HellerEhrman LLP

James N. Czaban
Chairman, FDA Practice Group
(202) 912-2720
james.czaban@hellerehrman.

February 23, 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Docket No. 2005P-0498

Comments of Impax Laboratories, Inc. In Opposition to Biovail's Citizen Petition

These comments are respectfully submitted on behalf of Impax Laboratories, Inc. in opposition to the above-referenced Citizen Petition filed on December 20, 2005 by Biovail Corporation. Biovail's Petition requests that FDA refuse to approve any Abbreviated New Drug Application (ANDA) for bupropion HCl extended release tablets (generic versions of Wellbutrin® XL) unless the ANDA includes additional bioequivalence data that goes beyond that which is authorized and necessary for FDA approval. Biovail's petition is objectively baseless, as its arguments rely on unsubstantiated theories lacking any scientific support, and misapplication of governing legal and regulatory standards. Thus, for the specific reasons set forth herein, the Petition should be promptly denied.

INTRODUCTION

Abusive and anti-competitive FDA Citizen Petitions have become an increasingly common problem in the last several years as brand name drug companies have sought to compensate for dwindling new product pipelines and the failure to focus corporate strategy on discovering and developing truly innovative new drug products for the benefit of American consumers. As FDA Chief Counsel Sheldon Bradshaw recently noted, FDA has received many citizen petitions "that appear designed not to raise timely concerns with respect to the legality or scientific soundness of approving a drug application, but rather to delay approval by compelling the agency to...consider arguments raised in the petition regardless of whether the petitioner could have made those very arguments months and months before," a trend that Mr. Bradshaw has "found...to be very troubling."[1] Biovail's Petition is nothing more than a last-minute petition seeking to extend a monopoly on an overpriced brand name drug in a crowded therapeutic field through the abuse of governmental processes to slow the market entry of equivalent but more affordable generic versions of the branded product. In other words, the Biovail petition is a quintessential example of the very type of "very troubling" petition described by Mr. Bradshaw.

[1] Remarks of Sheldon Bradshaw at the Generic Pharmaceutical Association's first annual Policy Conference, Sept. 19, 2005.

2005P-0498

C1

FDA has a comprehensive and well-established set of regulations and policies governing the review and approval of ANDAs by which competitors seek approval of generic versions of previously approved brand name drugs. These regulations and policies are based on FDA's high level of technical and legal expertise, and many years of experience in bioequivalence standards for generic drugs, including extended release drug products. Pursuant to its delegated authority and technical expertise, FDA has accepted ANDAs (including Impax's ANDA) for bupropion extended release tablet products which include appropriate bioequivalence data. Biovail, in its last minute tactical petition, requests that FDA revisit its longstanding bioequivalence policies, and its decision as to the specific bioequivalence data needed to support approval of generic bupropion extended release products, and instead adopt new, unwarranted, and impermissible standards for generic drug bioequivalence testing and generic drug labeling. Biovail offers no new legal or scientific rationale for its requested actions, nor is there any legitimate basis for Biovail's requests. Accordingly, for the reasons set forth herein below, Biovail's petition should be promptly denied, and FDA should also take remedial action against Biovail for its filing of a frivolous anti-competitive petition.

BACKGROUND

Biovail requests that FDA impose four additional criteria as conditions of approval of generic bupropion HCl extended release tablets:

1. That ANDA applicants conduct bioequivalence studies evaluating plasma levels of not only the parent drug compound, but also the three active metabolites, hydroxybupropion, erythrohydrobupropion, and threohydrobupropion;

2. That proposed generic products be shown through specific studies to be bioequivalent not only to the reference listed drug ("RLD") Wellbutrin® XL, but also to Wellbutrin® SR (a previous extended release product for BID dosing), and the immediate release Wellbutrin® product (dosed TID);

3. That the additional requested bioequivalence studies be conducted at steady-state and evaluate bioequivalence based on AUC, C_{max}, and C_{min}; and

4. That specific data be included in ANDAs to evaluate the effect of alcohol on the performance of the generic drug to ensure the absence of "dose dumping."

As discussed below, Biovail's Petition should be denied because: (1) there is no legal or scientific basis to require Biovail's proposed triple-metabolite bioequivalence testing of proposed generic bupropion extended release tablet products, especially given that Impax has shown its product to be bioequivalent with respect to both the parent drug (bupropion) and the major metabolite, hydroxybupropion; (2) there is no legal or medical basis to require bioequivalence testing against the sustained release and immediate release Wellbutrin® products; (3) steady-state bioequivalence testing is meaningless and unnecessary when comparing two extended release drug products that have the same strength and dosing regimen, such as Wellbutrin® XL and the proposed generic versions; and (4) Biovail incorrectly assumes that generic versions of

Wellbutrin® XL have not been studied to assure the absence of dose-dumping when used with alcohol.

ANALYSIS

I. THERE IS NO LEGAL OR SCIENTIFIC BASIS TO REQUIRE BIOEQUIVALENCE STUDIES OF BOTH THE PARENT DRUG AND ALL THREE OF ITS ACTIVE METABOLITES

Biovail argues that ANDA applicants for generic versions of Wellbutrin® XL should be required to conduct bioequivalence trials and "calculate and evaluate parameters based on concentrations of the parent drug and [all three] active metabolites" – specifically hydroxybupropion, threohydrobupropion, and erythrohydrobupropion – because these metabolites *allegedly* "play a very significant role in the clinical performance of Wellbutrin® XL." Such studies and data are required, according to Biovail, "in order to assure that the generic will provide similar effects" as Wellbutrin® XL. Petition at 1, 7. However, Biovail offers no competent basis to support this requested bioequivalence standard, and indeed, none exists.

A. FDA's Governing Guidance Does Not Mandate Triple-Metabolite Bioequivalence Testing For Generic Bupropion XL Products

Nowhere in the petition does Biovail discuss (much less cite to) FDA's governing Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* (March 2003) (the "BA/BE Guidance"), or the agency's recent and highly relevant citizen petition decision addressing the issue of metabolite bioequivalence standards, in the context of generic anagrelide products. *See* FDA Docket No. 2004P-0365 (FDA Denial of Petition, April 18, 2005) (The "Anagrelide Petition Decision"). Biovail's failure to address the BA/BE Guidance and the Anagrelide Petition Decision is as understandable as it is disingenuous, since the Guidance and the Anagrelide Petition Decision flatly contradict Biovail's position.

The BA/BE Guidance clearly states that "[f]or BE studies, measurement of only the parent drug released from the dosage form, rather than the metabolite, is generally recommended." BA/BE Guidance at 18 (emphasis added). The BA/BE Guidance lists only two scenarios in which FDA may consider an exception to this generally recommended approach, but for generic bupropion XL products, neither exception comes into play, and there is thus no basis for FDA to depart from the Guidance's recommended approach in order to adopt Biovail's requested bioequivalence methodology.

Under the first exception, measurement of a metabolite "may be preferred when parent drug levels are too low to allow reliable analytical measurement." This exception is inapplicable here because the parent bupropion compound is present at levels that are readily and reliably measured. As Biovail itself discloses on its own Contract Research Organization web site, the

limit of quantitation (LOQ) for bupropion (parent drug) is 1.0 ng/ml in human plasma using common validated bioanalytical methods.[2] Such assay sensitivity is more than adequate to allow reliable analytical measurement of circulating parent drug levels. Therefore, there is no basis to require measurement of bupropion metabolites under the first BA/BE Guidance exception to the preferred bioequivalence approach.[3]

The second scenario under the BA/BE Guidance for potentially requiring measurement of metabolite bioequivalence is described as follows:

> A metabolite may be formed as a result of gut wall or other presystemic metabolism. If the metabolite contributes meaningfully to safety and/or efficacy, we also recommend that the metabolite and the parent drug be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to safety and/or efficacy, it does not have to be measured. We recommend that the parent drug measured in these BE studies be analyzed using a confidence interval approach. The metabolite data can be used to provide supportive evidence of comparable therapeutic outcome.

BA/BE Guidance at 18 (emphasis added). FDA made clear in its Anagrelide Petition Decision that the BA/BE Guidance's second exception applies only when there is ***both*** pre-systemic formation of a metabolite, ***and*** the metabolite at issue "contributes meaningfully to the safety and/or efficacy of the drug product." *See* FDA Docket No. 2004P-0365 (FDA Denial of Petition, April 18, 2005) at 3 (emphasis added). Here, Biovail also fails to meet the mandatory elements of the exception.[4]

First, the parent drug and the major metabolite, hydroxybupropion, combined contribute approximately 82% of the overall pharmacologic activity, while the threohydro- and erythrohydro- metabolites contribute only 15% and 3% of the activity, respectively.[5] Thus, the

---

[2] *See* http://www.biovail-cro.com/validatedMethods.htm.

[3] Notwithstanding that measurement of the parent bupropion should be acceptable under the BA/BE Guidance, Impax nevertheless demonstrated that its product is bioequivalent with respect to both the parent bupropion drug, and with respect to the major metabolite hydroxybupropion. These measures are more than adequate to assure a fully bioequivalent, safe and effective generic version of Wellbutrin XL.

[4] In the Anagrelide Petition Decision, FDA rejected a request that generic versions of anagrelide HCL capsules be required to show bioequivalence with respect to the active metabolite 3-hydroxy anagrelide. Even though the Anagrelilde Petition tried to present some data purporting to show that anagrelide fit the BA/BE Guidance's criteria for requiring the measurement of active metabolite bioequivalence, FDA found that evidence to be "rather tenuous" and inadequate to support the petition's request for a metabolite bioequivalence requirement. *See* Anagrelide Petition Decision at p. 4. Here, where Biovail has presented ***no*** evidence whatsoever in support of its similar request, FDA should find no basis to grant Biovail's petition.

[5] The relative contribution of parent and metabolites to the overall activity for bupropion are derived using a composite parameter accounting for the exposure and the activity, defined as the Pharmacological Activity Weighted Composite (PAWC). Note that PAWC was also used to estimate overall activity of bupropion XL given

(Footnote continued)

last two metabolites are considered minor metabolites and their formation by the body presents no medically or legally sound basis for Biovail's proposed triple-metabolite bioequivalence approach. Indeed, the one study Biovail cites in support of its proposed approach noted that the lack of bioequivalence of the metabolites threohydrobupropion and erythrohydrobupropion in Wellbutrin® XL itself was "not considered clinically significant...particularly in the case of erythrohydrobupropion, which has only a minor contribution to the overall pharmacological activity due to its low potency." *See* Summary Report of Study No. AK1BIOVAIL2548, at p. 2 ("Study 2548") (attachment 2 to the Petition).

In addition, given that the absorption of bupropion is quantitative (87% ^{14}C dose is recovered in the urine), the total clearance (CL_{total}) of bupropion can be considered to be the sum of CL_{parent}, $CL_{hydroxybupropion}$, and $CL_{reduction}$ ($CL_{total} = CL_{parent} + CL_{hydroxybupropion} + CL_{reduction}$), where the $CL_{reduction}$ is associated with the formation of the two minor metabolites by reductase enzyme. The latter distribute in multiple tissues but have very low expression in the small intestine (approximately 100 fold lower than in the liver). Hence, when two bupropion products are bioequivalent with respect to bupropion and hydroxybupropion (i.e. equivalence in CL_{parent}, and $CL_{hydroxybupropion}$), they necessarily would be expected to be bioequivalent with respect to the minor metabolites as well (i.e. equivalence in $CL_{reduction}$). This further debunks any basis for Biovail's requested triple-metabolite bioequivalence criteria.

Finally, Biovail's request for a triple-metabolite bioequivalence standard implicitly assumes that a generic drug shown to be bioequivalent with respect to the parent drug (and in the case of Impax's ANDA, also with respect to hydroxybupropion) may nevertheless be *in*equivalent with respect to the other two metabolites. For this to be true, however, there would have to be some reason to suspect that the absorbed bupropion hydrochloride from a generic product would be metabolized differently than the identical parent compound as provided in Wellbutrin® XL. In other words, Biovail suggests that a given amount of its bupropion is chemically different than the same amount of Impax's bupropion. Biovail offers no proof, much less any basis to even speculate, that the molecule known as bupropion hydrochloride metabolizes in such a mysteriously divergent way depending on whose label is on the bottle.

Thus, there is no basis under either exception to the BA/BE Guidance's recommended bioequivalence approach to require separate bioequivalence studies for threohydrobupropion and erythrohydrobupropion, and Biovail's triple metabolite bioequivalence request must be denied.[6]

QD relative to bupropion IR given TID in the Wellbutrin XL SBA (pages 10, 18, and 76, Wellbutrin XL SBA, Clinical Pharmacology and Biopharmaceutics Review).

[6] Biovail's failure to address the BA/BE Guidance also violated FDA's Citizen Petition regulations, which unequivocally require Petitioners to attest, to the best of their knowledge and belief, that the Petition includes representative data and information known to the petitioner that are unfavorable to the petition. 21 C.F.R. § 10.30(b). In this respect, Biovail's Petition suffers the same flaw as the Petition filed by Ferring Pharmaceuticals Inc. with respect to desmopressin drug products, and FDA should, at the minimum, admonish Biovail and its counsel in the same manner that Ferring was admonished for this important procedural violation. *See* FDA Response in Docket No. 2004P-0068, p. 7, n. 19 (July 5, 2005). Even more appropriately, in egregious situations such as this, FDA should consider a policy of temporarily debarring Petitioners and counsel who engage in gross

(Footnote continued)

B. Biovail's Request Has Already Been Considered and Rejected by FDA

FDA is very familiar with the clinical and bioequivalence issues presented by bupropion and its metabolites, based on its prior review and approval of numerous innovator and generic bupropion drug products. The Agency itself has not required Impax to study bioequivalence of the three metabolites,[7] and there is no basis for FDA to now depart from this standard merely because Biovail has filed a last minute anticompetitive petition to block approval of generic versions of Wellbutrin® XL.

C. Triple-Metabolite Bioequivalence Testing Is Not Necessary To Assure Safe And Effective Generic Bupropion Extended Release Tablets

Biovail has not met, and cannot meet, the very high standard of proof that must be required for FDA to accept its radical new bioequivalence proposals for approval of safe and effective generic bupropion extended release products. Biovail has failed miserably in this regard, by raising only the generalized concerns that bupropion is associated with a dose-related risk of seizures, and that the relationship between serum levels of bupropion and its metabolites and the risk of seizure "is not well understood." Petition at 4. Biovail's most specific effort to demonstrate a clinical basis for triple-metabolite bioequivalence studies is a single 3-sentence paragraph that references a single small PK study summary, Petition at 4, yet in that effort Biovail manages to contradict its own position and grossly misrepresent what the cited study summary actually shows. Specifically, Biovail's Petition states that "recent data from ongoing research have led to the investigation of specific metabolites, and their influence on seizure potential. Conclusions on the assessment of bioequivalence in both the fasted and fed states can vary substantially depending on whether the assessment is based on the parent drug or individual metabolites." Petition at 4 (emphasis added), citing Summary Report of Study No. AK1BIOVAIL2548 ("Study 2548") (attachment 2 to the Petition). A closer look at Study 2548 reveals the flaws in Biovail's argument.

The 2548 Study included a mere 32 test subjects in a two-way crossover, open label, single dose food effect comparative bioavailability study of 300 mg Wellbutrin® XL. Contrary to Biovail's suggestion, the 2548 Study does not address the issue of seizure potential in any way shape or form, but was merely designed to "evaluate the effect of food on the rate and extent of absorption of [Wellbutrin® XL] under single dose conditions." Study 2548 at 1. And, given the small size and limited design of the study, there is simply no way the study results could have provided meaningful data or conclusions on whether the active metabolites have any clinical safety or efficacy effects on patients.

---

abuse of the Petition process by failing to address known unfavorable information in anti-competitive petitions such as this.

[7] As noted above, however, Impax did measure the bioequivalence of the major metabolite, hydroxybupropion, and the data generated showed bioequivalence to Wellbutrin XL.

Moreover, Biovail's reliance on the 2548 Study fails the "straight face test," because the study does not even support the proposition that Biovail cites it for (namely that there may be a clinically significant food effect with respect to the metabolites). Indeed, the study summary itself contradicts Biovail in multiple places, noting that:

> "[t]he pharmacokinetic parameters of the metabolites of bupropion and the pharmacological activity-weighted composite (PAWC) were also similar regardless of food intake;"
>
> "[t]he pharmacological activity-weighted composite of bupropion and its metabolites demonstrated...the absence of a food effect;" and
>
> the bioequivalence parameters for bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion "were bioequivalent (0.8-1.25) in the presence ***and*** absence of food."

For the reasons set forth above, Biovail's request for triple-metabolite bioequivalence studies should be rejected. [8]

II. THERE IS NO BASIS TO REQUIRE BIOEQUIVALENCE STUDIES COMPARING GENERIC EXTENDED RELEASE BUPROPION PRODUCTS TO THE IMMEDIATE RELEASE AND SUSTAINED RELEASE VERSIONS OF WELLBUTRIN®

Biovail also argues that labeling for generic bupropion extended release tablets would be "false or misleading" if it includes the statement from the Wellbutrin® XL labeling describing the bioequivalence study findings as between Wellbutrin® XL and the sustained release and immediate release versions of Wellbutrin®, unless the generic drug was itself shown to be bioequivalent to the Wellbutrin® SR and IR products. Pet. at 4-6. Thus, Biovail requests that FDA require generic drug applicants to conduct bioequivalence studies of their proposed extended release products compared to the immediate release and sustained release Wellbutrin® products. Biovail's position is facially without legal or regulatory merit, would overturn well-

[8] FDA should refuse to accept any "supplemental" submissions by Biovail in support of its petition that attempt to introduce new evidence or arguments in support of its requested actions. In far too many instances of anti-competitive petitions such as Biovail's, the petitioner embarks on a deliberate strategy of continuously "supplementing" the docket with previously available information that could have been included in the original petition. FDA's Petition regulations clearly require petitioners to include, and certify that they have included, "a full statement...of the factual and legal grounds on which the petition relies." 21 C.F.R. § 10.30(b) (emphasis added). The intent and effect of this abusive petitioning strategy are clear – every "new" submission forces FDA to devote more time and resources to review additional information and arguments, and doing so inevitably buys the petitioner more undeserved time before FDA is able to act on the approval of ANDAs for competing products. If FDA is serious about reforming the petition process, as many, including Chief Counsel Sheldon Bradshaw have stated, FDA must clamp down on "supplemental" petition submissions, and should not allow any further submissions by Biovail in this matter.

established FDA policy, and would establish an unconscionably burdensome and unnecessary standard for the approval of virtually all generic extended release drug products.

A. The Bioequivalence Requirement for ANDAs Is Strictly Limited To Comparisons With The Reference Listed Drug

The FDCA and FDA's governing regulations are clear and beyond doubt: an ANDA product need only be shown to be bioequivalent to the Reference Listed Drug upon which the requested ANDA approval is predicated. The Act requires an ANDA to "show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new [generic] drug have been previously approved for a listed drug." 21 U.S.C. § 355(j)(2)(A)(i) ("clause (i)"). With respect to bioequivalence, the Act further requires only that an ANDA include "information to show that the new [generic] drug is bioequivalent to the listed drug referred to in clause (i)...." 21 U.S.C. § 355(j)(2)(A)(iv) (emphasis added). Significantly, the Act forbids FDA from "requir[ing] that an abbreviated application contain [bioequivalence] information in addition to that required by clause[(v)]." 21 U.S.C. § 355(j)(2)(A).

FDA's regulations implement these statutory requirements in a consistent, straightforward, and unambiguously limited manner, by requiring an ANDA to "refer to a listed drug," and to include "[t]he name of the listed drug, including its dosage form and strength." 21 C.F.R. § 314.94(a)(3). All of the comparative requirements of the regulations are specifically and narrowly limited to comparisons of the proposed generic drug to the RLD identified in the ANDA, including:

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

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

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

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

- ***Inactive Ingredients for Certain Products***: Parenteral, ophthalmic, otic, or topical generic drugs "shall contain the same inactive ingredients and [except for

topical drugs] in the same concentration as the reference listed drug identified by the applicant." 21 C.F.R. § 314.94(a)(9)(iii), (iv), and (v) (emphasis added).[9]

B. Wellbutrin® XL Is The One And Only Reference Listed Drug For ANDAs Seeking Approval of Bupropion HCl Extended Release Tablets

FDA regulations require that if an approved (listed) drug is pharmaceutically equivalent ("PE") to the proposed generic drug product, the ANDA for the generic product must refer to that PE listed drug. 21 U.S.C. § 355(j)(2)(A)(ii)-(iii). "Pharmaceutical equivalents" are defined in FDA regulations as "drug products in identical dosage forms that contain the same amounts of the identical active drug ingredient...." 21 C.F.R. § 320.1(c) (emphases added). The Orange Book defines pharmaceutical equivalents as follows:

> Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.

APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, at vii (25th Ed., 2005) (emphasis added).

Wellbutrin® XL and the proposed generic versions have different dosage forms, strengths, and dosing schedules than the immediate release and sustained release versions of Wellbutrin®, as shown below:

[9] Although not relevant here, the regulations allow some differences in inactive ingredients even for parenteral, ophthalmic, otic, and topical drugs, including for example, differences in buffers, preservatives, and antioxidants. *See Id.*

Product	Dosage Form	Strength	Dosing Schedule
Proposed ANDA Products	Extended Release Tablets	150 mg; 300 mg	QD
Wellbutrin® XL	Extended Release Tablets	150 mg; 300 mg	QD
Wellbutrin® SR	Sustained Release Tablets	50 mg; 100 mg; 150 mg; 200 mg	BID
Wellbutrin®	Immediate Release Tablets	75 mg; 100 mg	TID

Thus, Wellbutrin® XL is the only pharmaceutically equivalent drug product to which bupropion HCL extended release tablet ANDAs can possibly reference, and such ANDAs may not reference the immediate release or sustained release versions of Wellbutrin®.

Accordingly, for the reasons discussed in section II.A. *supra*, FDA may not require or request ANDA applicants to submit bioequivalence data comparing their proposed extended release tablets to the non-RLD immediate release and sustained release Wellbutrin® products.

C. The Fact That The Wellbutrin® XL Labeling Describes Bioequivalence Studies Between Wellbutrin® XL, Wellbutrin®, and Wellbutrin® SR Does Not Require Additional Bioequivalence Studies For Generic Versions Of Wellbutrin® XL

Biovail ignores the foregoing limitations on what bioequivalence studies may be required of ANDA applicants, and focuses its anticompetitive attack on the "same labeling" requirement of section 505(j)(2)(A)(v) of the Act. Specifically, Biovail argues that "[t]here are numerous portions of the approved Wellbutrin® XL labeling that refer to specific test results or other scientific findings that are crucial to the safe and effective use of the product," and that generic versions must reproduce those labeling elements in order to be considered bioequivalent to Wellbutrin® XL. Specifically, Biovail points out that the Wellbutrin® XL labeling includes statements that describe bioequivalence findings as between Wellbutrin® XL and the Wellbutrin® IR and SR products. Thus, Biovail contends, the labeling of generic versions of Wellbutrin® XL would be false or misleading without such IR and SR bioequivalence statements, and that generic labeling cannot include such information unless the generic version was specifically tested for bioequivalence against Wellbutrin® IR and SR. Petition at 5-6.

Biovail specifically highlights the following language from the Wellbutrin® XL labeling, which, Biovail argues, cannot be included in generic labeling without generic drug-specific bioequivalence studies against Wellbutrin® IR and SR:

> As both WELLBUTRIN® XL and the sustained-release formulation of bupropion (WELLBUTRIN® SR) are bioequivalent to the immediate-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.
>
> * * *
>
> 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 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.

Biovail's position is based on an unfounded hypothesis as to the relevance of the Wellbutrin® XL bioequivalence findings to the safety of a generic version, and a fundamental misunderstanding of the bioequivalence and "same labeling" requirements for generic drugs.

1. FDA Has Approved Generic Extended Release Drugs Without Requiring Non-RLD Bioequivalence Studies Even Where The Extended Release RLD Was Itself The Subject Of Such Bioequivalence Studies.

If Biovail had properly researched its proposed non-RLD bioequivalence/labeling proposal, it would have discovered that the issue it presents is not new to FDA or the generic drug industry. Specifically, many branded extended release drugs that were approved as part of a line extension from immediate release versions of the drug were approved at least in part based on bioequivalence studies as between the branded extended release and branded immediate release products. The labeling of these line-extension products often describes the bioequivalence studies as part of the clinical pharmacology and/or other sections of the labeling. Nevertheless, FDA has never deemed it necessary or appropriate to require ANDA applicants to conduct their own bioequivalence studies comparing a generic extended release drug to the branded immediate release (and/or sustained release) products. Rather, as with any other aspect of labeling that may be modified for a generic product based on different manufacturers under 21 C.F.R. § 314.94(a)(8)(iv), the generic labeling may substitute the generic name of the drug for the brand name and provide the same bioequivalence information. As illustrated in the following

table, examples of this well-established approach include generic versions of Prozac® (fluoxetine), Tegretol® XR (carbamazapine), and Glucotrol® XL (glipizide):

Drug	Brand vs. Brand BE Information on Branded Label	Corresponding Generic Labeling for Brand vs. Brand BE Information
Fluoxetine	Prozac® (Eli Lilly and Company) **Absorption, Distribution, Metabolism, and Excretion** **Systemic Bioavailability** --"The Pulvule®, tablet, oral solution, and Prozac Weekly™ capsule dosage forms of fluoxetine are bioequivalent."	Generic Fluoxetine (Ivax Pharmaceuticals, Inc.) **Absorption, Distribution, Metabolism, and Excretion** **Systemic Bioavailability** -- "The capsule, tablet, and oral solution forms of fluoxetine are bioequivalent."
Carbamazepine	Tegretol®/Tegretol® XR (Novartis). **Pharmacokinetics** "In clinical studies, Tegretol suspension, conventional tablets, and XR tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster, and the XR tablet, somewhat slower, than the conventional tablet. The bioavailability of the XR tablet was 89% compared to suspension. Following a b.i.d dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a t.i.d dosage regiment, Tegretol suspension affords steady-state plasma levels comparable to Tegretol tablets given b.i.d. when administered at the same total mg daily dose."	Generic Carbamazepine Oral Suspension (Taro Pharmaceuticals, Inc.). **Pharmacokinetics** "In clinical studies, carbamazepine suspension, conventional tablets, and extended release tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster, and the carbamazepine extended release tablet, somewhat slower, than the conventional tablet. The bioavailability of the carbamazepine extended release tablet was 89% compared to suspension. Following a b.i.d dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a t.i.d dosage regiment, carbamazepine suspension affords steady-state plasma levels comparable to carbamazepine tablets given b.i.d. when administered at the same total mg daily dose."
Glipizide	Glucotrol® XL (Pfizer, Inc.) **Pharmacokinetics and Metabolism** "The mean relative bioavailability of glipizide in 21 males with type 2 diabetes after administration of 20 mg Glucotrol XL Extended Release Tablets, compared to immediate release Glucotrol (10 mg given twice daily), was 90% at steady state."	Glipizide Extended Release Tablets (Watson Pharmaceuticals, Inc.) **Pharmacokinetics and Metabolism** "The mean relative bioavailability of glipizide in 21 males with type 2 diabetes after administration of 20 mg glipizide extended Release Tablets, compared to immediate release Glucotrol (10 mg given twice daily), was 90% at steady state."

Biovail's position on labeling not only runs counter to well supported and longstanding FDA practice, it also calls into question the bedrock principle of the generic approval process, which allows generic labeling to describe clinical studies that were not conducted on the generic product itself. Moreover, if Biovail's proposed approach were adopted, it could require the market withdrawal of many approved generic products, and would open a pathway to further abuse of the Hatch-Waxman generic drug approval system.

2. The Wellbutrin® XL Bioequivalence Labeling Is Not Necessary For The Safe And Effective Use Of Generic Versions

Biovail's reliance on the XL/SR/IR bioequivalence statements in the Wellbutrin® XL labeling is misplaced. First, because the XL, SR, and IR products have different dosage forms, strengths, and dosing regimens, Wellbutrin® XL and the proposed generic equivalents are not interchangeable and would not be listed as "AB" rated in the Orange Book. The essence of the generic bioequivalence requirement is to assure that when a generic drug is substituted for the reference listed brand name drug, the generic will be therapeutically equivalent *to the RLD. See* Orange Book, Preface, at vii (26th Ed., 1006) ("A major premise underlying the 1984 law is that bioequivalent drug products are therapeutically equivalent, and therefore, interchangeable."). All that is required to make this showing is pharmaceutical equivalence and successful bioequivalence studies between the RLD and the proposed generic drug. In other words, generic versions of Wellbutrin® XL need only be shown to be bioequivalent to Wellbutrin® XL, and need not be shown to be bioequivalent to Wellbutrin® or Wellbutrin® SR, even though Wellbutrin® XL may in fact have been shown to be bioequivalent to the IR and SR versions, for reasons other than potential generic substitution.

Second, the explicit reason for the inclusion of the XL/SR/IR bioequivalence statement is to explain why the seizure incidence observed for Wellbutrin® IR and SR "may be" expected to be "similar" to that for Wellbutrin® XL, even though "the seizure incidence with Wellbutrin® XL [was] not formally evaluated in clinical trials." Wellbutrin® XL approved labeling at (Attachment 1 to Petition). The actual adverse reaction safety information included in the Wellbutrin® XL would, in any event, be included in the labeling for generic bupropion XL products. Biovail offers no suggestion as to how the already strong safety information in the Wellbutrin® XL labeling would have to be altered for generic versions in the absence of the XL/SR/IR bioequivalence information. Doctors would continue to receive the same appropriate warnings and would continue to prescribe the drug in a medically appropriate manner with full awareness of the potential adverse reactions, including seizure. Thus, the statement regarding Wellbutrin® XL's bioequivalence to Wellbutrin® SR and IR is not germane to the actual substance of the safety labeling for either Wellbutrin® XL or any generic equivalent and it would

not affect the safe and effective use of a generic version of Wellbutrin® XL if this information was described without the use of the Wellbutrin® tradename.[10]

III. STEADY-STATE BIOEQUIVALENCE STUDIES BASED ON AUC, C_{MAX}, AND C_{MIN} ARE NEITHER NECESSARY NOR REQUIRED

For the reasons described above in section II, it is legally and medically unnecessary for generic bupropion products to be compared in bioequivalence studies to Wellbutrin® SR and IR. Rather, the only necessary bioequivalence test is a comparison to Wellbutrin® XL. Steady state bioequivalence studies are sometimes appropriate when comparing extended release drugs to more frequently dosed, lower strength, immediate release versions. However, steady state testing is unnecessary when comparing two pharmaceutically equivalent extended release drug products. Because, as shown above, there is no basis for FDA to require generic drug applicants to compare their extended release bupropion products to Wellbutrin® SR and Wellbutrin® (IR), Biovail's steady state argument is irrelevant and unfounded.

IV. DOSE DUMPING IS NOT A CONCERN FOR IMPAX'S PRODUCT

Biovail's final line of attack against generic competition for Wellbutrin® XL is to request that generic drug applicants conduct *in vitro* studies on their extended release formulations to assure that there is no "dose dumping" if the drug is taken with alcohol. Impax recognizes the importance of this issue and has generated appropriate data demonstrating that its product will not be subject to dose dumping with alcohol. Thus, Biovail's alcohol dose dumping arguments fail to provide a basis for delaying approval of Impax's ANDA.

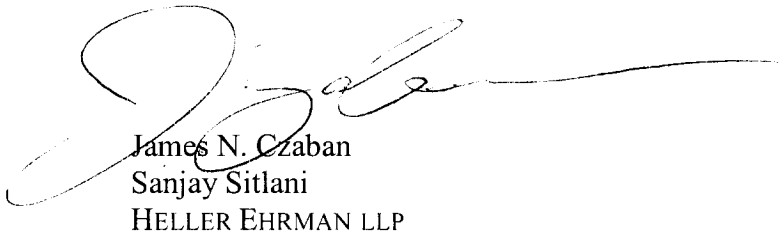
---

[10] Indeed, the prefatory labeling statement explaining the historical pathway FDA and Biovail took to arrive at the Wellbutrin XL safety information is clinically meaningless, and an appropriate alternative regulatory approach would be to allow generic labeling to completely omit the prefatory statement regarding Wellbutrin XL's bioequivalence to its predecessor SR and IR incarnations. This would be permissible under 21 C.F.R. § 314.94(a)(8)(iv) to the extent the change is required due to the different manufacturers of Wellbutrin and proposed generic versions. In any event, as noted above, the substantive safety information could, and should, continue to be included in generic labeling. This approach would not render a generic product less safe and effective than Wellbutrin.

CONCLUSION

Biovail's petition is a sham, designed solely to delay the onset of generic competition for its Wellbutrin® XL product. Biovail has wasted FDA's and Impax's time and resources, and has likely cost the American public millions of dollars in taxes and health care expenditures in selfish pursuit of further undeserved windfall profits. FDA should promptly deny Biovail's Petition and immediately approve eligible ANDAs for bupropion extended release tablets.

Respectfully submitted,



James N. Czaban
Sanjay Sitlani
HELLER EHRMAN LLP
Counsel to Impax Laboratories, Inc.