of success on the merits. As a result, the burden upon Biovail to bring forth evidence related to the remaining preliminary injunctive relief factors—irreparable harm, the balance of harms and the public interest—is significantly reduced. *See Chaplaincy of Full Gospel Churches v. England*, 454 F.3d 290, 297 (D.C. Cir. 2006) (finding that four injunctive relief factors should be balanced and a "particularly strong" showing in one area can justify an injunction "even if the showings in other areas are rather weak"); *Cuomo v. U.S. Nuclear Regulatory Comm'n*, 772 F.2d 972, 974 (D.C. Cir. 1985) (per curiam) (holding that "[p]robability of success is inversely proportional to the degree of irreparable injury evidenced" such that injunctive relief "may be granted with either a high probability of success and some injury, or *vice versa*").

Biovail's moving papers (at pp. 17-20) adequately demonstrate that the company will be irreparably harmed if this Court does not temporarily enjoin FDA from approving any additional ANDAs for generic WELLBUTRIN XL® and stay the effectiveness of any such prior approvals. The sale of WELLBUTRIN XL® constitutes more than 75% of Biovail's total profits and

approximately 42% of Biovail's sales. *Id.* at 17 (citing Howling Decl. ¶¶ 6-7).[10] 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, e.g.*, *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).[11] This type of economic harm is irreparable 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).[12]

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.[13] If not, there is a significant risk

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[10] References to the "Howling Decl." are to the December 17, 2006 Declaration of Kenneth G. Howling, a copy of which was attached as Exhibit 3 to Biovail's second motion for a temporary restraining order and preliminary injunction.

[11] Anchen's attempt to distinguish these cases is unavailing, as Biovail has made a strong showing that FDA's improper conduct has and will continue to directly harm Biovail's reputation and has and will continue to cause Biovail to lose customer goodwill and important business relationships. *See* Anchen Opp'n at 26 n.6.

[12] FDA and Intervenors rely heavily on Biovail's statements to analysts that it has been preparing for the launch of generic products into the marketplace. That Biovail has the fiscal responsibility to minimize economic injury from the entry of generics, however, does not somehow lessen the potentially devastating injury from the entry of an unauthorized and potentially dangerous generic into the marketplace. If generic versions of WELLBUTRIN XL® flood the marketplace, and those versions carry with them a greater risk of seizures because they are inadequately tested and improperly labeled, the reputational harm to bupropion products generally—including not least WELLBUTRIN XL® as the most well-known—could be devastating, and is not something contemplated in the public statements on which FDA and Intervenors rely.

[13] References to the "Silverstone Decl." are to the December 17, 2006 Declaration of Dr. Peter H. Silverstone, a copy of which was attached as Exhibit 4 to Biovail's second motion for a temporary restraining order (continued)

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, as FDA itself recognized when it first promulgated regulations interpreting the same-labeling requirement. *See* 57 Fed. Reg. at 17,961 ("FDA believes that a generic drug product approved on the basis of studies conducted on the listed drug and whose labeling is inconsistent with the listed drug's labeling might not be considered safe and effective for use under the conditions prescribed, suggested, or recommended in the listed drug's labeling.")

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. 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.

The public interest in cheaper drugs is, of course, outweighed by the significant public health risks in allowing a mislabeled product to remain on the market. As this Circuit has previously noted, if an ANDA was improperly granted because the safety standards of the FDCA

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and preliminary injunction. FDA challenges the Silverstone Declaration as being outside the administrative record. *See* FDA Opp'n at 29 n.28. It is well-settled that the administrative record may be supplemented (1) when agency action is not adequately explained in the record before the court; (2) when the agency failed to consider factors that are relevant to its final decision; (3) when a case is so complex that a court needs more evidence to enable it to understand the issues clearly; or (4) in cases where relief is at issue, especially at the preliminary injunction stage. *Esch v. Yeutter*, 876 F.2d 976, 991 (D.C. Cir. 1989) (citing Steven Stark & Sarah Wald, *Setting No Records: The Failed Attempts to Limit the Record in Review of Administrative Action*, 37 Admin. L. Rev. 333, 345 (1984)). Because any number of the foregoing apply to the instant case, FDA's objection should be overruled.

were not met, "then the public interest balance would plainly weigh in favor of an injunction." *Serono Labs. v. Shalala*, 158 F.3d 1313, 1326 (D.C. Cir. 1998). Here, because labeling has been improperly approved which implies certain safety standards were met when those safety standards were never tested, the public interest balance weighs decidedly in favor of Biovail's requested relief.

CONCLUSION

For the reasons stated above and in Biovail's moving papers, 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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