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Via Hand Delivery

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
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CITIZEN PETITION

The undersigned, on behalf of Biovail Corporation, submits this petition under 21 C.F.R. § 10.30 and section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDC Act) requesting that the Commissioner of Food and Drugs require that generic versions of Wellbutrin XL[®] (bupropion hydrochloride extended-release tablets) meet the criteria described below in order to be considered bioequivalent to Wellbutrin XL[®]. This action is necessary to protect patients against potentially serious risks (particularly seizures) which are currently disclosed in the approved Wellbutrin XL[®] labeling. Unless the factors described below are satisfied, there can be no assurance that these warnings are adequate to ensure that generic versions are as safe and effective as the innovator product. Biovail manufactures Wellbutrin XL[®] for GlaxoSmithKline (the holder of the approved New Drug Application).

I. Action Requested

In order to assess the potential risks of a new formulation of bupropion extended-release tablets in proper context, and to ensure that the labeling accurately reflects those anticipated risks, it is critical that FDA require that any Abbreviated New Drug Application (ANDA) for a generic version of Wellbutrin XL[®] satisfy the following criteria:

- a. All bioequivalence trials should calculate and evaluate parameters based on concentrations of the parent drug and active metabolites.
- b. Any generic formulation should be shown, based on the above criteria, to be bioequivalent to Wellbutrin XL[®], sustained-release, and immediate-release bupropion.
- c. The bioequivalence studies described above should be conducted at steady-state evaluating the performance of the dosage form based on AUC, C_{max}, C_{min}.
- d. Data using FDA's *in vitro* approach for evaluating the effect of alcohol on the performance of the controlled-release dosage form should be required to ensure the absence of "dose dumping" if the drug is consumed with alcohol.

The basis for these requests is described in detail below.

II. Statement of Grounds

A. Generic Drugs are Expected to Provide the Same Therapeutic Effect as the Innovator Drugs They Copy

The bedrock principal behind the generic drug approval system is the assurance that a generic drug will provide the same level of safety and efficacy demonstrated by the innovator drug. This concept has received significantly more public attention in the last few years through efforts by the government to promote the use of generic drugs. For example, "FDA requires that all drugs be safe and effective and that their benefits outweigh their risks. Since generics use the same active ingredients and are shown to work the same way in the body, they have the same risk-benefit profile as their brand-name counterparts."¹ In October 2002, President Bush echoed these comments during the announcement of an initiative to speed the approval of ANDAs, noting that "generic drugs [] are just as safe and effective as the brand name drugs. . ."² FDA also initiated a series of public service announcements to emphasize the message "Generic Drugs: Safe. Effective. FDA Approved."³ All of these activities are designed to reinforce the message that consumers can rely on generic drugs to provide the same performance as the innovators they copy. This confidence is only justified, however, to the extent that the generic has been shown to deliver the active ingredient in a way that does not raise potential issues concerning its safety or effectiveness.

B. Statutory and Regulatory Requirements are Intended to Assure the "Similarity" of the Generic and Innovator Drug Products

The Federal Food, Drug, and Cosmetic Act (FDC Act), identifies the information required to be included in an ANDA for any generic drug product, including (among other things) data to show that the generic drug is bioequivalent to the innovator product it seeks to copy (the "reference listed drug" (RLD)) and that the labeling of the two drugs is "the same" but for changes required because the drugs are produced by different manufacturers. *See* FDC Act § 505(j)(2)(A). Two drugs are considered bioequivalent if "the rate and extent of absorption of the [generic] drug do not show a significant difference from the rate and extent of absorption of the [RLD] when administered at the same molar dose of the therapeutic ingredient under similar

¹ "FDA Ensures Equivalence of Generic Drugs" (August 2002), page 2 (available at: <http://www.fda.gov/cder/about/whatwedo/testtube-17.pdf>).

² "President Takes Action to Lower Prescription Drug Prices - Remarks by the President on Prescription Drugs" (October 21, 2002) (available at: <http://www.whitehouse.gov/news/releases/2002/10/20021021-2.html>).

³ The campaign included six different headlines, including "Your generic drug is safe and effective. And we've got the results to prove it." (campaign available at: http://www.fda.gov/cder/consumerinfo/generic_info/default.htm).

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experimental conditions. . . .” FDC Act § 505(j)(8)(B)(i). The *in vivo* activity of the generic drug must be considered when assessing whether any difference between the two is “significant.”

Through its regulations, FDA has established what must be shown for a generic drug’s labeling to be considered “the same” as the RLD’s. Under 21 C.F.R. § 314.94(a)(8)(iv), the ANDA must include:

(iv) *Comparison of approved and proposed labeling.* A side-by-side comparison of the applicant’s proposed labeling . . . with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under [21 C.F.R.] 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant’s proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the [FDC] act. [Underlining added.]

Overall, the permitted variations between the generic and RLD labeling are very limited. The bioequivalence and labeling provisions must be read in conjunction with the FDC Act’s finding that a drug is “misbranded” if “its labeling is false or misleading in any particular.” FDC Act § 502(a). As a result, information in the drug labeling discussing specific performance results or performance characteristics for the innovator drug must also be true for the generic drug.

Importantly, the statute states that FDA “may not require that an [ANDA] contain information in addition to that required by” § 505(j)(2)(A). As a result, all decisions concerning the adequacy of the labeling of the generic drug (including determining that it is not “false or misleading in any particular”) must be based on the statutory elements required for an ANDA.

C. Bupropion Presents Potentially Serious Risks

FDA is very familiar with bupropion as an active ingredient, so Biovail does not intend to present a comprehensive discussion of the ingredient’s pharmacologic properties. However, there are several formulation-related issues that must be considered with respect to controlled-release dosage forms.

As is clearly disclosed in the approved labeling for Wellbutrin XL®, bupropion is associated with a dose-related risk of seizures.⁴ This risk is also related to patient factors, including certain concomitant medications and the excessive use of alcohol (for which warnings are provided). To reduce the risk of seizures, the labeling recommends that the total daily dose of bupropion not exceed 450 mg/day and that the rate of dose incrementation be gradual.⁵ 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, particularly if the effect were unpredictable. Therefore, seizure potential may be directly related to a particular dosage form and its release rate and performance characteristics in the presence of food and alcohol.

Bupropion is extensively metabolized. Of the circulating drug related materials, a substantial amount are active metabolites (such as hydroxybupropion, threohydrobupropion, and erythrohydrobupropion). While these active metabolites have intrinsic activities lower than bupropion, they are present in plasma concentrations that are as high as or higher than those of bupropion. Hence, along with bupropion, they contribute to both the activity and the toxicity of bupropion formulations, and represent the majority of what circulates in blood following doses of bupropion.

The relationship between serum levels of bupropion and its circulating active metabolites and seizures is not well understood. However, recent data from on-going 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.⁶

D. The Wellbutrin XL® Labeling Includes Conditions That any Generic Drug Must Duplicate

Wellbutrin XL® (bupropion hydrochloride extended-release) Tablets (NDA 21-515) was approved on August 28, 2003, for the treatment of major depressive disorder. The application

⁴ Wellbutrin XL® Labeling (“Warnings - - Seizures”). Complete prescribing information for Wellbutrin XL® is available at: http://us.gsk.com/products/assets/us_wellbutrinXL.pdf (Attachment 1).

⁵ Wellbutrin XL® Labeling (“Warnings - - Recommendations for Reducing the Risk of Seizure”).

⁶ See e.g., “A two-way, crossover, open-label, single dose, food-effect, comparative bioavailability study of bupropion HCl extended release 300mg tablets in normal healthy non-smoking male and female subjects.” Summary Report of Study No. AK1BIOVAIL2548, available from the GlaxoSmithKline Clinical Trial Register (http://ctr.gsk.co.uk/summary/bupropion/I_AK1BIOVAIL2548.pdf) (Attachment 2).

covered 150 mg and 300 mg dosage strengths. The 150 mg strength has been designated by FDA as the RLD.

There 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. Any proposed generic product must demonstrate that it satisfies these conditions as well. Absent such a finding, the generic may not be considered “bioequivalent” to Wellbutrin XL® and the labeling would be false or misleading if it included those conditions.

1. Any Generic Must Demonstrate Bioequivalence to Wellbutrin XL®, Sustained-Release, and Immediate-Release Bupropion

The approved labeling for Wellbutrin XL® contains the following statement:

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.⁷

In addition, the Wellbutrin XL® labeling specifically describes bioequivalence to sustained-release and immediate-release forms 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.⁸

⁷ Wellbutrin XL® Labeling (“Warnings - - Seizures”).

⁸ Wellbutrin XL® Labeling (“Clinical Pharmacology - - Pharmacokinetics”).

In order to appropriately use this labeling, any proposed generic drug must demonstrate bioequivalence to Wellbutrin XL®, sustained-release, and immediate-release bupropion.⁹ Unless such data are presented, there could be no assurance that the generic labeling would not be “false or misleading” with respect to the applicability of the seizure risk information presented in the labeling.

As noted in the Introduction to the Orange Book under the heading “Statistical Criteria for Bioequivalence”: “The primary concern from the regulatory point of view is the protection of the patient against approval of products that are not bioequivalent. The current practice of carrying out two one-sided tests at the 0.05 level of significance ensures that there is no more than a 5% chance that a generic product that is not truly equivalent to the reference will be approved.”¹⁰ “By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. Such variations could result if generic drugs were compared to different reference listed drugs.”¹¹ The same potential for significant variations arises between a generic version of a RLD and the immediate release version of the drug to which the RLD was shown to be bioequivalent. The relevance and accuracy of data regarding seizure incidence and other side effects is open to question if the generic drug has not been shown to be bioequivalent to the same reference that was relied upon for approval of the RLD.¹²

2. The Evaluation of Any Generic Version of Wellbutrin XL® Must Consider the Metabolites of Bupropion

⁹ This assessment would also require a demonstration of the absence of a “food effect” on the release of the active ingredient in the generic product. The approved Wellbutrin XL® labeling states that “time to peak plasma concentrations for bupropion was approximately 5 hours and food did not affect the C_{max} or AUC of bupropion.” Wellbutrin XL® Labeling (“Clinical Pharmacology - - Absorption”). In the Patient Information leaflet, it states that “You may take WELLBUTRIN XL with or without food.”

¹⁰ “Approved Drug Products with Therapeutic Equivalence Evaluations” (25th Edition) (2005) (the “Orange Book”), Sec. 1.3, pages x – xi (available at: <http://www.fda.gov/cder/orange/obannual.pdf>).

¹¹ 2005 Orange Book, Sec. 1.4, page xi.

¹² Significant adverse reaction data in the Wellbutrin XL® labeling refer to the sustained release product, Wellbutrin SR®, which itself was approved on the basis of bioequivalence to immediate release Wellbutrin®. Data referenced in the labeling establish that Wellbutrin XL® is also bioequivalent to Wellbutrin SR®. Unless generic versions of Wellbutrin XL® are also shown to be bioequivalent to immediate release Wellbutrin® and Wellbutrin SR®, the relevance of the adverse effect data is not established.

The metabolites of bupropion play a very significant role in the clinical performance of Wellbutrin XL® and any generic version should demonstrate similar results in order to assure that the generic will provide similar effects. The Wellbutrin XL® labeling discusses specific findings and methodology:

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.¹³

The most reliable means to assess the rate and extent of exposure of bupropion is through the conduct of bioequivalence trials at steady-state. Any comparison to immediate-release bupropion based on single dose data would be tenuous at best. Steady-state comparisons are the most accurate and relevant since they make it possible to evaluate C_{min} (which ensures that the coverage is adequate over the entire 24 hour dosing interval and cannot be estimated in any other manner) as well as C_{max} and AUC.

Comparisons of the AUC between immediate- and extended-release bupropion become problematic under single dose conditions as a result of the difficulty in estimating the area from the last sampling point to infinity. The immediate-release estimate from time zero to infinity is straight forward; the extended-release estimate is difficult because one is not measuring the true half life or elimination rate, but rather an apparent one. If the studies are done at steady state, there is no estimation involved, because the AUC of the dosing interval is being measured directly.

3. Any Generic Formulation Must be Assessed for the Impact of Alcohol Consumption on Dose Release

The potential effects of alcohol on the dose-release mechanism of extended-release tablets is a serious concern. This is especially true for patients suffering from major depressive disorder, who are generally more likely to consumer alcohol with medication despite warnings not to. The Wellbutrin XL® labeling includes numerous references to avoiding the use of

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Wellbutrin XL® Labeling (“Clinical Pharmacology - - Pharmacokinetics”).

alcohol when taking the drug and a sober awareness of the fact that such warnings may not be heeded:

- “WELLBUTRIN XL is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).”¹⁴
- “Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives . . .”¹⁵
- “The consumption of alcohol during treatment with WELLBUTRIN XL should be minimized or avoided (also see CONTRAINDICATIONS).”¹⁶
- Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives (including benzodiazepines) may alter the seizure threshold. Some patients have reported lower alcohol tolerance during treatment with WELLBUTRIN XL. Patients should be advised that the consumption of alcohol should be minimized or avoided.¹⁷

FDA discussed the potential concerns with the effect of alcohol on extended-release dosage forms at a recent meeting of the Advisory Committee for Pharmaceutical Science.¹⁸ Although styled as an “awareness presentation,”¹⁹ FDA clearly indicated its concern with the potential effect that alcohol might have on extended-release drug delivery systems. Given these concerns, the potentially serious risks posed by alcohol consumption with bupropion, and the tendency of depressed patients to consume alcohol despite appropriate warnings, FDA should require *in vitro* data on any generic version of Wellbutrin XL® confirming that there are no substantial differences in the dose-release profile in the presence of alcohol. To the extent that any such differences exist, they should be weighed to determine whether the risks posed by the generic version are adequately addressed by the Wellbutrin XL® labeling.

¹⁴ Wellbutrin XL® Labeling (“Contraindications”).

¹⁵ Wellbutrin XL® Labeling (“Warnings - - Seizures - - Clinical situations”).

¹⁶ Wellbutrin XL® Labeling (“Precautions - - Alcohol”).

¹⁷ Wellbutrin XL® Labeling (“Information for Patients”). The patient information leaflet repeats the acknowledgement that warnings to not consume alcohol may be ignored: “What should I avoid while taking WELLBUTRIN XL? Do not drink a lot of alcohol while taking WELLBUTRIN XL. If you usually drink a lot of alcohol, talk with your doctor before suddenly stopping. If you suddenly stop drinking alcohol, you may increase your chance of having seizures.”

¹⁸ Advisory Committee for Pharmaceutical Science meeting on October 26, 2005 (transcript available at: <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4187T2.pdf>).

¹⁹ See Meeting Transcript at 9.

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E. Conclusion

For the reasons discussed above, FDA should require that any ANDA for a generic version of Wellbutrin XL® satisfy the criteria outlined in Section I of this petition.

III. Environmental Impact

Biovail claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

IV. Economic impact

This information will be provided upon request of the Commissioner.

V. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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Attachments:

- (1) Complete prescribing information for Wellbutrin XL®.
- (2) Summary Report of Study No. AK1BIOVAIL2548, "A two-way, crossover, open-label, single dose, food-effect, comparative bioavailability study of bupropion HCl extended release 300mg tablets in normal healthy non-smoking male and female subjects." (GlaxoSmithKline Clinical Trial Register)