CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-913

***Name*:** Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

***Sponsor*:** Impax Laboratories, Inc.

***Approval Date*:** January 28, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-913

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Tentative Approval Letter	
Labeling	X
Labeling Reviews	X
Medical Review(s)	
Chemistry Reviews	X
Bioequivalence Reviews	X
Statistical Review(s)	
Microbiology Review	
Administrative Documents	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-913

APPROVAL LETTER

ANDA 75-913

JAN 28 2004

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated June 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg (Twice-A-Day Dosing).

Reference is made to your amendments dated August 25, 2000; and January 17, March 10, April 3 (two amendments), June 27, July 9, August 1 (two amendments), September 5, October 2, November 14, December 2, and December 8, 2003; and January 15, and January 23, 2004. We acknowledge receipt of your correspondence dated August 28, and October 4, 2000; September 5, 2002; March 19, 2003; and January 15, 2004, addressing the patent issues noted below. We also acknowledge receipt of your correspondence dated February 20, 2002, regarding exclusivity associated with the reference listed drug product (RLD).

We have completed the review of this abbreviated application, and based upon the information you have presented to date, we have concluded that both strengths of the drug product are safe and effective for use as recommended in the submitted labeling. However, final approval of your Bupropion Hydrochloride Extended-release Tablets, 150 mg is blocked at this time by another applicant's eligibility for 180-day generic drug exclusivity as noted in further detail below. **Therefore, final approval is granted for your Bupropion Hydrochloride Extended-release Tablets, 100 mg.** Please note that the 150 mg strength is regarded as tentatively approved, and will be eligible for final approval upon the expiration of another applicant's 180-day generic drug exclusivity, or until that applicant's eligibility for 180-day generic drug

exclusivity for Bupropion Hydrochloide Extended-release Tablets, 150 mg has been satisfactorily resolved.

The Division of Bioequivalence has determined your Bupropion Hydrochloride Extended-release Tablets, 100 mg, to be bioequivalent and therapeutically equivalent to the listed drug (Wellbutrin SR® Sustained-Release Tablets, 100 mg, of GlaxoSmithKline). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

> Dissolution testing should be conducted in 900 mL of water, at 37°C, using USP Apparatus 2(paddle) at 50 rpm. The test product should meet the following "interim" specifications:
>
> | Time (Hours) | % Dissolved |
> |---|---|
> | 1 | ——— |
> | 2 | ——— |
> | 4 | ——— |
> | 6 | NLT — |
>
> The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a "Special Supplement - Changes Being Effected" when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The listed drug product referenced in your application, Wellbutrin SR® Tablets, 100 mg and 150 mg, of GlaxoSmithKline, is subject to multiple periods of patent protection. The following United States patents and their expiration dates currently appear in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book":

Patent Number	Expiration Date
5,358,970 (the '970 patent)	August 12, 2013
5,427,798 (the '798 patent)	August 12, 2013
5,731,000 (the '000 patent)	August 12, 2013
5,763,493 (the '493 patent)	August 12, 2013

Your application contains paragraph IV certifications to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that none of these patents will be infringed by your manufacture, use, offer for sale, or sale of Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against IMPAX Laboratories, Inc. (IMPAX) for infringement of one or more of the patents which were the subjects of the paragraph IV certifications. This action must be brought against IMPAX prior to the expiration of forty-five (45) days from the date the notice you provided under paragraph (2)(B)(i) was received by the patent and NDA holder(s). You have informed the agency that IMPAX complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for infringement of the '970, '000, or '493 patents was brought against IMPAX within the statutory forty-five day period. You have also informed the agency that with regard to the '798 patent, Glaxo Wellcome, Inc. initiated a patent infringement action against IMPAX in the United States District Court for the Northern District of California (Glaxo Wellcome, Inc. v. IMPAX Laboratories, Inc.), Civil Action No. CA-00-21009.

The agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act and associated with Civil Action CA-00-21009 for the '798 patent, during which time the FDA was precluded from approving your application, has expired.

Under Section 506(A) of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change can be made.

Post-marketing requirements for this ANDA for Bupropion Hydrochloride Extended-release Tablets, 100 mg are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the

marketing status of your Bupropion Hydrochloride Extended-release Tablets, 100 mg.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns for the 100 mg strength. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Our decision to grant tentative approval to your Bupropion Hydrochloride Extended-release Tablets, 150 mg, is based upon information currently available to the agency; (i.e., data in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This decision is subject to change on the basis of new information that may come to our attention.

As noted previously, we are unable to grant final approval to your Bupropion Hydrochloride Extended-release Tablets, 150 mg, at this time because an ANDA for the 150 mg strength containing paragraph IV certifications to the patents listed in the Orange Book was submitted to OGD prior to the submission of your application. Accordingly, your Bupropion Hydrochloride Extended-release Tablets, 150 mg, will be eligible for final approval beginning on the date that is one-hundred eighty days after the date the agency received notice of the first commercial marketing of the 150 mg strength under the previous application, or the date of a court decision described under Section 505(j)(5)(B)(iv), whichever event occurs earlier. For additional information, we refer you to the Agency's guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1988).

In order to reactivate this application to provide for final approval of the 150 mg strength, you must submit a "Supplemental Application - Expedited Review Requested". This supplemental application should be submitted for prior approval approximately 30 days prior to the date you believe that your Bupropion Hydrochloride Extended-release Tablets, 150 mg, will be eligible for final approval. The supplement should include a detailed explanation of why and when you believe final approval should be granted. Please include a copy of a final order or judgement, settlement or licensing agreement, or other relevant agreement as appropriate. It should also include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This supplemental application should be submitted even if no changes have been made to the application since the date of this tentative approval. Significant changes, as well as an update of the status of the manufacturing and testing facilities' compliance with cGMPs are subject to Agency review before final approval of the supplemental application will be granted. We request that you categorize the changes as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt.

In addition to the supplemental application requested above, the Agency may request at any time prior to the date of final approval that you submit an additional document containing the requested information. Failure to submit either or, if requested, both documents may result in the rescission of the tentative approval status of your application for Bupropion Hydrochloride Extended-release Tablets, 150 mg, or may result in a delay in the issuance of the final approval letter.

Please note that under Section 505 of the Act, your Bupropion Hydrochloride Extended-release Tablets, 150 mg, may not be marketed without final agency approval. The introduction or delivery for introduction into interstate commerce of your Bupropion Hydrochloride Extended-release Tablets, 150 mg, before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the agency issues the final approval letter, your Bupropion Hydrochloride Extended-release Tablets, 150 mg will not be deemed approved for marketing under 21 U.S.C. 355, and will not be listed in the "Orange Book".

For further information on the status of this application, or prior to submitting an amendment providing for the final approval of your Bupropion Hydrochloride Extended-release Tablets, 150 mg, please contact Stanley Shepperson, Pharm.D., Project Manager, at (301) 827-5798.

Sincerely yours,

Gary Buehler 1/28/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-913
Division File
Field Copy
HFD-600/R.West
HFD-330
HFD-205
HFD-600/Orange Book
HFD-600/D.Hare

Endorsements:

HFD-647/M.Selvam/ 1/15/2004
HFD-647/U.Venkataram/ U.V. Venkataram 1/15/2004
HFD-617/S.Shepperson/ S Shepperson 1/16/04
HFD-613/P.Birch/ P.D. Golson Jr/ 1/16/04
HFD-613/L.Golson 1/16/04
Robert West 1/28/2004

V:\FIRMSAM\IMPAX\LTRS&REV\75913.TA&AP.DOC

APPROVAL - 100 MG

TENTATIVE APPROVAL - 150 MG

cmc satisfactory
Vilayat Sayeed
1/27/04.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-913

LABELING

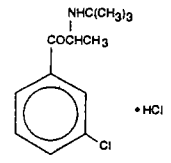
75-913

Bupropion HCl Extended-Release Tablets

Rx only

"Information for the Patient" enclosed.

DESCRIPTION: Bupropion hydrochloride extended-release tablets (bupropion hydrochloride) an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



Bupropion hydrochloride extended-release tablets are supplied for oral administration as 100 mg film-coated, extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: colloidal silicon dioxide, hydroxy-propylcellulose, magnesium stearate, and microcrystalline cellulose. The 100 mg tablet also contains FD&C red # 40, FD&C yellow # 5, hypromellose, iron oxide yellow, macrogol, polydextrose, titanium dioxide and triacetin.

CLINICAL PHARMACOLOGY:

Pharmacodynamics: Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase. While the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

Pharmacokinetics: Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied. Following oral administration of bupropion hydrochloride extended-release tablets to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. Food increased C_{max} and AUC of bupropion by 11% and 17%, respectively, indicating that there is no clinically significant food effect.

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion.

The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days.

Bupropion is extensively metabolized in humans. Three metabolites have been shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. *In vitro* findings suggest that cytochrome P450II2B6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. Nevertheless, they may be clinically important because their plasma concentrations are higher than those of bupropion.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6 (CYP2B6) isoenzyme. Although bupropion is not metabolized by cytochrome P450IID6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme (see PRECAUTIONS: Drug Interactions).

Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 6 hours after administration of bupropion hydrochloride extended-release tablets. Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 20 (±5) hours, and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

In a study comparing chronic dosing with bupropion hydrochloride extended-release tablets 150 mg twice daily to the immediate-release formulation of bupropion at 100 mg three times daily, peak plasma concentrations of bupropion at steady state for bupropion hydrochloride extended-release tablets were approximately 85% of those achieved with the immediate-release formulation. There was equivalence for bupropion AUCs, as well as equivalence for both peak plasma concentration and AUCs for all three of the detectable bupropion metabolites. Thus, at steady state, bupropion hydrochloride extended-release tablets, given twice daily, and the immediate-release formulation of bupropion, given three times daily, are essentially bioequivalent for both bupropion and the three quantitatively important metabolites.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 450 mg/day.

Population Subgroups: Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Hepatic: The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in patients with mild to severe cirrhosis. The first study showed that the half-life of hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8 healthy volunteers (32±14 hours versus 21±5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 patient groups were minimal.

The second study showed that there were no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($t_{1/2}$) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with severe hepatic cirrhosis vs.19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by about $1\frac{1}{2}$ fold for hydroxybupropion and about $2\frac{1}{2}$ fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal: The effect of renal disease on the pharmacokinetics of bupropion has not been studied. The elimination of the major metabolites of bupropion may be affected by reduced renal function.

Left Ventricular Dysfunction: During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared to healthy normal volunteers, was revealed.

Age: The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on a three times daily schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another pharmacokinetic study, single and multiple dose, had suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS: Geriatric Use).

Gender: A single-dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex-related differences in the pharmacokinetic parameters of bupropion.

Smokers: The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150 mg dose of bupropion, there was no statistically significant difference in C_{max}, half-life, t_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

CLINICAL TRIALS: The efficacy of the extended-release formulation of bupropion as a treatment for depression was established in two 4-week, placebo-controlled trials in adult inpatients with depression and in one 6-week, placebo-controlled trial in adult outpatients with depression. In the first study, patients were titrated in a bupropion dose range of 300 to 600 mg/day on a three times daily schedule; 78% of patients received maximum doses of 450 mg/day or less. This trial demonstrated the effectiveness of the immediate-release formulation of bupropion on the Hamilton Depression Rating Scale (HDRS) total score, the depressed mood item (item 1) from the scale, and the Clinical Global Impressions (CGI) severity score. A second study included two fixed doses of the immediate-release formulation of bupropion (300 and 450 mg/day) and placebo. This trial demonstrated the effectiveness of the immediate-release formulation of bupropion, but only at the 450 mg/day dose; the results were positive for the HDRS total score and the CGI severity score, but not for HDRS item 1. In the third study, outpatients received 300 mg/day of the immediate-release formulation of bupropion. This study demonstrated the effectiveness of the immediate-release formulation of bupropion on the HDRS total score, HDRS item 1, the Montgomery-Asberg Depression Rating Scale, the CGI severity score, and the CGI improvement score.

Although there are not as yet independent trials demonstrating the antidepressant effectiveness of the extended-release formulation of bupropion, studies have demonstrated the bioequivalence of the immediate-release and extended-release forms of bupropion under steady-state conditions, i.e., bupropion extended-release 150 mg twice daily was shown to be bioequivalent to 100 mg three times daily of the immediate-release formulation of bupropion, with regard to both rate and extent of absorption, for parent drug and metabolites.

INDICATIONS AND USAGE: Bupropion hydrochloride extended-release is indicated for the treatment of depression.

The efficacy of bupropion in the treatment of depression was established in two 4-week controlled trials of depressed inpatients and in one 6-week controlled trial of depressed outpatients whose diagnoses corresponded most closely to the Major Depression category of the APA Diagnostic and Statistical Manual (DSM) (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies the presence of 1) depressed mood or 2) loss of interest or pleasure; in addition, at least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicide ideation.

The physician who elects to use bupropion for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS: Bupropion hydrochloride extended-release tablets are contraindicated in patients with a seizure disorder.

Bupropion hydrochloride extended-release tablets are contraindicated in patients treated with ZYBAN® (bupropion hydrochloride) Sustained-Release Tablets, or any other medications that contain bupropion because the incidence of seizure is dose dependent.

Bupropion hydrochloride extended-release tablets are contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion.

Bupropion hydrochloride extended-release tablets are contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).

The concurrent administration of bupropion and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion.

Bupropion hydrochloride extended-release is contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up bupropion hydrochloride extended-release tablets.

WARNINGS: Patients should be made aware that bupropion contains the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion should not be used in combination with ZYBAN®, or any other medications that contain bupropion.

Seizures: Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with bupropion. Bupropion hydrochloride extended-release should be discontinued and not restarted in patients who experience a seizure while on treatment.

- **Dose: At doses of bupropion hydrochloride extended-release up to a dose of 300 mg/day, the incidence of seizure is approximately 0.1% (1/1000) and increases to approximately 0.4% (4/1000) at the maximum recommended dose of 400 mg/day.**

  Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (i.e., 13 of 3200 patients followed prospectively) in patients treated at doses in a range of 300 to 450 mg/day. The 450 mg/day upper limit of this dose range is close to the currently recommended maximum dose of 400 mg/day for bupropion hydrochloride extended-release tablets. This seizure incidence (0.4%) may exceed that of other marketed antidepressants and bupropion hydrochloride extended-release up to 300 mg/day by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted.

  Additional data accumulated for the immediate-release formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day, which is twice the usual adult dose and one and one-half the maximum recommended daily dose (400 mg) of bupropion hydrochloride extended-release tablets. This disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

  Data for bupropion hydrochloride extended-release revealed a seizure incidence of approximately 0.1% (i.e., 3 of 3100 patients followed prospectively) in patients treated at doses in a range of 100 to 300 mg/day. It is not possible to know if the lower seizure incidence observed in this study involving the sustained-release formulation of bupropion resulted from the different formulation or the lower dose used. However, as noted above, the immediate-release and sustained-release formulations are bioequivalent with regard to both rate and extent of absorption during steady state (the most pertinent condition to estimating seizure incidence), since most observed seizures occur under steady-state conditions.

- **Patient factors: Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold.**
- **Clinical situations: Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.**
- **Concomitant medications: Many medications (e.g., antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold.**

Recommendations for Reducing the Risk of Seizure: **Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if**

- **The total daily dose of bupropion hydrochloride extended-release tablets does *not* exceed 400 mg,**
- **The daily dose is administered twice daily, and**
- **The rate of incrementation of dose is gradual.**
- **No single dose should exceed 200 mg to avoid high peak concentrations of bupropion and/or its metabolites.**
- **Bupropion hydrochloride extended-release tablets should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (e.g. antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.**

Hepatic Impairment: Bupropion hydrochloride extended-release should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC, levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 100 mg every day or 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

PRECAUTIONS:

General: ***Agitation and Insomnia:*** Patients in placebo-controlled trials with bupropion hydrochloride extended-release tablets experienced agitation, anxiety, and insomnia as shown in Table 1.

Table. 1: Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials

Adverse Event Term	Bupropion hydrochloride extended-release 300 mg/day (n=376)	Bupropion hydrochloride extended-release 400 mg/day (n=114)	Placebo (n=385)
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Insomnia	11%	16%	6%

In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs.

Symptoms were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of bupropion hydrochloride extended-release tablets and 0.8% of patients treated with placebo.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Depressed patients treated with an immediate-release formulation of bupropion or with bupropion hydrochloride extended-release tablets have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Bupropion hydrochloride extended-release is expected to pose similar risks.

Altered Appetite and Weight: In placebo-controlled studies, patients experienced weight gain or weight loss as shown in Table 2.

Table. 2: Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials

Weight Change	Bupropion hydrochloride extended-release 300 mg/day (n=339)	Bupropion hydrochloride extended-release 400 mg/day (n=112)	Placebo (n=347)
Gain >5 lbs	3%	2%	4%
Lost >5 lbs	14%	19%	6%

In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of bupropion hydrochloride extended-release tablets should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for bupropion hydrochloride extended-release tablets should be written for the smallest number of tablets consistent with good patient management.

Allergic Reactions: Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking bupropion hydrochloride extended-release and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin sensitivity.

Cardiovascular Effects: In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of preexisting hypertension.

Data from a comparative study of the extended-release formulation of bupropion(ZYBAN® Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-released bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of ZYBAN®, and NTS and one patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with ZYBAN®, or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of bupropion in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in two patients for exacerbation of baseline hypertension.

Hepatic Impairment: Bupropion hydrochloride extended-release should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required. Bupropion should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis.

All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels (see CLINICAL PHARMACOLOGY, WARNINGS, and DOSAGE AND ADMINISTRATION).

Renal Impairment: No studies have been conducted in patients with renal impairment. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. Bupropion hydrochloride extended-release should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects that could indicate high drug or metabolite levels.

Information for Patients: See the tear-off leaflet for information for the Patient.

Patients should be made aware that bupropion hydrochloride extended-release contains the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended-release should not be used in combination with ZYBAN® or any other medications that contain bupropion hydrochloride.

Physicians are advised to discuss the following issues with patients:

As dose is increased during initial titration to doses above 150 mg/day, patients should be instructed to take bupropion hydrochloride extended-release tablets in two divided doses, preferably with at least 8 hours between successive doses, to minimize the risk of seizures.

Patients should be told that bupropion should be discontinued and not restarted if they experience a seizure while on treatment.

Patients should be told that any CNS-active drug like bupropion may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that bupropion hydrochloride extended-release tablets do not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.

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 bupropion. Patients should be advised that the consumption of alcohol should be minimized or avoided.

Patients should be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs. Concern is warranted because bupropion and other drugs may affect each other's metabolism.

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to swallow bupropion hydrochloride extended-release tablets whole so that the release rate is not altered. Do not chew, divide, or crush tablets.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: Few systemic data have been collected on the metabolism of bupropion hydrochloride extended-release tablets following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of bupropion hydrochloride extended-release tablets on the metabolism of other drugs.

Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. *In vitro* studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between bupropion hydrochloride extended-release tablets and drugs that affect the CYP2B6 isoenzyme (e.g., orphenadrine and cyclophosphamide). The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of two 150 mg bupropion hydrochloride extended-release tablets with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

While not systematically studied, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin).

Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In one study, following chronic administration of bupropion, 100 mg three times daily to eight healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically important alterations of blood levels of coadministered drugs.

397-01

Bupropion HCl Extended-Release Tablets

APPROVAL JAN 28 2004

ENLARGED TO 150% BY FOIA STAFF

P. 1 OF 2

Drug Metabolized By Cytochrome P450IID6 (CYP2D6): Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme *in vitro*. In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $T_{1/2}$ of desipramine by an average of approximately two-, five- and two-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

Therefore, coadministration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index.

MAO Inhibitors: Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Levodopa and Amantadine: Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of bupropion to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

Drugs that Lower Seizure Threshold: Concurrent administration of bupropion and agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and gradual dose increases should be employed.

Nicotine Transdermal System: (see PRECAUTIONS: Cardiovascular Effects).

Alcohol: In post marketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol intolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with bupropion should be minimized or avoided (also see **CONTRAINDICATIONS**).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg per day, respectively. These doses are approximately seven and two times the maximum recommended human dose (MRHD), respectively, on a mg/m^2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg per day (approximately two to seven times the MRHD on a mg/m^2 basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a positive response (two to three times control mutation rate) in two of five strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in one of three *in vivo* rat bone marrow cytogenetic studies.

A fertility study in rats at doses up to 300 mg/kg revealed no evidence of impaired fertility.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Teratology studies have been performed at doses up to 450 mg/kg in rats, and at doses up to 150 mg/kg in rabbits (approximately 7 to 11 and 7 times the MRHD, respectively, on a mg/m^2 basis), and have revealed no evidence of harm to the fetus due to bupropion. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of bupropion on labor and delivery in humans is unknown.

Nursing Mothers: Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from bupropion, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of bupropion in pediatric patients below 18 years old have not been established. The immediate-release formulation of bupropion was studied in 104 pediatric patients (age range, 6 to 16) in clinical trials of the drug for other indications. Although generally well tolerated, the limited exposure is insufficient to assess the safety of bupropion in pediatric patients.

Geriatric Use: Of the approximately 6000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see CLINICAL PHARMACOLOGY).

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see PRECAUTIONS: Renal Impairment and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: (See also WARNINGS and PRECAUTIONS)

The information included under the Incidence in Controlled Trials subsection of ADVERSE REACTIONS is based primarily on data from controlled clinical trials with bupropion hydrochloride extended-release tablets. Information on additional adverse events associated with the sustained-release formulation of bupropion in smoking cessation trials, as well as the immediate-release formulation of bupropion, is included in a separate section (see Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion).

Incidence in Controlled Trials With Bupropion Hydrochloride Extended-Release Tablets: ***Adverse Events Associated With Discontinuation of Treatment Among Patients Treated With Bupropion Hydrochloride Extended-Release Tablets:*** In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of bupropion hydrochloride extended-release tablets and 4% of patients treated with placebo discontinued treatment due to adverse events. The specific adverse events in these trials that led to discontinuation in at least 1% of patients treated with either 300 or 400 mg/day of bupropion hydrochloride extended-release tablets and at a rate at least twice the placebo rate are listed in Table 3.

Table. 3: Treatment Discontinuations Due to Adverse Events in Placebo Controlled Trials

Adverse Event Term	Bupropion hydrochloride extended-release 300 mg/day (n=376)	Bupropion hydrochloride extended-release 400 mg/day (n=114)	Placebo (n=385)
Rash	2.4%	0.9%	0.0%
Nausea	0.8%	1.8%	0.3%
Agitation	0.3%	1.8%	0.3%
Migraine	0.0%	1.8%	0.3%

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With bupropion hydrochloride extended-release tablets: Table 4 enumerates treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of bupropion hydrochloride extended-release tablets and with placebo in placebo-controlled trials. Events that occurred in either the 300- or 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse events were classified using a COSTART-based Dictionary.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions. Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of bupropion is provided in the WARNINGS and PRECAUTIONS sections.

Table. 4: Treatment-Emergent Adverse Events in Placebo-Controlled Trials*

Body System/ Adverse Event	Bupropion hydrochloride extended-release 300 mg/day (n=376)	Bupropion hydrochloride extended-release 400 mg/day (n=114)	Placebo (n=385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	–
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	–
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	--
Nervous system			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	--	3%	1%
Paresthesia	1%	2%	1%
CNS stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	--
Amblyopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	--	2%	0%
Vaginal hemorrhage†	0%	2%	--
Urinary tract infection	1%	0%	--

* Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of bupropion hydrochloride extended-release tablets, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.
† Incidence based on the number of female patients.
-- Hyphen denotes adverse events occurring in greater than 0 but less than 0.5% of patients.

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials: Adverse events from Table 4 occurring in at least 5% of patients treated with bupropion and at a rate at least twice the placebo rate are listed below for the 300 and 400 mg/day dose groups.

Bupropion Hydrochloride Extended-Release 300 mg/day: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

Bupropion Hydrochloride Extended-Release 400 mg/day: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion: In addition to the adverse events noted above, the following events have been reported in clinical trials and postmarketing experience with the sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion.

Adverse events for which frequencies are provided below occurred in clinical trials with the sustained-release formulation of bupropion. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n=987) or smoking cessation (n=1013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with bupropion hydrochloride extended-release tablets (n=3100). All treatment-emergent adverse events are included except those listed in Tables 1 through 4, those events listed in other safety-related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than two patients. Events of major clinical importance are described in the WARNINGS and PRECAUTIONS sections of labeling.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients. Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with bupropion. Only those adverse events not previously listed for sustained-release bupropion are included. The extent to which these events may be associated with bupropion hydrochloride extended-release is unknown.

Body (general): Infrequent were chills, facial edema, musculoskeletal chest pain, and photosensitivity. Rare was malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS)

Cardiovascular: Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

Endocrine: Also observed were hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic: Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Metabolic and Nutritional: Infrequent were edema and peripheral edema. Also observed was glycosuria.

Musculoskeletal: Infrequent were leg cramps. Also observed were muscle rigidity/fever/rhabdomyolysis and muscle weakness.

Nervous System: Infrequent were abnormal coordination, decreased libido, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and unmasking tardive dyskinesia.

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

Skin: Rare was maculopapular rash. Also observed were alopecia, angioedema, exfoliative dermatitis, and hirsutism.

Special Senses: Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, and mydriasis.

Urogenital: Infrequent were impotence, polyuria, and prostate disorder. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

DRUG ABUSE AND DEPENDENCE:

Controlled Substance Class: Bupropion is not a controlled substance.

Humans: Controlled clinical studies of bupropion conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients showed some increase in motor activity and agitation/excitement.

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion produced mild amphetamine-like activity as compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability.

Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be especially reinforcing to amphetamine or stimulant abusers. However, higher doses that could not be tested because of the risk of seizure might be modestly attractive to those who abuse stimulant drugs.

Animals: Studies in rodents and primates have shown that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavioral response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models to assess the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

OVERDOSAGE:

Human Overdose Experience: There has been very limited experience with overdosage of bupropion hydrochloride extended-release tablets; three cases were reported during clinical trials. One patient ingested 3000 mg of bupropion hydrochloride extended-release tablets and vomited quickly after the overdose; the patient experienced blurred vision and lightheadedness. A second patient ingested a "handful" of bupropion hydrochloride extended-release tablets and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3600 mg. of bupropion hydrochloride extended-release tablets and a bottle of wine; the patient experienced nausea, visual hallucinations, and "grogginess." None of the patients experienced further sequelae.

There has been extensive experience with overdosage of the immediate-release formulation of bupropion. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of the immediate-release formulation of bupropion and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

Since introduction, overdoses of up to 17,500 mg of the immediate-release formulation of bupropion have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of the immediate-release formulation of bupropion alone included hallucinations, loss of consciousness, and sinus tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when the immediate-release formulation of bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of the immediate-release formulation of bupropion alone have been reported rarely in patients ingesting massive doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

Overdosage Management: Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first 48 hours post-ingestion. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion overdoses. No specific antidotes for bupropion are known.

Due to the dose-related risk of seizures with bupropion hydrochloride extended-release, hospitalization following suspected overdose should be considered. Based on studies in animals, it is recommended that seizures be treated with intravenous benzodiazepine administration and other supportive measures, as appropriate.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION:

General Dosing Considerations: It is particularly important to administer bupropion hydrochloride extended-release tablets in a manner most likely to minimize the risk of seizure (see WARNINGS). Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped. Bupropion hydrochloride extended-release should be swallowed whole and not crushed, divided, or chewed.

Initial Treatment: The usual adult target dose for bupropion hydrochloride extended-release tablets is 300 mg/day, given as 150 mg twice daily. Dosing with bupropion hydrochloride extended-release tablets should begin at 150 mg/day given as a single daily dose in the morning. If the 150 mg initial dose is adequately tolerated, an increase to the 300 mg/day target dose, given as 150 mg twice daily, may be made as early as day 4 of dosing. There should be an interval of at least 8 hours between successive doses.

Increasing the Dosage Above 300 mg/day: As with other antidepressants, the full antidepressant effect of bupropion hydrochloride extended-release tablets may not be evident until 4 weeks of treatment or longer. An increase in dosage to the maximum of 400 mg/day, given as 200 mg twice daily, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day.

Maintenance: It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Dosage Adjustment for Patients with Impaired Hepatic Function: Bupropion hydrochloride extended-release should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 100 mg every day or 150 mg every other day in these patients. Bupropion hydrochloride extended-release should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

Dosage Adjustment for Patients with Impaired Renal Function: Bupropion hydrochloride extended-release should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED: Bupropion hydrochloride extended-release tablets, 100 mg of bupropion hydrochloride, are yellow, round, convex, film-coated tablets, debossed with "G" on one side and "2442" on the other side.

Bottles of 100 ..... NDC 0115-2442-01
Bottles of 500 ..... NDC 0115-2442-02

Store at 20-25°C (68-77°F). (See USP Controlled Room Temperature).
Dispense in tightly closed, light-resistant container (USP).

Mfg. by:
IMPAX Laboratories, Inc.
Hayward, CA 94544 USA

Dist. by:
Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124 USA

Rev. 11/2003
397-01

PATIENT INFORMATION LEAFLET

PHARMACIST - DETACH HERE AND GIVE LEAFLET TO PATIENT

Patient Information

Bupropion Hydrochloride Extended-Release Tablets

Read this information completely before you start taking bupropion hydrochloride extended-release tablets. Read the information each time you get more medicine. There may be something new. This leaflet provides a summary about bupropion hydrochloride extended-release tablets. It does not include everything there is to know about your medicine. This information should not take the place of discussions with your doctor about your medical condition or bupropion hydrochloride extended-release tablets.

What is the most important information I should know about bupropion hydrochloride extended-release tablets?

• At a dose of up to 300 mg each day, there is a chance that approximately 1 out of every 1000 people taking bupropion hydrochloride, the active ingredient in bupropion hydrochloride extended-release tablets, will have a seizure. The chance of seizures further increases with doses above 300 mg a day. Seizures are also called convulsions. They can cause you to fall with uncontrolled shaking.

• **You may have an increased risk of seizures while taking bupropion hydrochloride extended-release tablets if you have certain medical problems.** Be sure to tell your doctor about all of your medical problems.

• **You may have an increased risk of seizures while taking bupropion hydrochloride extended-release tablets if you take certain medicines.** Be sure to tell your doctor about all the medicines you take, including non-prescription medicines and herbal or natural supplements. For more information, see the section "Who should not take bupropion hydrochloride extended-release tablets?"

If you have a seizure while taking bupropion hydrochloride extended-release tablets, stop taking the tablets and call your doctor right away. Do not take bupropion hydrochloride extended-release tablets again if you have a seizure.

What are bupropion hydrochloride extended-release tablets? Bupropion hydrochloride extended-release tablets are a prescription medicine used to treat depression. Bupropion hydrochloride extended-release tablets are thought to treat depression by correcting an imbalance of certain chemicals in your brain.

Who should not take bupropion hydrochloride extended-release tablets? Do not take bupropion hydrochloride extended-release tablets if you • have or have ever had a seizure disorder such as epilepsy. • are taking ZYBAN® (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, the active ingredient in bupropion hydrochloride extended-release tablets. • are abruptly discontinuing use of alcohol or sedatives (including benzodiazepines). • have taken within the last 14 days one of the medicines for depression known as a monoamine oxidase inhibitor (MAOI), such as Nardil® (phenelzine sulfate), Parnate® (tranylcypromine sulfate), or Marplan® (isocarboxazid). • have or have ever had an eating disorder, such as anorexia nervosa or bulimia. • are allergic to the active ingredient, bupropion, or to any of the inactive ingredients. Your doctor and pharmacist have a list of the inactive ingredients.

What should I tell my doctor before using bupropion hydrochloride extended-release tablets?

• **Tell your doctor about all your medical conditions.** Tell your doctor if you • are pregnant or plan to become pregnant. It is not known if bupropion can harm the unborn baby. • are breast feeding. Bupropion passes through your milk. It is not known whether bupropion in breast milk can harm the baby. • have liver or kidney problems • have an eating disorder, such as anorexia nervosa or bulimia • have had a head injury • have had a seizure • have a tumor in your nervous system • recently had a heart attack, have heart problems, or have high blood pressure • are a diabetic taking insulin or other medicines to control your blood sugar • are a heavy drinker of alcoholic beverages • use tranquilizers or sedatives frequently

• **Tell your doctor about all the medicines you take,** including non-prescription medicines and herbal or natural remedies. Some may increase your chance of getting seizures or other side effects if you take bupropion hydrochloride extended-release tablets.

How should I take bupropion hydrochloride extended-release tablets?

• Take bupropion hydrochloride extended-release tablets at the same time each day exactly as prescribed by your doctor. You may take bupropion hydrochloride extended-release tablets with or without food. • It may take 4 weeks or more for you to feel that bupropion hydrochloride extended-release tablets are working. Once you feel better, it is important to keep taking bupropion hydrochloride extended-release tablets as directed by your doctor. • Take your doses at least 8 hours apart. • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and take your next tablet the regular time. It is important so you do not increase your chance of having a seizure. • It is important to swallow bupropion hydrochloride extended-release tablets whole. Do not chew, divide, or crush tablets.

FRONT

What should I avoid while taking bupropion hydrochloride extended-release tablets?

• Limit the amount of alcohol you drink while taking bupropion hydrochloride extended-release tablets. 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 risk of seizures. • Do not drive a car or use heavy machinery until you know if bupropion hydrochloride extended-release tablets affect your ability to perform these tasks.

What are possible side effects of bupropion hydrochloride extended-release tablets?

• **Seizures.** Some patients get seizures while taking bupropion hydrochloride extended-release tablets. **If you have a seizure while taking bupropion hydrochloride extended-release tablets, stop taking the tablets and call your doctor right away.** Do not take bupropion hydrochloride extended-release tablets again if you have a seizure.

• **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes severe, while taking bupropion hydrochloride extended-release tablets. The chance of high blood pressure may be increased if you also use nicotine replacement therapy (for example, a nicotine patch) to help you stop smoking.

Call your doctor right away if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, swelling of the lips or tongue, or have trouble breathing. These could be signs of a serious allergic reaction. The most common side effects of bupropion hydrochloride extended-release tablets are loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, difficulty sleeping, muscle pain, nausea, rapid heart beat, sore throat, and urinating more often. If you have nausea, you may want to take your medicine with food. If you have difficulty sleeping, avoid taking your medicine too close to bedtime. These are not all the side effects of bupropion hydrochloride extended-release tablets. For a complete list, ask your doctor or pharmacist. Tell your doctor right away about any side effects that bother you. Do not change your dose or stop taking bupropion hydrochloride extended-release tablets without talking with your doctor first.

BACK

General information about bupropion hydrochloride extended-release tablets.

• Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use bupropion hydrochloride extended-release tablets for a condition for which it was not prescribed. Do not give bupropion hydrochloride extended-release tablets to other people, even if they have the same symptoms you have. It may harm them. Keep bupropion hydrochloride extended-release tablets out of the reach of children. • Store bupropion hydrochloride extended-release tablets at room temperature, out of direct sunlight. Keep bupropion hydrochloride extended-release tablets in a tightly closed container. • Bupropion hydrochloride extended-release tablets may have a characteristic odor. If present, this odor is normal. This leaflet summarizes the most important information about bupropion hydrochloride extended-release tablets. For more information, talk with your doctor or pharmacist. They can give you information about bupropion hydrochloride extended-release tablets that is written for health professionals.

Mfg. by:
IMPAX Laboratories, Inc.
Hayward, CA 94544 USA
Rev. 11/2003 187-04

Dist. by:
Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124 USA

ENLARGED TO 120% BY FOIA STAFF.

Exp. Date

N 3 0115-2442-02 2

GLOBAL®

NDC 0115-2442-02

buPROPion HCl

Extended-release Tablets

100 mg

WARNING: Do not use in combination with Zyban® or any other medicines that contain bupropion hydrochloride.

Rx only

500 TABLETS

USUAL DOSAGE: See accompanying outsert for complete prescribing information. Dispense in tightly-closed, light-resistant containers with safety closures.
Each tablet contains 100 mg of bupropion HCl.
Contains FD&C Yellow No. 5 (tartrazine) as a color additive.
Store at 20°-25°C (68°-77°F).
(See USP Controlled Room Temperature).
Keep this and all medication out of reach of children.
Zyban® is a registered trademark of Glaxo Wellcome, Inc.

Mfg. by: IMPAX Laboratories, Inc.
Hayward, CA 94544 USA

Dist. by: Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124 USA

Rev. 11/2003
187-04

N 3 0115-2442-02 2

JAN 28 2004

Lot No.:

Exp. Date

N 3 0115-2442-01 5

GLOBAL®

NDC 0115-2442-01

buPROPion HCl

Extended-release Tablets

100 mg

WARNING: Do not use in combination with Zyban® or any other medicines that contain bupropion hydrochloride.

Rx only

100 TABLETS

USUAL DOSAGE: See accompanying outsert for complete prescribing information. Dispense in tightly-closed, light-resistant containers with safety closures.
Each tablet contains 100 mg of bupropion HCl.
Contains FD&C Yellow No. 5 (tartrazine) as a color additive.
Store at 20°-25°C (68°-77°F).
(See USP Controlled Room Temperature).
Keep this and all medication out of reach of children.
Zyban® is a registered trademark of Glaxo Wellcome, Inc.

Mfg. by: IMPAX Laboratories, Inc.
Hayward, CA 94544 USA

Dist. by: Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124 USA

Rev. 11/2003
186-03

N 3 0115-2442-01 5

JAN 28 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-913

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-913** Date of Submission: **June 22 and August 9, 2000**

Applicant's Name: **Impax Pharmaceuticals, Inc**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

Labeling Deficiencies:

1. CONTAINER 100s and ——— (100 mg and 150 mg)

   a. We encourage you to further differentiate your product strengths by boxing, contrasting colors, or some other means.

   b. WARNING: Do not use in combination with Zyban® or any other medicines that contain bupropion hydrochloride.

   c. We encourage you to include the disclaimer "Zyban® is a registered trademark of Glaxo Wellcome.".

2. INSERT

   a. GENERAL COMMENTS

      i. "*in vitro*" and "*in vivo*" (*italics*) throughout the insert labeling

      ii. Delete the hyphen between the number and the units when expressing a dose (e.g., "150 mg" rather than "150-mg").

      iii. "Zyban®" and "ZYBAN®" rather than "Zyban" and "ZYBAN" throughout the insert labeling.

      iv. Replace "sustained" with "extended" throughout the insert labeling except in association with "Zyban®".

      v. Replace "Bupropion ER" with "bupropion hydrochloride extended-release tablets" throughout the insert labeling.

   b. DESCRIPTION

      There is no need to list "NF" with the inactive ingredients.

   c. CLINICAL PHARMACOLOGY

      Pharmacokinetics, eighth paragraph, last sentence - "(±10)" and "(±13)" (delete hyphens)

   d. INDICATIONS AND USAGE

      i. Add a blank line space before this section to be consistent with your formatting.

      ii. Penultimate paragraph - ... previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, ...

e. WARNINGS

"Patient factors:" rather than "Patients factors:"

f. PRECAUTIONS

i. General: Agitation and Insomnia, first sentence - "experienced" rather than "experiences"

ii. Cardiovascular Effects, second paragraph

A). First sentence - ... "extended-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of extended-release bupropion and NTS. In this study ..."

B). Penultimate sentence - "treated" rather than "treted"

iii. Renal or Hepatic Impairment, first sentence - "... kidney and metabolites ..." (delete "the")

iv. Drug Interactions

A). Second paragraph, first sentence - "Because bupropion ..." (delete "of")

B). Drugs Metabolized By ..., second paragraph, first sentence - "coadministration" (delete hyphen)

v. Geriatric Use, last sentence - Delete "(see Use in Patients with Systemic Illness)".

g. ADVERSE REACTIONS

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials

i. Add "Observed" to the title.

ii. First sentence - "... below for the 300 and ..." (add "the")

h. HOW SUPPLIED

Your tablet descriptions as seen in your Specification and Quality Assurance Reports do not agree with those seen in this section. Please revise and/or comment.

i. INFORMATION FOR THE PATIENT (PATIENT PACKAGE INSERT)

i. How many will accompany each container size and how will they accompany the drug product?

ii. See GENERAL COMMENTS 2(a)(ii), (iii), and (v).

Please revise your container labels and physician and patient package insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: 100s and ———

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Wellbutrin SR®

NDA Number: 20-358

NDA Drug Name: Wellbutrin SR® (bupropion hydrochloride extended-release) Tablets

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: 4-10-00 (S-015)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or			X

cap incorrect?			
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) HOW SUPPLIED says tabs are imprinted but there is no mention of an imprinting ink anywhere			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	??		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative			

supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

The description of the tablets in the HOW SUPPLIED section does not agree with those seen in the Specification and Quality Assurance Reports.

FOR THE RECORD:

1. This review was based on the labeling for Wellbutrin SR® (Glaxo Wellcome; Approved 4-10-00; Revised 9-99) NDA 20-358/S-015.

2. The inactive ingredients are listed accurately in the DESCRIPTION section (p 6196 v B 1.1).

3. IMPAX is the manufacturer (p 6304 v B 1.1).

4. The RLD is available in 100 mg and 150 mg strengths - both in 60s. The ANDA will be available (100 mg and 150 mg) in container sizes of 100s and ———

5. The tablet descriptions in the HOW SUPPLIED section do not agree with those seen in the Specification and Quality Assurance Reports. I have mentioned this to the firm and to the chemist in my review (pp 6664, 6679 v 1.21).

6. There are 5 patents (no exclusivities) for this drug product.

5,358,970	8-12-13
5,427,798	8-12-13
RE33994	8-18-04
5,763,493	8-12-13
5,731,000	8-12-13

The firm has filed under Paragraph IV.

7. It is unclear whether or not this drug product is sensitive to light. The containers are made of amber glass in any case.

8. Storage/dispensing recommendations:

   RLD - Store at CRT 20°-25°C (68°-77°F)(see USP). Dispense in a tight, light-resistant container as defined in the USP.

   ANDA - Store at———————————. Dispense in tightly-closed, light-resistant container (USP).

   USP - not USP

9. Both the RLD (see PDR) and this ANDA have unscored tablets. The tablet descriptions in the submission do not mention the scoring configuration. I am assuming that the tablets are unscored (the tablets are extended-release).

10. IMPAX's ANDA 75-914 is also for bupropion but it is based on Zyban® whereas ANDA 75-913 is based on Wellbutrin SR®.

Date of Review: 8-23-00 **Date of Submission:** 6-22-00

Primary Reviewer: Adolph Vezza A. Vezza **Date:** 8/28/00

Team Leader: Charlie Hoppes Charlie Hoppes **Date:** 8/28/00

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-913** Dates of Submission: **May 16, 2001 and November 27, 2001**

Applicant's Name: **Impax Pharmaceuticals, Inc**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No – Tentative Approval

Container Labels: 100s (100 mg and 150 mg) and 500s (100 mg)
Satisfactory in draft as of November 27, 2001 submission.

Professional Package Insert Labeling:
Satisfactory in draft as of November 27, 2001 submission.

Patient Package Insert Labeling:
Satisfactory in draft as of November 27, 2001 submission.

Revisions needed post-approval: PI - DESCRIPTION - 100 mg tab also contains "iron oxide yellow" ADVERSE REACTIONS, Table 4 - Realign the data in the rows "Amblyopia", "Urinary urgency", "Vaginal hemorrhage" and "Urinary tract infection" HOW SUPPLIED - the 150 mg tablet is '

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Wellbutrin SR®

NDA Number: 20-358

NDA Drug Name: Wellbutrin SR® (bupropion hydrochloride extended-release) Tablets

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: 4-10-00 (S-015)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	

Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) Tablets are debossed.		X	

USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	??		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Wellbutrin SR® (Glaxo Wellcome; Approved 4-10-00; Revised 9-99) NDA 20-358/S-015. Supplement 16 had nothing to do with labeling and Supplement 19 (for the use of the drug in maintaining an antidepressant effect when dosed up to one year) will be getting 3 years exclusivity.

2. The inactive ingredients are listed accurately in the DESCRIPTION section (p 3508 v 4 11) except the firm has failed to mention that the 100 mg tab also contains "iron oxide yellow".

3. IMPAX is the manufacturer (p 6304 v B 1.1).

4. The RLD is available in 100 mg and 150 mg strengths - both in 60s. The ANDA will be available in container sizes of 100s (100 mg and 150 mg) and 500s (100 mg).

5. The tablet descriptions in the HOW SUPPLIED section are accurate (pp 4226, 4277 v 4.12) except the submission describes the 150 mg tablet as " _____ while the HOW SUPPLIED section describes it as " ____ .

6. There are 5 patents (no exclusivities) for this drug product.

5,358,970	8-12-13
5,427,798	8-12-13
RE33994	8-18-04
5,763,493	8-12-13
5,731,000	8-12-13

   The firm has filed under Paragraph IV.

7. It is unclear whether or not this drug product is sensitive to light. The containers are made of amber glass in any case.

8. Storage/dispensing recommendations:

   RLD - Store at CRT 20°-25°C (68°-77°F)(see USP). Dispense in a tight, light-resistant container as defined in the USP.

   ANDA - Store at _____. Dispense in tightly-closed, light-resistant container (USP).

   USP - not USP

9. Both the RLD (see PDR) and this ANDA have unscored tablets. The tablet descriptions in the submission are silent on the scoring (pp 6664, 6679 v 1.21) so I am assuming that the tablets are unscored (the tablets are extended-release).

10. IMPAX's ANDA 75-914 is also for bupropion but it is based on Zyban® whereas ANDA 75-913 is based on Wellbutrin SR®.

Date of Review: **12-10-01** **Dates of Submission:** **5-16-01 & 11-27-01**

Primary Reviewer: **Adolph Vezza** **Date:** 12/11/01

A. Vezza

Team Leader: **Charlie Hoppes** **Date:** 12/11/01

cc:

ANDA: 75-913
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/12/10/01|V:\FIRMSAM\IMPAX\LTRS&REV\75913TAP.L2
Review

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-913** Dates of Submission: **December 2 and December 16, 2002**

Applicant's Name: **Impax Pharmaceuticals, Inc**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

Labeling Deficiencies:

1. INSERT

   a. CLINICAL TRIALS

      First paragraph, Sentence beginning "This trial ..." - "450 mg/day dose" (delete the hyphen)

   b. CONTRAINDICATIONS

      Revise so that the following becomes the fourth paragraph:

      "Bupropion hydrochloride extended-release tablets are contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines)."

   c. WARNINGS (Seizures)

      i. First bullet, third line - "0.4%" (add "%")

      ii. Recommendations for Reducing the Risk of Seizure, first bullet - "***not***" (***bold and italics***)

      iii. Hepatic Impairment, second sentence - "... as peak bupropion, as well as AUC, levels are ..."

   d. PRECAUTIONS

      i. General - Cardiovascular Effects

         A). First paragraph, first sentence - "... in some cases severe, requiring acute treatment, has been ..." (add two commas)

         B). Third paragraph, third sentence - "... well tolerated in depressed patients who ..."

      ii. Information for Patients, Physicians are advised to discuss the following issues with patients

         A). Add the following as the second paragraph:

         "Patients should be told that bupropion should be discontinued and not restarted if they experience a seizure while on treatment.

         Patients should be told that any CNS-active ..."

B). Revise the paragraph which discusses alcohol use as follows:

"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 bupropion. Patients should be advised that the consumption of alcohol should be minimized or avoided.

Patients should be advised to ..."

iii. Laboratory Tests - Revise the title ("Tests" rather than "Test").

iv. Drug Interactions

A). Levodopa and Amantadine

1). Retitle this sub-subsection as shown above.

2). Revise this sub-subsection as follows:

"... in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of bupropion to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

B). Add the following sub-subsection immediately after the "Nicotine Transdermal System" sub-subsection:

Alcohol: In post marketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol intolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with bupropion should be minimized or avoided (also see CONTRAINDICATIONS).

f. ADVERSE REACTIONS

Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion, Hemic and Lymphatic - Add the following as the last sentence:

"... thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.."

g. OVERDOSAGE

Human Overdose Experience, first paragraph, second sentence - "vomited" rather than "[redacted]"

h. HOW SUPPLIED

State "[redacted]" rather than "[redacted]" as the color of the 150 mg tablet.

2. PATIENT INFORMATION LEAFLET

a. What is the most important information..., first bullet, second line - Place a space between "bupropion" and "hydrochloride"

b. What should I tell my doctor ...,

i. Delete "hydrochloride extended-release tablets" (three instances). You may retain it in the question if you wish.

ii. "Bupropion passes through your milk."

iii. "anorexia nervosa"

iv. "Tell your doctor about all the medicines you take" ("you" rather than "your")

c. How should I take ..., third line up from the last line

i. "... your next tablet the regular ..." (delete "at")

ii. "It is important ..." rather than "This is important ..."

Please revise your physician and patient package insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling?
Container Labels: 100s (100 mg and 150 mg) and 500s (100 mg)
Satisfactory in FPL as of December 2, 2002 submission.
Professional Package Insert Labeling:
Satisfactory as of submission.
Patient Package Insert Labeling (attached to Container Labels):
Satisfactory as of submission.
Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Wellbutrin SR®
NDA Number: 20-358
NDA Drug Name: Wellbutrin SR® (bupropion hydrochloride extended-release) Tablets
NDA Firm: Glaxo Wellcome
Date of Approval of NDA Insert and supplement #: 10-22-02 (S-029)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) Tablets are debossed.		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	??		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Wellbutrin SR® (Glaxo Wellcome; Approved 10-22-02; Revised 10-02) NDA 20-358/S-029.

2. The inactive ingredients are listed accurately in the DESCRIPTION section (p 3508 v 4 11).

3. IMPAX is the manufacturer (p 6304 v B 1.1).

4. The RLD is available in 100 mg and 150 mg strengths - both in 60s. The ANDA will be available in container sizes of 100s (100 mg and 150 mg) and 500s (100 mg).

5. The tablet descriptions in the HOW SUPPLIED section are accurate (pp 4226, 4277 v 4.12) except the submission describes the 150 mg tablet as " ——— while the HOW SUPPLIED section describes it as "———

6. There are 5 patents and one exclusivity for this drug product.

5,358,970	8-12-13
5,427,798	8-12-13
RE33994	8-18-04
5,763,493	8-12-13
5,731,000	8-12-13

The firm has filed under Paragraph IV.

Patent/ Exclusivities

Patent Data – 20-358

No	Expiration	Use Code	Use	File
5,358,970	8-12-13		Pharmaceutical composition containing bupropion HCl & a stabilizer	IV
5,427,798	8-12-13		Controlled sustained release tablets containing bupropion	IV
RE 33994	8-18-04		Pharmaceutical delivery system	IV
5,763,493	8-12-13		Stabilized pharmaceutical	IV
5,731,000	8-12-13		Stabilized pharmaceutical composition containing bupropion	IV

Exclusivity Data - 20-358

Code/sup	Expiration	Use Code	Description		Labeling Impact
M-10	6-11-04	M-10	Information regarding maintenance of an antidepressant effect up to 1 year of dosing		SEE BELOW

See the table and the model labeling in the file for how the insert labeling was modified to accommodate the exclusivity.

7. It is unclear whether or not this drug product is sensitive to light. The containers are made of amber glass in any case.

8. Storage/dispensing recommendations:

RLD - Store at CRT 20°-25°C (68°-77°F)(see USP). Dispense in a tight, light-resistant container as defined in the USP.

ANDA - Store at ——— Dispense in tightly-closed, light-resistant container (USP).

USP - not USP

9. Both the RLD (see PDR) and this ANDA have unscored tablets. The tablet descriptions in the submission are silent on the scoring (pp 6664, 6679 v 1.21) so I am assuming that the tablets are unscored (the tablets are extended-release).

10. IMPAX's ANDA 75-914 is also for bupropion but it is based on Zyban® whereas ANDA 75-913 is based on Wellbutrin SR®.

Date of Review: 1-3-03 Dates of Submission: 12-2-02 & 12-16-02

Primary Reviewer: Adolph Vezza Date: 1/22/03

A. Vezza

Team Leader: Lillie Golson Date: 1/22/03

Lil Golson

cc:

ANDA: 75-913
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)
aev/1/3/03|V:\FIRMSAM\IMPAX\LTRS&REV\75913na2.l
Review

APPEARS THIS WAY
ON ORIGINAL

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-913** Dates of Submission: **July 9 and August 1, 2003**

Applicant's Name: **Impax Pharmaceuticals, Inc**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No

Professional Package Insert Labeling:
Satisfactory in FPL as of July 9, 2003 submission

Container Labels and Patient Package Insert Labeling (attached to Container Labels):

Revisions needed PRE-approval:

a. 100s container size

It is unclear how the patient information leaflet will appear on the bottles. Please submit as FPL the actual labeling piece.

b. 500s container size

i. It is difficult to read your insert labeling. Please enhance the readability of your insert labeling. The information on the labels/labeling lacks the conspicuousness required by section 502c of the Act. In order to assure that the computer generated labels/labeling meet this requirement, they must be of true size, color and clarity. Refer to 21 CFR 201.15(a)(6) for guidance.

ii. You have included one patient information leaflet for this bottle size. It is expected that this bottle size is intended for the dispensing of multiple prescriptions. Please describe your plans for supplying the patient information leaflet with your product, e.g., how many leaflets will you supply for each container size and how will these leaflets be supplied.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Wellbutrin SR®
NDA Number: 20-358
NDA Drug Name: Wellbutrin SR® (bupropion hydrochloride extended-release) Tablets
NDA Firm: Glaxo Wellcome
Date of Approval of NDA Insert and supplement #: 10-22-02 (S-029)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	

Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) Tablets are debossed.		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	??		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Wellbutrin SR® (Glaxo Wellcome; Approved 10-22-02; Revised 10-02) NDA 20-358/S-029.

2. The inactive ingredients are listed accurately in the DESCRIPTION section (p 3508 v 4 11).

3. IMPAX is the manufacturer (p 6304 v B 1.1).

4. The RLD is available in 100 mg and 150 mg strengths - both in 60s. The ANDA will be available in container sizes of 100s (100 mg and 150 mg) and 500s (100 mg).

5. The tablet descriptions in the HOW SUPPLIED section are accurate (pp 4226, 4277 v 4.12).

6. There are 5 patents and one exclusivity for this drug product.

5,358,970	8-12-13
5,427,798	8-12-13
RE33994	8-18-04
5,763,493	8-12-13
5,731,000	8-12-13

The firm has filed under Paragraph IV.

Patent/ Exclusivities

Patent Data – 20-358

No	Expiration	Use Code	Use	File
5,358,970	8-12-13		Pharmaceutical composition containing bupropion HCl & a stabilizer	IV
5,427,798	8-12-13		Controlled sustained	IV

			release tablets containing bupropion	
RE 33994	8-18-04		Pharmaceutical delivery system	IV
5,763,493	8-12-13		Stabilized pharmaceutical	IV
5,731,000	8-12-13		Stabilized pharmaceutical composition containing bupropion	IV

Exclusivity Data - 20-358

Code/sup	Expiration	Use Code	Description		Labeling Impact
M-10	6-11-04	M-10	Information regarding maintenance of an antidepressant effect up to 1 year of dosing		SEE BELOW

See the table and the model labeling in the file for how the insert labeling was modified to accommodate the exclusivity.

7. USP does not indicate this product is light sensitive.

8. Storage/dispensing recommendations:

   RLD - Store at CRT 20°-25°C (68°-77°F)(see USP). Dispense in a tight, light-resistant container as defined in the USP.

   ANDA - Store at CRT 20°-25°C (68°-77°F). (See USP Controlled Room Temperature). Dispense in a tightly closed, light-resistant container (USP).
   *Container labels request containers with safety closures.

   USP - not USP

9. Both the RLD (see PDR) and this ANDA have unscored tablets. The tablet descriptions in the submission are silent on the scoring (pp 6664, 6679 v 1.21) so I am assuming that the tablets are unscored (the tablets are extended-release).

10. IMPAX's ANDA 75-914 is also for bupropion but it is based on Zyban® whereas ANDA 75-913 is based on Wellbutrin SR®.

Date of Review: **September 23, 2003** **Dates of Submissions:** **7/9 and 8/1/ 2003**

Primary Reviewer: **Postelle Birch** **Date:** **September 24, 2003**

Team Leader: **Lillie Golson** **Date:** 9/25/03

---

cc:

ANDA: 75-913
DUP/DIVISION FILE
HFD-613/PBirch/LGolson (no cc)
V:\FIRMSAM\IMPAX\LTRS&REV\75913na3.l.doc
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-913** Dates of Submission: **September 5, 2003**

Applicant's Name: **Impax Pharmaceuticals, Inc**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

Labeling Deficiencies:

1. Professional Package Insert Labeling:

   a. DESCRIPTION

   We note that the listing of the inactive ingredients does not include all of the ingredients appearing in your Components and Composition Statements and Raw Materials Controls. Please insert "iron oxide yellow" in the listing of inactive ingredients for the 100mg tablet.

   b. PRECAUTIONS

      i. Your product contains FD & C yellow #5. According to CFR 201.20(b) it is required that you insert the following statement to the PRECAUTIONS section of your insert:

      "This product contains FD & C Yellow No. 5 (tartrazine) which may cause allergic type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD & C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity."

      ii. In the *Cardiovascular Effects* subsection please revise the first sentence of the second paragraph to read, "Data from a comparative study of the extended-release formulation of bupropion...".

   c. DRUG ABUSE AND DEPENDENCE

   In "Animals" subsection please revise the last sentence to read, "In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms...".

2. Container Labels and Patient Package Insert Labeling (attached to Container Labels):

   a. GENERAL COMMENT

   Please add the statement, "Contains FD&C Yellow No. 5 (tartrazine) as a color additive" or "Contains color additives including FD&C Yellow No. 5 (tartrazine).

   b. 100s container size

   It is unclear how the patient information leaflet will appear on the bottles. Please submit as FPL the actual labeling piece.

   c. 500s container size

i. It is difficult to read your insert labeling. Please enhance the readability of your insert labeling. The information on the labels/labeling lacks the conspicuousness required by section 502© of the Act. In order to assure that the computer generated labels/labeling meet this requirement, they must be of true size, color and clarity. Refer to 21 CFR 201.15(a)(6) for guidance.

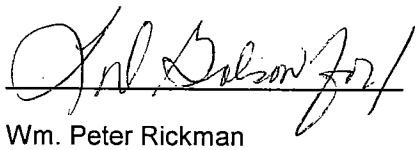
ii. You have included one patient information leaflet for this bottle size. It is expected that this bottle size is intended for the dispensing of multiple prescriptions. Please describe your plans for supplying the patient information leaflet with your product, e.g., how many leaflets will you supply for each container size and how will these leaflets be supplied.

Please revise your labels and labeling, as instructed above, and submit final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs

APPEARS THIS WAY
ON ORIGINAL

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Wellbutrin SR®
NDA Number: 20-358
NDA Drug Name: Wellbutrin SR® (bupropion hydrochloride extended-release) Tablets
NDA Firm: Glaxo Wellcome
Date of Approval of NDA Insert and supplement #: 10-22-02 (S-029)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	

Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) Tablets are debossed.		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	??		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

Note for the chemist: Please note that the 100 mg and 150 mg tablets contain iron oxide in the film-coating. Please verify that the amount of iron oxide in a 300 mg dose (3 x 100 mg tablets or 2 x 150 mg tablets) does not exceed the 5 mg per day maximum.

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Wellbutrin SR® (Glaxo Wellcome; Approved 10-22-02; Revised 10-02) NDA 20-358/S-029.

2. The inactive ingredients are listed accurately in the DESCRIPTION section (p 3508 v 4 11).

3. IMPAX is the manufacturer (p 6304 v B 1.1).

4. The RLD is available in 100 mg and 150 mg strengths - both in 60s. The ANDA will be available in container sizes of 100s (100 mg and 150 mg) and 500s (100 mg).

5. The tablet descriptions in the HOW SUPPLIED section are accurate (pp 4226, 4277 v 4.12).

6. There are 5 patents and one exclusivity for this drug product.

5,358,970	8-12-13
5,427,798	8-12-13

RE33994 8-18-04
5,763,493 8-12-13
5,731,000 8-12-13

The firm has filed under Paragraph IV.

Patent/ Exclusivities

Patent Data – 20-358

No	Expiration	Use Code	Use	File
5,358,970	8-12-13		Pharmaceutical composition containing bupropion HCl & a stabilizer	IV
5,427,798	8-12-13		Controlled sustained release tablets containing bupropion	IV
5,763,493	8-12-13		Stabilized pharmaceutical	IV
5,731,000	8-12-13		Stabilized pharmaceutical composition containing bupropion	IV

Exclusivity Data - 20-358

Code/sup	Expiration	Use Code	Description		Labeling Impact
M-10	6-11-04	M-10	Information regarding maintenance of an antidepressant effect up to 1 year of dosing		SEE BELOW

See the table and the model labeling in the file for how the insert labeling was modified to accommodate the exclusivity.

7. USP does not indicate this product is light sensitive.

8. Storage/dispensing recommendations:

RLD - Store at CRT 20°-25°C (68°-77°F)(see USP). Dispense in a tight, light-resistant container as defined in the USP.

ANDA - Store at CRT 20°-25°C (68°-77°F). (See USP Controlled Room Temperature). Dispense in a tightly closed, light-resistant container (USP).
*Container labels request containers with safety closures.

USP - not USP

9. Both the RLD (see PDR) and this ANDA have unscored tablets. The tablet descriptions in the submission are silent on the scoring (pp 6664, 6679 v 1.21) so I am assuming that the tablets are unscored (the tablets are extended-release).

10. IMPAX's ANDA 75-914 is also for bupropion but it is based on Zyban® whereas ANDA 75-913 is based on Wellbutrin SR®.

Date of Review: **October 21, 2003** **Dates of Submissions:** **September 5, 2003**

Primary Reviewer: **Postelle Birch** **Date:** **October 28, 2003**

Team Leader: **Lillie Golson** **Date:** 10/28/03

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-913** Dates of Submission: **November 14, 2003**

Applicant's Name: **Impax Pharmaceuticals, Inc**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 150 mg**

NOTE: WE ARE FULLY APPROVING THE 100 MG ONLY AT THIS TIME, THEREFORE, THE 150 MG EXTENDED-RELEASE TABLETS WITH COMBINED LABELING IS TENTATIVELY APPROVED UNTIL THE GENERIC EXCLUSIVITY IS EXPIRED OR BECOMES INVALID.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Professional Package Insert Labeling:

Satisfactory in FPL as of November 14, 2003 submission (Vol. 10.1)

Container Labels and Patient Information Sheet Labeling (attached to Container Labels):

Satisfactory in FPL as of November 14, 2003 submission (Vol. 10.1)

Revisions needed post-approval:

The firm has committed to indicate the presence of the patient information sheet on the container label for the pharmacist.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Wellbutrin SR®
NDA Number: 20-358
NDA Drug Name: Wellbutrin SR® (bupropion hydrochloride extended-release) Tablets
NDA Firm: Glaxo Wellcome
Date of Approval of NDA Insert and supplement #: 10-22-02 (S-029)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	

Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) Tablets are debossed.		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	??		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Wellbutrin SR® (Glaxo Wellcome; Approved 10-22-02; Revised 10-02) NDA 20-358/S-029.

2. The inactive ingredients are listed accurately in the DESCRIPTION section (p 3508 v 4 11).

3. IMPAX is the manufacturer (p 6304 v B 1.1).

4. The RLD is available in 100 mg and 150 mg strengths - both in 60s. The ANDA will be available in container sizes of 100s (100 mg and 150 mg) and 500s (100 mg).

5. The tablet descriptions in the HOW SUPPLIED section are accurate (pp 4226, 4277 v 4.12).

6. There are 5 patents and one exclusivity for this drug product.

5,358,970	8-12-13
5,427,798	8-12-13
RE33994	8-18-04
5,763,493	8-12-13
5,731,000	8-12-13

The firm has filed under Paragraph IV.

Patent/ Exclusivities

Patent Data – 20-358

No	Expiration	Use Code	Use	File
5,358,970	8-12-13		Pharmaceutical composition containing bupropion HCl & a stabilizer	IV
5,427,798	8-12-13		Controlled sustained release tablets containing bupropion	IV

RE 33994	8-18-04		Pharmaceutical delivery system	IV
5,763,493	8-12-13		Stabilized pharmaceutical	IV
5,731,000	8-12-13		Stabilized pharmaceutical composition containing bupropion	IV

Exclusivity Data - 20-358

Code/sup	Expiration	Use Code	Description		Labeling Impact
M-10	6-11-04	M-10	Information regarding maintenance of an antidepressant effect up to 1 year of dosing		SEE BELOW

See the table and the model labeling in the file for how the insert labeling was modified to accommodate the exclusivity.

7. USP does not indicate this product is light sensitive.

8. Storage/dispensing recommendations:

   RLD - Store at CRT 20°-25°C (68°-77°F)(see USP). Dispense in a tight, light-resistant container as defined in the USP.

   ANDA - Store at CRT 20°-25°C (68°-77°F). (See USP Controlled Room Temperature). Dispense in a tightly closed, light-resistant container (USP).
   *Container labels request containers with safety closures.

   USP - not USP

9. Both the RLD (see PDR) and this ANDA have unscored tablets. The tablet descriptions in the submission are silent on the scoring (pp 6664, 6679 v 1.21) so I am assuming that the tablets are unscored (the tablets are extended-release).

10. IMPAX's ANDA 75-914 is also for bupropion but it is based on Zyban® whereas ANDA 75-913 is based on Wellbutrin SR®.

11. Since the firm is using a combined container label and patient information sheet, the professional package insert will be glued to the top of the bottle.

Date of Review: **November 24, 2003**

Dates of Submission: **November 14, 2003**

Primary Reviewer: **Postelle Birch** **Date:** **December 1, 2003**

Team Leader: **Lillie Golson** **Date:** 12/1/03

---

cc:

ANDA: 75-913
DUP/DIVISION FILE
HFD-613/PBirch/LGolson (no cc)
V:\FIRMSAM\IMPAX\LTRS&REV\75913ap150.label.doc
Review

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-913** Dates of Submission: **November 14, 2003**

Applicant's Name: **Impax Pharmaceuticals, Inc**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg**

NOTE: WE ARE FULLY APPROVING THE 100 MG ONLY AT THIS TIME, THEREFORE, THE 150 MG EXTENDED-RELEASE TABLETS WITH COMBINED LABELING IS TENTATIVELY APPROVED UNTIL THE GENERIC EXCLUSIVITY IS EXPIRED OR BECOMES INVALID.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Professional Package Insert Labeling:

Satisfactory in FPL as of November 14, 2003 submission (Vol. 10.1)

Container Labels and Patient Package Insert Labeling (attached to Container Labels):

Satisfactory in FPL as of November 14, 2003 submission (Vol. 10.1)

Revisions needed post-approval:

The firm has committed to indicate the presence of the patient information sheet on the container label for the pharmacist.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Wellbutrin SR®
NDA Number: 20-358
NDA Drug Name: Wellbutrin SR® (bupropion hydrochloride extended-release) Tablets
NDA Firm: Glaxo Wellcome
Date of Approval of NDA Insert and supplement #: 10-22-02 (S-029)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	

Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) Tablets are debossed.		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	??		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Wellbutrin SR® (Glaxo Wellcome; Approved 10-22-02; Revised 10-02) NDA 20-358/S-029.

2. The inactive ingredients are listed accurately in the DESCRIPTION section (p 3508 v 4 11).

3. IMPAX is the manufacturer (p 6304 v B 1.1).

4. The RLD is available in 100 mg and 150 mg strengths - both in 60s. The ANDA will be available in container sizes of 100s (100 mg and 150 mg) and 500s (100 mg).

5. The tablet descriptions in the HOW SUPPLIED section are accurate (pp 4226, 4277 v 4.12).

6. There are 5 patents and one exclusivity for this drug product.

5,358,970	8-12-13
5,427,798	8-12-13
RE33994	8-18-04
5,763,493	8-12-13
5,731,000	8-12-13

The firm has filed under Paragraph IV.

Patent/ Exclusivities

Patent Data – 20-358

No	Expiration	Use Code	Use	File
5,358,970	8-12-13		Pharmaceutical composition containing bupropion HCl & a stabilizer	IV
5,427,798	8-12-13		Controlled sustained	IV

			release tablets containing bupropion	
RE 33994	8-18-04		Pharmaceutical delivery system	IV
5,763,493	8-12-13		Stabilized pharmaceutical	IV
5,731,000	8-12-13		Stabilized pharmaceutical composition containing bupropion	IV

Exclusivity Data - 20-358

Code/sup	Expiration	Use Code	Description		Labeling Impact
M-10	6-11-04	M-10	Information regarding maintenance of an antidepressant effect up to 1 year of dosing		SEE BELOW

See the table and the model labeling in the file for how the insert labeling was modified to accommodate the exclusivity.

7. USP does not indicate this product is light sensitive.

8. Storage/dispensing recommendations:

   RLD - Store at CRT 20°-25°C (68°-77°F)(see USP). Dispense in a tight, light-resistant container as defined in the USP.

   ANDA - Store at CRT 20°-25°C (68°-77°F). (See USP Controlled Room Temperature). Dispense in a tightly closed, light-resistant container (USP).
   *Container labels request containers with safety closures.

   USP - not USP

9. Both the RLD (see PDR) and this ANDA have unscored tablets. The tablet descriptions in the submission are silent on the scoring (pp 6664, 6679 v 1.21) so I am assuming that the tablets are unscored (the tablets are extended-release).

10. IMPAX's ANDA 75-914 is also for bupropion but it is based on Zyban® whereas ANDA 75-913 is based on Wellbutrin SR®.

Date of Review: **November 24, 2003**

Dates of Submission: **November 14, 2003**

Primary Reviewer: **Postelle Birch** **Date:** **December 1, 2003**

Team Leader: **Lillie Golson** **Date:** 12/1/03

---

cc:

ANDA: 75-913
DUP/DIVISION FILE
HFD-613/PBirch/LGolson (no cc)
V:\FIRMSAM\IMPAX\LTRS&REV\75913ap100.label.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-913

CHEMISTRY REVIEWS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs

Chemistry Division II - Branch VIII
Abbreviated New Drug Application Review

ORIG

1. **CHEMISTRY REVIEW NO:** 1

2. **ANDA # 75-913**

3. **NAME AND ADDRESS OF APPLICANT:**
IMPAX Pharmaceuticals, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. **LEGAL BASIS FOR SUBMISSION:**
The basis for Impax' ANDA 75-913 for Bupropion HCl extended release tablet is the approved, reference listed drug, Wellbutrin SR, the subject of NDA 20-358 held by Glaxo Wellcome, Inc. and containing 100 or 150 mg Bupropion HCl. Wellbutrin SR, NDA 20-358 was approved on October 4, 1996. Orange Book lists two expired patents and five patents claimed by the Innovator as being relevant to the application.

5. **SUPPLEMENT(s):**
N/A

6. **PROPRIETARY NAME:**
N/A

7. **NONPROPRIETARY NAME:**
Bupropion HCl, ER

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**
Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000
Patent Amendment	08/28/2000
Patent Amendment	10/04/2000

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000

10. **PHARMACOLOGICAL CATEGORY:**
Anti-Depressant

11. **Rx or OTC:**
Rx

12. **RELATED IND/NDA/DMF(s):**

NDA 20-358 Wellbutrin (Burroughs Wellcome)
Approved on 10/04/1996

DMF
DMF
DMF

DMF
DMF

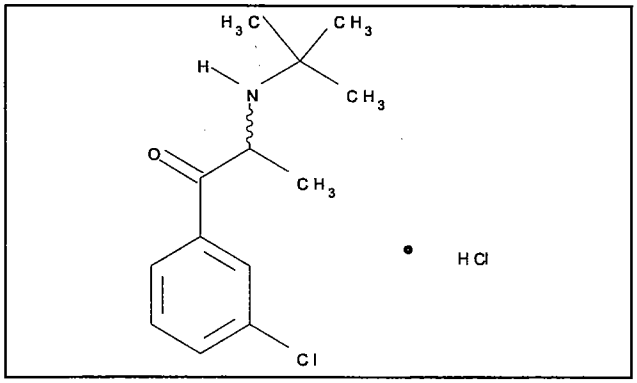
13. **DOSAGE FORM:**
ER tablet (100 mg and 150 mg), for oral administration.

14. **POTENCIES:**
100 and 150 mg

APPEARS THIS WAY
ON ORIGINAL

15. **CHEMICAL NAME AND STRUCTURE:**

Bupropion Hydrochloride
$C_{13}H_{18}ClNO.HCl$; M.W. = 276.21



( )-2-(*tert*-Butylamino)-3'-chloropropiophenone hydrochloride.
CAS [31677-93-7]; [34911-55-2] (bupropion)

16. **RECORDS AND REPORTS:**

Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000
Patent Amendment	08/28/2000
Patent Amendment	10/04/2000

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000

17. **COMMENTS:**

a. EER status: Acceptable for two out of four Facilities.

b. Method Validation status: Pending, Non-Compendial.

Required since both drug substance and finished product, are not official USP items.

c. Bio-review status: Satisfactory

The waiver of in vivo bioavailability was granted and satisfactory per M. Makary reviewed on 09-28-2000.

d. Labeling review status:
Not Satisfactory as per A. Vezza, reviewed on 8-28-2000.

e. DMF ——— is Adequate
DMF# ——— was reviewed by Mouna P. Selvam and found satisfactory on November 30, 2000.

f. Several CMC deficiencies as noted in the Review.

17. **CONCLUSIONS AND RECOMMENDATIONS:**

Application is Not Approved (Major)

19. **REVIEWER:** Mouna P. Selvam

DATE COMPLETED: 12/06/2000

Redacted 19 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

systems to be tested in the formal protocol. Please revise and resubmit the protocol to indicate testing of at least the smallest and largest container/closure systems.

6. Please submit available room temperature stability data accrued to date.

7. We request you to provide data comparing your Drug Product impurity/degradant profile with the innovator's impurity/degradant profile.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Methods validation will be performed on the drug substance and drug product by the FDA field Laboratory.

2. A satisfactory compliance evaluation for the Firms referenced in the ANDA is required for approval. The Establishment Evaluation Request (EER) is pending for two out of four Firms.

Sincerely yours,

fas

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

12/19/00

cc: ANDA 75-913
DUP Jacket
Division File
Field Copy

Endorsements:

HFD-647/ MSelvam/12/06/00

HFD-647/UVenkataram/12/12/00 U.V. Venkataram

HFD-647/BmcNeal/12/14/00 B. McNeal 12/18/00 12/14/2000

FT by: pah/12/15/00
V:\firmsam\Impax\ltrs&rev\75913No1.rf

Fax
Not Approvable (~~Major~~)

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VIII
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO: 2

2. ANDA # 75-913

3. NAME AND ADDRESS OF APPLICANT:
IMPAX Pharmaceuticals, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
The basis for Impax' ANDA 75-913 for Bupropion HCl extended release tablet is the approved, reference listed drug, Wellbutrin SR, the subject of NDA 20-358 held by Glaxo Wellcome, Inc. and containing 100 or 150 mg Bupropion HCl. Wellbutrin SR, NDA 20-358 was approved on October 4, 1996. Orange Book lists two expired patents and five patents claimed by the Innovator as being relevant to the application.

5. SUPPLEMENT(s):
N/A

6. PROPRIETARY NAME:
N/A

7. NONPROPRIETARY NAME:
Bupropion HCl, ER

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000
Patent Amendment	08/28/2000
Patent Amendment	10/04/2000

Amendment	05/16/2001

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000
Deficiency Letter	12/20/2000
Telecon	01/04/2001
Labeling Approval	05/30/2001
Telecon	06/14/2001
Bio Review	07/31/2001

10. PHARMACOLOGICAL CATEGORY:

Anti-Depressant

11. Rx or OTC:

Rx

12. RELATED IND/NDA/DMF(s):

NDA 20-358 Wellbutrin (Burroughs Wellcome)
Approved on 10/04/1996

DMF
DMF
DMF

DMF
DMF

[redacted]

13. DOSAGE FORM:

ER tablet (100 mg and 150 mg), for oral administration.

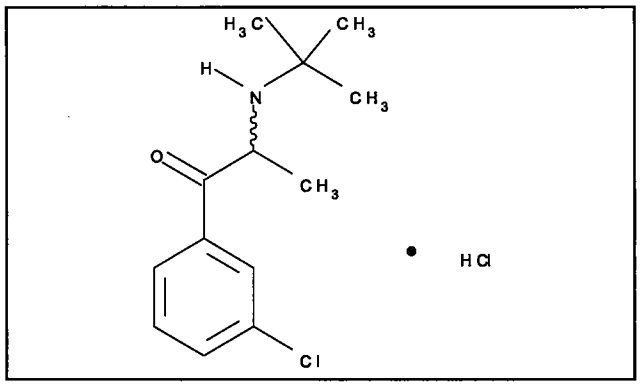
14. POTENCIES:

100 and 150 mg

APPEARS THIS WAY
ON ORIGINAL

15. CHEMICAL NAME AND STRUCTURE:

Bupropion Hydrochloride
$C_{13}H_{18}ClNO.HCl$; M.W. = 276.21



(±)-2-(*tert*-Butylamino)-3'-chloropropiophenone hydrochloride.
CAS [31677-93-7]; [34911-55-2] (bupropion)

16. RECORDS AND REPORTS:

Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000
Patent Amendment	08/28/2000
Patent Amendment	10/04/2000
Amendment	05/16/2001

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000
Deficiency Letter	12/20/2000
Telecon	01/04/2001
Labeling Approval	05/30/2001
Telecon	06/14/2001
Bio Review	07/31/2001

17. COMMENTS:

a. EER status: Acceptable for all Facilities as of April, 19, 2001.

b. Method Validation status: Samples received by the Lab

c. Bio-review status: Satisfactory

d. Labeling review status:
Satisfactory as per A. Vezza, reviewed on 05-30-2001.

e. DMF ——— is Adequate
DMF# ——— was reviewed by Mouna P. Selvam and found satisfactory on November 30, 2000. Thereafter there is no amendment.

17. CONCLUSIONS AND RECOMMENDATIONS:
Application is not Approved (Facsimile Deficiency)

19. REVIEWER: Mouna P. Selvam, Ph.D.,

DATE COMPLETED: 10/16/2001

Redacted 22 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

cc: ANDA 75-913
DUP Jacket
Division File
Field Copy

Endorsements:

HFD-647/ MSelvam/06/06/2001

HFD-647/U.V. Venkataram/

HFD-647/B.McNeal/
FT by:

V:\firmsam\Impax\ltrs&rev\75913No2.rf

Not Approvable (FAX)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VIII
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO: 3

2. ANDA # 75-913

3. NAME AND ADDRESS OF APPLICANT:
IMPAX Pharmaceuticals, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
The basis for Impax' ANDA 75-913 for Bupropion HCl extended release tablet is the approved, reference listed drug, Wellbutrin SR, the subject of NDA 20-358 held by Glaxo Wellcome, Inc. and containing 100 or 150 mg Bupropion HCl. Wellbutrin SR, NDA 20-358 was approved on October 4, 1996. Orange Book lists two expired patents and five patents claimed by the Innovator as being relevant to the application.

5. SUPPLEMENT(s):
N/A

6. PROPRIETARY NAME:
N/A

7. NONPROPRIETARY NAME:
Bupropion HCl, ER

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000
Patent Amendment	08/28/2000
Patent Amendment	10/04/2000

Amendment	05/16/2001

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000
Deficiency Letter	12/20/2000
Telecon	01/04/2001
Labeling Approval	05/30/2001
Telecon	06/14/2001
Bio Review	07/31/2001
Bio Review	11/15/2001

10. PHARMACOLOGICAL CATEGORY:

Anti-Depressant

11. Rx or OTC:

Rx

12. RELATED IND/NDA/DMF(s):

NDA 20-358 Wellbutrin (Burroughs Wellcome)
Approved on 10/04/1996

DMF
DMF
DMF

DMF
DMF

13. DOSAGE FORM:

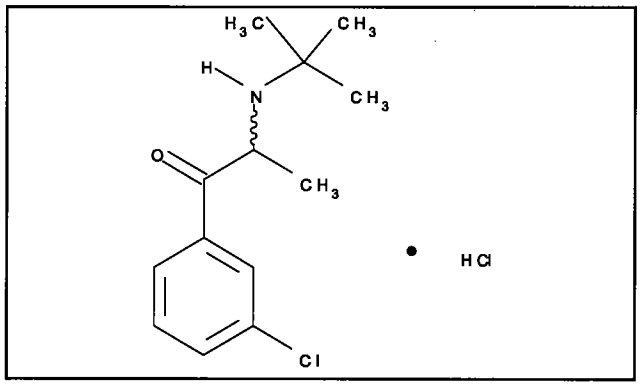
ER tablet (100 mg and 150 mg), for oral administration.

14. POTENCIES:

100 and 150 mg

15. CHEMICAL NAME AND STRUCTURE:

Bupropion Hydrochloride
$C_{13}H_{18}ClNO.HCl$; M.W. = 276.21



(±)-2-(*tert*-Butylamino)-3'-chloropropiophenone hydrochloride.
CAS [31677-93-7]; [34911-55-2] (bupropion)

16. RECORDS AND REPORTS:

Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000
Patent Amendment	08/28/2000
Patent Amendment	10/04/2000
Amendment	05/16/2001

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000
Deficiency Letter	12/20/2000
Telecon	01/04/2001
Labeling Approval	05/30/2001
Telecon	06/14/2001
Bio Review	07/31/2001

17. COMMENTS:

a. EER status: Acceptable for all Facilities as of April, 19, 2001.

b. Method Validation status: Samples received by the Lab

c. Bio-review status: Satisfactory
Moheb Makary, 11/15/2001

d. Labeling review status:
Satisfactory as per A. Vezza, reviewed on 05-30-2001.

e. DMF ——— is Adequate
DMF# ——— was reviewed by Mouna P. Selvam and found satisfactory on May 30, 2001. Thereafter there is no amendment.

17. CONCLUSIONS AND RECOMMENDATIONS:
Application is not Approved (Facsimile Deficiency)

19. REVIEWER: Mouna P. Selvam, Ph.D.,

DATE COMPLETED: 11/21/2001

Redacted 22 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

38. Chemistry Comments to be provided to the Applicant

ANDA: 75-913 APPLICANT: IMPAX

DRUG PRODUCT: Bupropion Hydrochloride Extended release Tablets 100 mg and 150 mg

The deficiencies presented below represent Facsimile

Deficiencies:

A. **Chemistry Deficiencies:**

1. Please submit the revised finished product release and stability specification, based on Bio's recommendation.

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-913
DUP Jacket
Division File
Field Copy

Endorsements:

HFD-647/ MSelvam/10/16/2001

HFD-647/U.V. Venkataram/

HFD-647/S.Sheppard/

FT by:

V:\firmsam\Impax\ltrs&rev\75913No3.rf

Not Approvable (FAX)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VIII
Abbreviated New Drug Application Review

1. **CHEMISTRY REVIEW NO:** 4

2. **ANDA # 75-913**

3. **NAME AND ADDRESS OF APPLICANT:**
IMPAX Pharmaceuticals, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. **LEGAL BASIS FOR SUBMISSION:**
The basis for Impax' ANDA 75-913 for Bupropion HCl extended release tablet is the approved, reference listed drug, Wellbutrin SR, the subject of NDA 20-358 held by Glaxo Wellcome, Inc. and containing 100 or 150 mg Bupropion HCl. Wellbutrin SR, NDA 20-358 was approved on October 4, 1996. Orange Book lists two expired patents and five patents claimed by the Innovator as being relevant to the application.

5. **SUPPLEMENT(s):**
N/A

6. **PROPRIETARY NAME:**
N/A

7. **NONPROPRIETARY NAME:**
Bupropion HCl, ER Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**
Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000
Patent Amendment	08/28/2000
Patent Amendment	10/04/2000
Amendment	05/16/2001

Major Amendment	11/29/2001

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000
Deficiency Letter	12/20/2000
Telecon	01/04/2001
Labeling Approval	05/30/2001
Telecon	06/14/2001
Bio Review	07/31/2001
Bio Review	11/15/2001
Bio Approval	12/12/2001
Labeling Approval	12/11/2001

10. PHARMACOLOGICAL CATEGORY:
Anti-Depressant

11. Rx or OTC:
Rx

12. RELATED IND/NDA/DMF(s):

NDA 20-358 Wellbutrin (Burroughs Wellcome)
Approved on 10/04/1996

DMF [redacted]
DMF
DMF

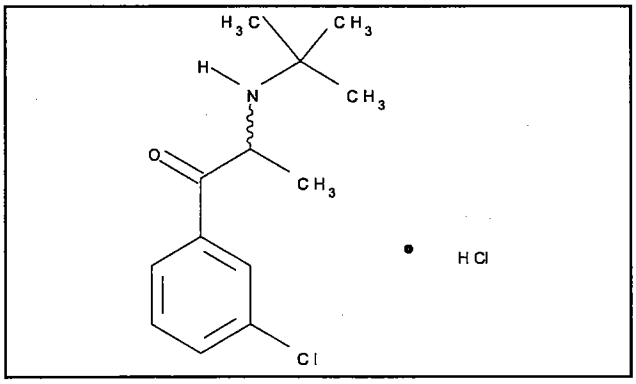
DMF
DMF

13. DOSAGE FORM:
ER tablet (100 mg and 150 mg), for oral administration.

14. POTENCIES:
100 mg and 150 mg

15. CHEMICAL NAME AND STRUCTURE:

Bupropion Hydrochloride
$C_{13}H_{18}ClNO.HCl$; M.W. = 276.21



( )-2-(*tert*-Butylamino)-3'-chloropropiophenone hydrochloride.
CAS [31677-93-7]; [34911-55-2] (bupropion)

16. RECORDS AND REPORTS:

Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000
Patent Amendment	08/28/2000
Patent Amendment	10/04/2000
Amendment	05/16/2001
Major Amendment	11/29/2001

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000
Deficiency Letter	12/20/2000
Telecon	01/04/2001

Labeling Approval	05/30/2001
Telecon	06/14/2001
Bio Review	07/31/2001
Bio Review	11/15/2001
Bio Approval	12/12/2001
Labeling Approval	12/11/2001

17. **COMMENTS:**

a. EER status: Acceptable for all Facilities as of April, 19, 2001.

b. Method Validation status: Methods were validated with the previous samples satisfactorily. Analytical methods for validation with the new dosage forms will not be submitted until all formulation and manufacturing issues are resolved.

b. Bio-review status: Satisfactory
Moheb Makary, 12/12/2001

d. Labeling review status:
Satisfactory as per A. Vezza, reviewed on 12-11-2001.

e. DMF ——— is Adequate. DMF# ———, reviewed by Mouna P. Selvam and found satisfactory on April 25, 2002.

f. Chemistry related deficiencies have been cited for clarification.

17. **CONCLUSIONS AND RECOMMENDATIONS:**
Application is not Approvable (MAJOR)

19. **REVIEWER:** Mouna P. Selvam, Ph.D.,

DATE COMPLETED: 05/07/2002

Redacted 28 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #4

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

We will not be submitting your analytical methods for validation until all formulation and manufacturing issues are resolved.

Sincerely yours,

5/20/02

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-913
DUP Jacket
Division File
Field Copy

Endorsements:

HFD-647/ M.P. Selvam/05/07/2002 5/15/02

HFD-647/U.V. Venkataram/5/9/02 U.V. Venkataram 5/17/02

HFD-647/S.Shepperson/5/13/02 S Shepperson 5/17/02

HFD-615/A.Vezza

HFD-600/Micro

FT by: rad5/14/02

V:\firmsam\Impax\ltrs&rev\75913No4.rms

Not Approvable (MAJOR)

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VIII
Abbreviated New Drug Application Review

1. **CHEMISTRY REVIEW NO:** 5

2. **ANDA # 75-913**

3. **NAME AND ADDRESS OF APPLICANT:**
IMPAX Pharmaceuticals, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. **LEGAL BASIS FOR SUBMISSION:**
The basis for Impax' ANDA 75-913 for Bupropion HCl extended release tablet is the approved, reference listed drug, Wellbutrin SR, the subject of NDA 20-358 held by Glaxo Wellcome, Inc. and containing 100 or 150 mg Bupropion HCl. Wellbutrin SR, NDA 20-358 was approved on October 4, 1996. Orange Book lists two expired patents and five patents claimed by the Innovator as being relevant to the application.

5. **SUPPLEMENT(s):**
N/A

6. **PROPRIETARY NAME:**
N/A

7. **NONPROPRIETARY NAME:**
Bupropion HCl, ER Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**
Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000

Patent Amendment	08/28/2000
Patent Amendment	10/04/2000
Amendment	05/16/2001
Major Amendment	11/29/2001
Minor Amendment	07/17/2002
Patent Amendment	09/05/2002
Tel Amendment	09/11/2002

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000
Deficiency Letter	12/20/2000
Telecon	01/04/2001
Labeling Approval	05/30/2001
Telecon	06/14/2001
Bio Review	07/31/2001
Bio Review	11/15/2001
Bio Approval	12/12/2001
Labeling Approval	12/11/2001
Deficiency Letter	05/20/2002
Telecon	09/05/2002

10. PHARMACOLOGICAL CATEGORY:
Anti-Depressant

11. Rx or OTC:
Rx

12. RELATED IND/NDA/DMF(s):

NDA 20-358 Wellbutrin (Burroughs Wellcome)
Approved on 10/04/1996

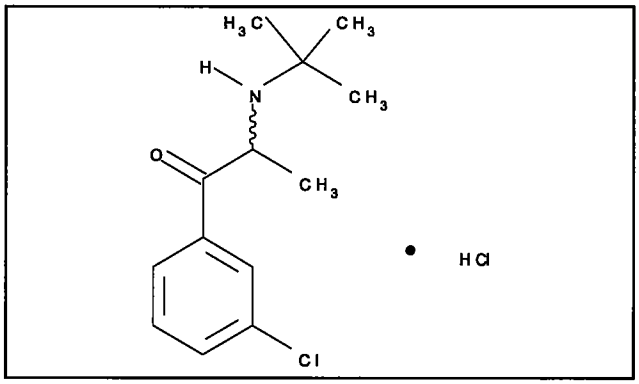
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM:
ER tablet (100 mg and 150 mg), for oral administration.

14. **POTENCIES:** 100 mg and 150 mg

15. CHEMICAL NAME AND STRUCTURE:

Bupropion Hydrochloride
$C_{13}H_{18}ClNO.HCl$; M.W. = 276.21



(±)-2-(*tert*-Butylamino)-3'-chloropropiophenone hydrochloride.
CAS [31677-93-7]; [34911-55-2] (bupropion)

16. RECORDS AND REPORTS:

Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000
Patent Amendment	08/28/2000
Patent Amendment	10/04/2000
Amendment	05/16/2001
Major Amendment	11/29/2001
Minor Amendment	07/17/2002
Patent Amendment	09/05/2002
Tel Amendment	09/11/2002

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000
Deficiency Letter	12/20/2000
Telecon	01/04/2001
Labeling Approval	05/30/2001
Telecon	06/14/2001
Bio Review	07/31/2001

Bio Review	11/15/2001
Bio Approval	12/12/2001
Labeling Approval	12/11/2001
Deficiency Letter	05/20/2002
Telecon	09/05/2002

17. COMMENTS:

a. EER status: Acceptable for all Facilities as of April, 19, 2001.

b. Method Validation status: Methods were validated with the previous samples satisfactorily. Analytical methods for validation with the new dosage forms will be submitted.

b. Bio-review status: Satisfactory
Moheb Makary, 12/12/2001

d. Labeling review status:
Satisfactory as per A. Vezza, reviewed on 12-11-2001.

e. DMF [redacted] is Adequate. DMF# [redacted] reviewed by Mouna P. Selvam and found satisfactory on August 22, 2002.

17. CONCLUSIONS AND RECOMMENDATIONS:
Application is approved.

19. REVIEWER:	**DATE COMPLETED:**
Mouna P. Selvam, Ph.D.,	09/13/2002

Redacted 29 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #5

cc: ANDA 75-913
DUP Jacket
Division File
Field Copy

Endorsements:

HFD-647/ M.P. Selvam/09/13/2002

HFD-647/U.V. Venkataram/9.16.02

HFD-647/S.Shepperson/

HFD-615/A.Vezza

HFD-600/Micro

FT by:

V:\firmsam\Impax\ltrs&rev\75913N05.rms

Approved

1. **CHEMISTRY REVIEW NO:** 6

2. **ANDA # 75-913**

3. **NAME AND ADDRESS OF APPLICANT:**
IMPAX Pharmaceuticals, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. **LEGAL BASIS FOR SUBMISSION:**
The basis for Impax' ANDA 75-913 for Bupropion HCl extended release tablet is the approved, reference listed drug,
Wellbutrin SR, the subject of NDA 20-358 held by Glaxo Wellcome, Inc. and containing 100 or 150 mg Bupropion HCl. Wellbutrin SR, NDA 20-358 was approved on October 4, 1996. Orange Book lists two expired patents and five patents claimed by the Innovator as being relevant to the application.

5. **SUPPLEMENT(s):**
N/A

6. **PROPRIETARY NAME:**
N/A

7. **NONPROPRIETARY NAME:**
Bupropion HCl, ER Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**
Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000
Patent Amendment	08/28/2000

Patent Amendment	10/04/2000
Amendment	05/16/2001
Major Amendment	11/29/2001
Minor Amendment	07/17/2002
Patent Amendment	09/05/2002
Tel Amendment	09/11/2002
Bio Amendment	11/05/2002
Labeling Amendment	12/02/2002 & 12/16/2002

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000
Deficiency Letter	12/20/2000
Telecon	01/04/2001
Labeling Approval	05/30/2001
Telecon	06/14/2001
Bio Review	07/31/2001
Bio Review	11/15/2001
Bio Approval	12/12/2001
Labeling Approval	12/11/2001
Deficiency Letter	05/20/2002
Telecon	09/05/2002
Bio Review	12/16/2002
Labeling review	01/03/2003

10. PHARMACOLOGICAL CATEGORY:

Anti-Depressant

11. Rx or OTC:

Rx

12. RELATED IND/NDA/DMF(s):

NDA 20-358 Wellbutrin (Burroughs Wellcome)
Approved on 10/04/1996

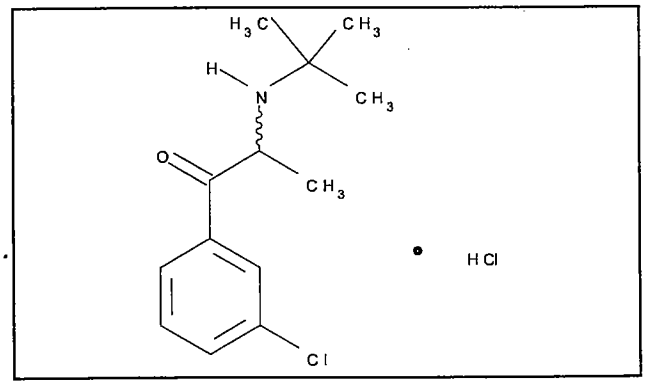
DMF [redacted]
DMF
DMF
DMF
DMF

13. DOSAGE FORM:
ER tablet (100 mg and 150 mg), for oral administration.

14. **POTENCIES:** 100 mg and 150 mg

15. CHEMICAL NAME AND STRUCTURE:

Bupropion Hydrochloride
$C_{13}H_{18}ClNO.HCl$; M.W. = 276.21



(±)-2-(*tert*-Butylamino)-3'-chloropropiophenone hydrochloride.
CAS [31677-93-7]; [34911-55-2] (bupropion)

16. RECORDS AND REPORTS:

Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000
Patent Amendment	08/28/2000
Patent Amendment	10/04/2000
Amendment	05/16/2001
Major Amendment	11/29/2001
Minor Amendment	07/17/2002
Patent Amendment	09/05/2002
Tel Amendment	09/11/2002
Bio Amendment	11/05/2002
Labeling Amendment	12/02/2002 & 12/16/2002

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000
Deficiency Letter	12/20/2000
Telecon	01/04/2001
Labeling Approval	05/30/2001
Telecon	06/14/2001
Bio Review	07/31/2001
Bio Review	11/15/2001
Bio Approval	12/12/2001
Labeling Approval	12/11/2001
Deficiency Letter	05/20/2002
Telecon	09/05/2002
Bio Review	12/16/2002
Labeling review	01/03/2003

17. COMMENTS:

a. EER status: Acceptable for all Facilities as of April, 19, 2001.

b. Method Validation status: Methods were validated with the previous samples satisfactorily. Analytical methods for validation with the new dosage forms have been submitted.

b. Bio-review status: Not Satisfactory ; Moheb Makary, 12/16/2002

d. Labeling review status: Not Satisfactory as per A. Vezza, reviewed on 01-03-2003.

e. DMF ——— is Adequate. DMF# ———; reviewed by Mouna P. Selvam and found satisfactory on August 22, 2002 and it is current.

17. CONCLUSIONS AND RECOMMENDATIONS:

Application is Not Approved (Major).

19. **REVIEWER:** Mouna P. Selvam, Ph.D.,

DATE COMPLETED: 01/03/2003

Redacted 23 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #6

38. Chemistry Comments to be provided to the Applicant:

ANDA: 75-913 **APPLICANT:** IMPAX Laboratories, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Extended-release Tablets 100 mg and 150 mg

The Deficiency presented below represents a Major Deficiency:

The Division of Chemistry has no further comments regarding the Chemistry, Manufacturing and Controls (CMC) issues. We note that the Division of Bioequivalence (DOB) has requested additional studies in their 12/16/2002 letter. Any changes made to the CMC portion of the ANDA (such as formulation change, manufacturing of a new batch, etc.) in response to the DOB deficiency letter should be submitted for review.

Sincerely yours,

2/6/03

for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-913
DUP Jacket
Division File
Field Copy

Endorsements:

HFD-647/ M.P. Selvam/01/03/2003 2/4/03

HFD-647/U.V. Venkataram/1.30.03 U.V. Venkataram 2/5/2003

HFD-647/S.Shepperson/1.31.03 S.Shepperson 2/6/03

FT by: rad1/31/03

V:\firmsam\Impax\ltrs&rev\75913N06.rms

Not Approved (Major)

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VIII
Abbreviated New Drug Application Review

1. **CHEMISTRY REVIEW NO:** 7

2. **ANDA # 75-913**

3. **NAME AND ADDRESS OF APPLICANT:**
IMPAX Pharmaceuticals, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. **LEGAL BASIS FOR SUBMISSION:**
The basis for Impax' ANDA 75-913 for Bupropion HCl extended release tablet is the approved, reference listed drug, Wellbutrin SR, the subject of NDA 20-358 held by Glaxo Wellcome, Inc. and containing 100 or 150 mg Bupropion HCl. Wellbutrin SR, NDA 20-358 was approved on October 4, 1996. Orange Book lists two expired patents and five patents claimed by the Innovator as being relevant to the application.

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Bupropion HCl, ER Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**
Firm:

Original Submission	06/22/2000
Tel Amendment for Bio	08/25/2000
Patent Amendment	08/28/2000
Patent Amendment	10/04/2000
Amendment	05/16/2001
Major Amendment	11/27/2001
Minor Amendment	07/17/2002
Patent Amendment	09/05/2002
Tel Amendment	09/11/2002
Bio Amendment	11/05/2002
Labeling Amendment	12/02/2002 & 12/16/2002

Labeling Amendment	03/10/2003
Major Amendment	04/03/2003
Labeling Amendment	06/27/2003
Telephone Amendment	08/01/2003
Labeling Amendment	08/01/2003
Telephone Amendment	09/05/2003
Telephone Amendment	10/02/2003
Labeling Amendment	11/14/2003
Labeling Amendment	12/02/2003
Labeling Amendment	12/08/2003
Patent Amendment	01/15/2004

FDA:

Acknowledgement	08/14/2000
Labeling Deficiency letter	08/28/2000
Bio Approval Letter	09/28/2000
Deficiency Letter	12/20/2000
Telecon	01/04/2001
Labeling Approval	05/30/2001
Telecon	06/14/2001
Bio Review	07/31/2001
Bio Review	11/15/2001
Bio Approval	12/12/2001
Labeling Approval	12/11/2001
Deficiency Letter	05/20/2002
Telecon	09/05/2002
Bio Review	12/16/2002
Labeling review	01/03/2003
Major deficiency letter	02/07/2003
Bio deficienc letter	03/19/2003
Bio Review	05/19/2003
Labeling review	06/23/2003
Labeling review	07/25/2003
Telecon	07/31/2003
Telecon	08/21/2003
Telecon	10/02/2003

10. PHARMACOLOGICAL CATEGORY:
Anti-Depressant

11. Rx or OTC:
Rx

12. RELATED IND/NDA/DMF(s):

NDA 20-358 Wellbutrin (Burroughs Wellcome) - Approved on 10/04/1996

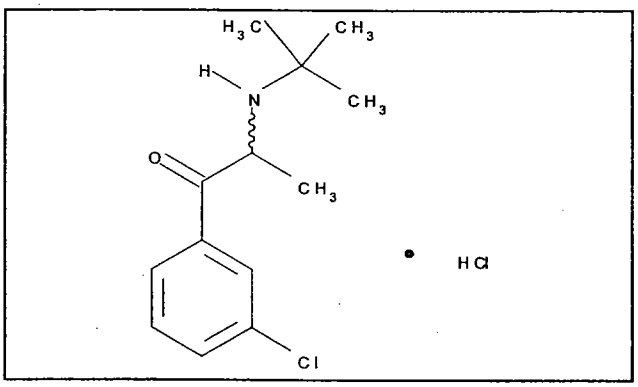
DMF [redacted]
DMF
DMF
DMF
DMF

13. **DOSAGE FORM:** ER tablet for oral administration.

14. **POTENCIES:** 100 mg and 150 mg

15. **CHEMICAL NAME AND STRUCTURE:**

Bupropion Hydrochloride
$C_{13}H_{18}ClNO.HCl$; M.W. = 276.21



(±)-2-(*tert*-Butylamino)-3'-chloropropiophenone hydrochloride.
CAS [31677-93-7]; [34911-55-2] (bupropion)

16. **RECORDS AND REPORTS:**

17. **COMMENTS:**

a. EER status: Acceptable for all facilities as of November 26, 2003.
b. Method Validation status: Satisfactory
c. Bio-review status: Satisfactory ; Moheb Makary, 05/19/2003
d. Labeling review status: Satisfactory as per A. Vezza, reviewed on 07-25-2003.
e. DMF [redacted] is Adequate, reviewed by Mouna P. Selvam and found satisfactory on July 22, 2003 and it is current.

17. **CONCLUSIONS AND RECOMMENDATIONS:**

Impax submitted satisfactory data including _____ data to demonstrate that their product meets USP monograph specifications. They have also proposed DS and DP specifications according to the USP Monograph. Application is approved for the 100 mg strength and tentatively approved for the 150 mg strength.

19. **REVIEWER:** Mouna P. Selvam, Ph.D.,

DATE COMPLETED: 10/17/2003

APPEARS THIS WAY
ON ORIGINAL

Redacted 24 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #7

cc: ANDA 75-913
DUP Jacket
Division File
Field Copy

Endorsements:

HFD-647/ M.P. Selvam/1~~0/17/200~~3 1/15/2004

HFD-647/U.V. Venkataram/10.20.03 U.V. Venkataram 1/16/2004.

HFD-647/S.Shepperson/1.15.2004 1/16/04

HFD-615/ A. Vezza

FT by: EW 1/15/04

V:\firmsam\Impax\ltrs&rev\75913N07.rms

Approved

for changes to CMC 2 letter dated 11/20/04. amendment

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-913

BIOEQUIVALENCE REVIEWS

Bupropion HCl ER Tablets	Impax Pharmaceuticals, Inc.
150 mg and 100 mg	Hayward, CA
ANDA #75-913	Submission Date:
Reviewer: Moheb H. Makary	June 22, 2000
W 75913SD.600	August 25, 2000

Review of Bioequivalence Studies and Dissolution Data

I. Objective:

The firm has submitted three *in vivo* bioequivalence studies (single-dose fasting, nonfasting, and multiple-dose fasting studies) for its Bupropion HCl Extended Release (ER) Tablet, 150 mg, and a single-dose fasting for its Bupropion HCl Extended Release (ER) Tablet, 100 mg, comparing them with RLD Wellbutrin SR^{R} Tablets (Glaxo Wellcome), 150 mg and 100 mg, respectively.

II. Introduction:

Bupropion hydrochloride is an antidepressant of the aminoketone class and is chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl) amino]-1-propanone hydrochloride. The molecular weight is 276.2 and the empirical formula is $C_{13}H_{18}ClNO.HCl$.

It is a weak blocker of the neuronal uptake of serotonin and norepinephrine. It also inhibits the neuronal re-uptake of dopamine to some extent.

Following oral administration, peak plasma bupropion concentrations are achieved within 2 hours, followed by a biphasic decline. The average half-life of the second (post- distributional) phase is approximately 14 hours (range 8-24 hours). Plasma bupropion concentrations are dose-proportional following single doses of 100 to 250 mg. The absolute bioavailability of bupropion tablets is not known because an intravenous formulation for human use is not available. In animals, the absolute bioavailability ranges from 5% to 20%.

There is evidence that bupropion undergoes extensive metabolism. Several of the known metabolites are pharmacologically active and have long elimination half-lives.

Plasma concentrations of at least two of the known metabolites can be expected to be higher than the plasma concentration of the parent compound. Four basic metabolites have been identified: erythro- and threo- amino alcohols of bupropion, the erythro- amino diol of bupropion, and a morpholinol metabolite. The erythro-amino alcohol and erythro-amino diol metabolites generally can not be detected in the systemic circulation following a single oral dose of the parent drug.

Morpholinol: This metabolite appears in the systemic circulation as rapidly as the parent drug following a single oral dose. Its peak level is three times the peak level of the parent drug; it has a half-life of about 24 hours, and its $AUC_{0\text{-}60\ hours}$ is about 15 times that of bupropion.

Threo-amino alcohol: Its plasma concentration-time profile is similar to that of the morpholinol. In animal studies, morpholinol and threo-amino alcohol metabolites were found to be half as potent as bupropion.

Bupropion is indicated for the treatment of depression. It is given in equally divided doses three or four times a day to minimize the risk of seizure. The dosing should begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg t.i.d. No single dose should exceed 150 mg.

The reference listed drug is Wellbutrin^{R} (Glaxo Wellcome) and is available as 75 and 100 mg tablets. The orange book also lists 50, 100 and 150 mg oral extended release tablets (Wellbutrin SR$^{R)}$ approved in October 1996.

III. Study #99266 for Single-Dose, two-way Crossover Study of Bupropion HCl ER Tablets, 100 mg, Under Fasting Conditions

Clinical site: [redacted]

Analytical site: [redacted]

Study design: Open-label, single-dose, fasted, randomized, two-period crossover.

Dosing date:	Period I January 15, 2000 Period II February 5, 2000
Analytical date:	Samples were analyzed between February 20 to March 3, 2000.
Subjects:	Thirty-six (36) male subjects enrolled and completed the crossover.
Dose and Treatments:	After a supervised overnight fast (at least 10 hours) subjects received an oral dose of the assigned formulation with 240 mL of water. Treatment A: 1x100 mg Bupropion HCl ER Tablet (Impax), lot #R99040-60, Exp. N/A, batch size [redacted] Tablets, potency 101.0%, content uniformity 99.9% (%CV=1.03). Treatment B: 1x100 mg Wellbutrin SR^{R} Tablet (Glaxo Wellcome), lot #9H1752, Exp. 6/00, potency 98.7%, content uniformity 98.7% (%CV=1.42).
Washout period:	Three weeks
Food and fluid intake:	Standardized, caffeine-free meals or snacks were served at 4, 10 and 14 hours after dosing. Water was not allowed from 1 hour before until 1 hour after dosing, except for the dosing water (240 mL).
Blood samples:	Blood samples were collected at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 60, 72, 96, 120, 144 and 168 hours after dosing. Plasma samples were immediately frozen.

Assay Methodology:

Determination of Bupropion, Hydroxybupropion and Threo-bupropion plasma concentrations was performed by [redacted].

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW (OF 6/22/00 SUBMISSIONS 8/25/00)

plasma at -80°C.
Freeze-Thaw Stability: Bupropion, Hydroxybupropion and Threo-bupropion were stable after three freeze-thaw cycles in human whole plasma.

Statistical Methods

AUC(0-t), AUCinf, Cmax, Tmax, Ke and T1/2 were calculated from the individual concentration versus time data for Bupropion, Hydroxybupropion and Threo-bupropion. Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure.

IV. In Vivo Results

Two subjects experienced three adverse events during the study. Of these events, 1 was judged to have a possible association with the study drug, the other 2 were unrelated to the study drug. A summary of adverse events is presented in page 276, Vol. 1.2.

The plasma concentrations and pharmacokinetic parameters for Bupropion, Hydroxybupropion and Threo-bupropion are summarized below.

TABLE I
FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99266
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 36 SUBJECTS
BUPROPION

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B	
0	0.00	(0.0)	0.00	(0.0)
0.5	5.21	(108)	4.10	(114)
1	29.17	(49.2)	27.14	(41.6)
1.5	41.71	(38.6)	39.33	(36.6)
2	50.12	(43.2)	48.79	(39.6)
3	54.19	(34.9)	55.92	(38.0)
4	48.77	(31.4)	53.36	(33.9)
5	43.19	(29.9)	48.86	(31.1)
6	34.15	(26.9)	36.88	(27.5)
8	22.63	(24.5)	23.36	(24.6)
10	16.41	(26.7)	16.07	(25.4)
12	11.25	(28.5)	11.32	(27.1)
24	3.82	(38.2)	3.87	(31.1)

36	2.13	(46.6)	2.17	(44.9)
48	1.12	(87.1)	1.23	(74.1)
60	0.58	(126)	0.54	(136)
72	0.30	(181)	0.30	(183)
96	0.03	(600)	0.00	(0.0)
120	0.00	(0.0)	0.00	(0.0)
144	0.00	(0.0)	0.00	(0.0)
168	0.00	(0.0)	0.00	(0.0)

Pharmacokinetic Parameters

	Test	Reference	T/R	90% CI
AUC(0-t) (ng.hr/mL)	518.3(31)	531.8(30)	0.97	
AUCinf (ng.hr/mL)	546.9(31)	563.6(29)	0.97	
Cmax (ng/mL)	58.2(37)	59.9(33)	0.97	
Tmax (hr)	2.9	3.5		
Kel(1/hr)	0.06	0.06		
t1/2 (hr)	15.93	16.58		
LnAUC(0-t)				90.80-104.4%
LnAUCinf				90.63-103.8%
LnCmax				87.95-106.3%

1. The mean bupropion plasma levels peaked at 3 hours for both the test and the reference products following their administration under fasting conditions.

2. For Impax's bupropion, the mean AUCT, AUCI and Cmax values were 2.5%, 3.0% and 2.8% lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCT, AUCI and Cmax.

TABLE II
FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99266
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 36 SUBJECTS
HYDROXYBUPROPION

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B	
0	0.00	(0.0)	0.00	(0.0)
0.5	8.94	(120)	8.17	(112)

1	49.83	(65.5)	44.03	(54.7)
1.5	78.03	(50.5)	71.61	(43.6)
2	103.02	(43.9)	96.40	(37.1)
3	145.24	(43.0)	139.01	(35.5)
4	170.91	(41.7)	169.08	(40.2)
5	180.20	(41.0)	184.09	(37.9)
6	177.78	(41.4)	181.73	(36.2)
8	173.19	(38.2)	177.36	(35.6)
10	173.76	(38.7)	174.33	(38.2)
12	149.97	(37.2)	153.58	(37.5)
24	125.07	(37.5)	122.82	(41.9)
36	84.24	(40.5)	83.61	(46.7)
48	59.88	(48.1)	59.52	(47.9)
60	39.41	(54.5)	39.62	(54.6)
72	27.20	(68.3)	25.85	(61.2)
96	11.63	(88.1)	12.22	(94.3)
120	3.70	(175)	4.86	(152)
144	0.92	(354)	1.28	(300)
168	0.39	(415)	0.46	(419)

Pharmacokinetic Parameters

	Test	Reference	T/R	90% CI
AUC(0-t) (ng.hr/mL)	7146.3(42)	7223.8(45)	0.99	
AUCinf (ng.hr/mL)	7404.2(41)	7480.3(43)	0.99	
Cmax (ng/mL)	190.2(40)	193.2(37)	0.98	
Tmax (hr)	6.7	6.3		
Kel(1/hr)	0.04	0.04		
t1/2 (hr)	20.09	20.46		
LnAUC(0-t)				93.40-110.3%
LnAUCinf				93.66-109.7%
LnCmax				91.56-103.7%

1. The mean hydroxybupropion plasma levels peaked at 5 hours for both the test and the reference products following their administration under fasting conditions.

2. For Impax's hydroxybupropion, the mean AUCT, AUCI and Cmax values were 1.1%, 1.0% and 1.6% lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCT, AUCI and Cmax.

TABLE III
FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99266
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 36 SUBJECTS
THREO-BUPROPION

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B	
0	0.00	(0.0)	0.00	(0.0)
0.5	0.64	(187)	0.49	(198)
1	9.96	(57.8)	9.50	(54.3)
1.5	20.59	(44.1)	20.18	(44.8)
2	30.53	(44.8)	31.12	(45.9)
3	43.06	(38.8)	46.49	(45.8)
4	51.23	(39.5)	55.96	(43.0)
5	56.30	(38.0)	65.25	(44.1)
6	54.87	(42.2)	62.41	(42.2)
8	51.10	(46.7)	57.06	(44.6)
10	47.47	(47.3)	51.17	(44.0)
12	42.60	(52.5)	46.85	(51.4)
24	32.89	(58.3)	35.92	(57.7)
36	25.73	(60.4)	27.85	(56.6)
48	20.62	(60.0)	22.73	(59.1)
60	17.04	(58.7)	18.53	(57.0)
72	14.61	(62.2)	15.63	(57.0)
96	9.68	(56.4)	10.91	(59.3)
120	6.67	(59.9)	7.78	(63.2)
144	4.88	(61.9)	5.87	(67.6)
168	3.45	(66.9)	3.96	(80.5)

Pharmacokinetic Parameters

	Test	Reference	T/R	90% CI
AUC(0-t) (ng.hr/mL)	2733.8(53)	3035.1(52)	0.90	
AUCinf (ng.hr/mL)	3019.3(52)	3374.0(55)	0.89	
Cmax (ng/mL)	58.6(41)	66.9(43)	0.88	
Tmax (hr)	5.3	5.6		
Kel(1/hr)	0.015	0.016		
t1/2 (hr)	50.06	49.57		
LnAUC(0-t)				86.47-97.7%
LnAUCinf				86.48-99.1%
LnCmax				83.50-94.4%

1. The mean Threo-bupropion plasma levels peaked at 5 hours for both the test and the reference products following their administration under fasting conditions.

2. For Impax's Threo-bupropion, the mean AUCT, AUCI and Cmax values were 9.9%, 10.5% and 12.4% lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCT, AUCI and Cmax.

V. Study #99231 for Single-Dose, two-way Crossover Study of Bupropion HCl ER Tablets, 150 mg, Under Fasting Conditions

Clinical site:	[redacted]
Analytical site:	[redacted]
Study design:	Open-label, single-dose, fasted, randomized, two-period crossover.
Dosing date:	Period I December 12, 1999 Period II January 9, 2000
Analytical date:	Samples were analyzed between January 19 to February 17, 2000.
Subjects:	Thirty-six (36) male subjects enrolled and thirty-five completed the crossover. Subject #1 dropped from the study during period I, due to flu symptoms and concomitant medication therapy.
Dose and Treatments:	After a supervised overnight fast (at least 10 hours) subjects received an oral dose of the assigned formulation with 240 mL of water. Treatment A: 1x150 mg Bupropion HCl ER Tablet (Impax), lot #R99026-100-2, Exp. N/A, batch size [redacted] Tablets, potency 101.6%, content uniformity 101.4% (%CV=0.86). Treatment B: 1x150 mg Wellbutrin SR^{R} Tablet (Glaxo Wellcome), lot #8L2475,

Exp. 8/00, potency 99.5%, content uniformity 98.8% (%CV=0.77).

Washout period: Three weeks

Assay Methodology:

Determination of Bupropion, Hydroxybupropion and Threo-bupropion plasma concentrations was performed by [redacted]. The analytical method validation reports in this study are the same as reported in the fasting study for the 100 mg strength.

Precision: Between-run coefficient of variation from quality control samples ranged from [redacted] to [redacted] for Bupropion.

Between-run coefficient of variation from quality control samples ranged from [redacted] to [redacted] for Hydroxybupropion.

Between-run coefficient of variation from quality control samples ranged from [redacted] to [redacted] for Threo-bupropion.

VI. In Vivo Results

Four subjects experienced twelve adverse events during the study. Of these events, eight were judged to have a possible association with the study drug, the other four were unrelated or remotely related to the study drug. A summary of adverse events is presented in page 1707, Vol. 1.6.

The plasma concentrations and pharmacokinetic parameters for Bupropion, Hydroxybupropion and Threo-bupropion are summarized below.

TABLE IV
FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99231
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 35 SUBJECTS
BUPROPION

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B	
0	0.00	(0.0)	0.00	(0.0)
0.5	7.20	(160)	6.49	(117)
1	42.49	(57.7)	40.11	(49.9)
1.5	60.22	(35.4)	62.24	(35.5)
2	70.45	(32.0)	73.99	(32.3)
3	78.48	(29.2)	83.72	(26.0)
4	74.24	(28.5)	80.86	(26.3)
5	74.68	(40.5)	76.29	(27.7)
6	60.81	(39.6)	57.33	(26.6)
8	38.14	(33.3)	34.97	(24.8)
10	26.07	(32.0)	23.72	(24.9)
12	17.98	(28.6)	16.71	(25.5)
16	10.03	(29.5)	9.90	(28.9)
24	5.09	(35.7)	4.97	(32.9)
36	2.77	(40.3)	2.68	(43.3)
48	1.67	(60.6)	1.46	(76.6)
60	0.71	(111)	0.68	(118)
72	0.24	(222)	0.28	(206)
96	0.00	(0.0)	0.00	(0.0)
120	0.00	(0.0)	0.00	(0.0)
144	0.00	(0.0)	0.00	(0.0)
168	0.00	(0.0)	0.00	(0.0)

Pharmacokinetic Parameters

	Test	Reference	T/R	90% CI
AUC(0-t) (ng.hr/mL)	776.5(28)	765.7(26)	1.01	
AUCinf (ng.hr/mL)	806.4(27)	795.6(26)	1.01	
Cmax (ng/mL)	88.8(30)	89.5(27)	0.99	
Tmax (hr)	3.4	3.2		
Kel(1/hr)	0.05	0.06		
t1/2 (hr)	15.09	14.97		
LnAUC(0-t)				94.9-107.4%
LnAUCinf				95.2-107.2%

LnCmax 91.5-105.9%

1. The mean bupropion plasma levels peaked at 3 hours for both the test and the reference products following their administration under fasting conditions.

2. For Impax's bupropion, the mean AUCT, AUCI and Cmax values were 1.4%, 1.4% and 0.8% higher and lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCT, AUCI and Cmax.

3. It should be noted that subject #9 failed to return for three blood draws in period I and for six blood draws in period II. Additional analysis of variance was performed by the reviewer after excluding this subject. The 90% confidence intervals for log-transformed AUC(0-t), AUCinf and Cmax remained within the acceptable range of 80-125% for bupropion.

TABLE V
FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99231
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 35 SUBJECTS
HYDROXYBUPROPION

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B	
0	0.00	(0.0)	0.00	(0.0)
0.5	12.14	(121)	11.83	(120)
1	67.14	(60.3)	66.98	(49.8)
1.5	113.68	(46.6)	118.93	(40.5)
2	151.77	(41.3)	161.64	(39.2)
3	217.55	(42.6)	234.57	(36.6)
4	266.43	(41.0)	279.97	(33.7)
5	287.51	(39.6)	304.03	(31.8)
6	296.46	(37.2)	298.14	(33.2)
8	292.80	(37.9)	288.86	(31.7)
10	285.17	(36.8)	288.80	(33.6)
12	260.97	(37.8)	260.43	(33.5)
16	216.45	(38.8)	217.76	(35.8)
24	188.80	(44.4)	186.31	(39.7)
36	133.04	(53.5)	128.88	(43.5)
48	99.99	(57.1)	90.67	(49.3)
60	66.31	(59.9)	60.69	(51.7)
72	42.03	(61.8)	40.54	(56.8)
96	21.09	(81.6)	18.40	(75.4)

120	9.08	(107)	8.10	(103)
144	3.74	(134)	2.72	(153)
168	0.67	(400)	0.72	(284)

Pharmacokinetic Parameters

Pharmacokinetic Parameters

	Test	Reference	T/R	90% CI
AUC(0-t) (ng.hr/mL)	11674.2(49)	11277.6(42)	1.04	
AUCinf (ng.hr/mL)	11960.9(48)	11543.0(42)	1.04	
Cmax (ng/mL)	311.9(37)	315.9(32)	0.99	
Tmax (hr)	6.7	6.1		
Kel(1/hr)	0.034	0.035		
t1/2 (hr)	21.50	21.02		
LnAUC(0-t)				94.4-108.0%
LnAUCinf				94.8-107.6%
LnCmax				92.3-102.3%

1. The mean hydroxybupropion plasma levels peaked at 5 and 6 hours for the reference and the test products, respectively, following their administration under fasting conditions.

2. For Impax's hydroxybupropion, the mean AUCT, AUCI and Cmax values were 3.5%, 3.6% and 1.3% higher and lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCT, AUCI and Cmax.

3. It should be noted that subject #9 failed to return for three blood draws in period I and for six blood draws in period II. Additional analysis of variance was performed by the reviewer after excluding this subject. The 90% confidence intervals for log-transformed AUC(0-t), AUCinf and Cmax remained within the acceptable range of 80-125% for hydroxybupropion.

TABLE VI
FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99231
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 35 SUBJECTS
THREO-BUPROPION

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B	
0	0.00	(0.0)	0.00	(0.0)
0.5	1.28	(257)	0.92	(171)
1	17.59	(85.9)	15.21	(64.1)
1.5	34.16	(49.7)	33.75	(43.5)
2	48.96	(42.3)	49.96	(35.1)
3	72.00	(40.5)	76.21	(25.6)
4	84.05	(38.4)	93.20	(30.2)
5	99.05	(39.1)	109.16	(33.6)
6	101.32	(42.4)	105.71	(36.5)
8	94.47	(42.8)	95.39	(35.4)
10	85.83	(45.5)	86.38	(39.1)
12	77.93	(45.0)	79.39	(41.8)
16	63.43	(52.0)	65.36	(47.8)
24	50.43	(54.5)	52.15	(58.9)
36	39.47	(64.1)	39.98	(57.5)
48	33.26	(70.6)	33.10	(65.2)
60	27.51	(72.0)	27.65	(73.8)
72	22.78	(85.6)	23.36	(76.9)
96	17.21	(90.5)	16.99	(91.7)
120	12.21	(99.2)	12.19	(102)
144	8.77	(95.6)	8.88	(123)
168	6.18	(95.2)	6.15	(124)

Pharmacokinetic Parameters

	Test	Reference	T/R	90% CI
AUC(0-t) (ng.hr/mL)	4600.2(64)	4641.5(63)	0.99	
AUCinf (ng.hr/mL)	5082.5(67)	5153.9(71)	0.99	
Cmax (ng/mL)	104.7(40)	110.9(35)	0.94	
Tmax (hr)	5.5	5.4		
Kel(1/hr)	0.016	0.017		
t1/2 (hr)	47.10	46.55		
LnAUC(0-t)				92.2-104.1%
LnAUCinf				91.8-104.7%
LnCmax				87.0-99.2%

1. The mean threo-bupropion plasma levels peaked at 5 and 6 hours for the reference and the test products, respectively, following their administration under fasting conditions.

2. For Impax's threo-bupropion, the mean AUCT, AUCI and Cmax values were 0.9%, 1.4% and 5.6% lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCT, AUCI and Cmax.

3. It should be noted that subject #9 failed to return for three blood draws in period I and for six blood draws in period II. Additional analysis of variance was performed by the reviewer after excluding this subject. The 90% confidence intervals for log-transformed AUC(0-t), AUCinf and Cmax remained within the acceptable range of 80-125% for threo-bupropion.

V. Study #99232 For Single Dose post-prandial Bioequivalence Study

Clinical site:	[redacted]
Analytical site:	[redacted]
Study design:	Open-label, randomized, 3-way crossover, three-sequence study under fasting and nonfasting conditions.
Dosing date:	Period I January 8, 2000 Period II January 29, 2000 Period III February 19, 2000
Analytical date:	Samples were analyzed between March 8 to April 21, 2000.
Subjects:	Twenty-seven (27) male subjects enrolled and twenty-six completed the crossover. Subject #26 was unable to participate in study period III after becoming ill with the flu.

Dose and Treatments:

Treatment A: 1x150 mg Bupropion HCl ER Tablet (Impax), lot #R99026-100-2, Administered after an overnight fast.

Treatment B: 1x150 mg Bupropion HCl ER Tablet (Impax), lot #R99026-100-2, administered following a standard meal preceded by an overnight fast.

Treatment C: 1x150 mg Wellbutrin SR^{R} Tablet (Glaxo Wellcome), lot #8L2475, administered following a standard meal preceded by an overnight fast.

Washout period: Three weeks

Food and fluid intake:

Subjects were required to fast overnight for 10 hours prior to dosing in each treatment phase. Subjects on regimen A ingested the tablet with 240 mL of water. Subjects on regimen B and C ingested the tablet with 240 mL of water following the complete ingestion of a standardized high-fat content breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice). Water was not permitted from 1 hour before until 1 hour after the dose, but was allowed at all other times. Subjects received a standard meal 4 hours post-dose and at appropriate times thereafter.

Assay Methodology:

Determination of Bupropion, Hydroxybupropion and Threo-bupropion plasma concentrations was performed by [redacted]. The analytical method validation reports in this study are the same as reported in the fasting study for the 100 mg strength.

Precision:

Between-run coefficient of variation from quality control samples ranged from [redacted] to

——— for Bupropion (values which exceeded ±20% nominal were included in the calculations).

Between-run coefficient of variation from quality control samples ranged from ——— to ——— for Hydroxybupropion (values which exceeded ±20% nominal were included in the calculations).

Between-run coefficient of variation from quality control samples ranged from ——— to ——— for Threo-bupropion (values which exceeded ±20% nominal were included in the calculations).

VI. In Vivo Results:

Three subjects experienced five adverse events during the study. All events were unrelated to the study drug. A summary of adverse events is presented in page 003121, Vol. 1.10.

The plasma concentrations and pharmacokinetic parameters for Bupropion, Hydroxybupropion and Threo-bupropion are summarized below.

TABLE VII
FED/FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99232
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 26 SUBJECTS
BUPROPION

TIME (HR)	TEST FAST TREATMENT A		TEST FED TREATMENT B		REFERENCE FED TREATMENT C	
0	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
0.5	5.87	(81.3)	11.05	(217.5)	5.63	(98.3)
1	45.17	(35.9)	37.11	(113.6)	32.51	(57.6)
1.5	62.50	(31.5)	62.74	(69.1)	57.09	(42.2)
2	68.11	(35.4)	83.11	(54.6)	74.64	(34.8)
3	75.37	(42.1)	96.05	(43.8)	94.34	(31.8)
4	71.70	(35.1)	99.23	(37.3)	102.72	(28.3)
5	77.30	(35.0)	96.27	(33.2)	98.45	(28.7)
6	60.71	(37.0)	65.19	(32.0)	71.88	(35.7)
8	36.54	(33.5)	37.83	(33.6)	39.68	(26.2)
10	24.07	(33.2)	25.18	(26.4)	26.25	(25.5)
12	16.60	(32.9)	18.30	(26.8)	18.49	(26.4)

24	5.60	(33.8)	6.24	(27.8)	6.08	(27.5)
36	3.24	(40.0)	3.57	(39.1)	3.39	(32.3)
48	2.20	(42.9)	2.37	(45.3)	2.30	(52.4)
60	1.30	(55.4)	1.49	(53.2)	1.49	(51.1)
72	0.73	(100.2)	0.88	(91.0)	0.77	(108.2)
96	0.15	(285.8)	0.15	(282.4)	0.18	(289.9)
120	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
144	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
168	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)

Pharmacokinetic Parameters

AUC(0-t) (ng.hr/mL)	797.3(30)	917.7(26)	916.2 (21)
AUCinf (ng.hr/mL)	839.9(29)	958.3(24)	963.9 (22)
Cmax (ng/mL)	86.6(36)	119.2(36)	117.6 (20)
Tmax (hr)	3.8	3.8	3.9
Kel(1/hr)	0.038	0.041	0.041
t1/2 (hr)	22.77	21.17	23.42

	B/C Arithmetic Mean	B/C Geometric Mean
AUC(0-t)	1.00	0.99
AUCinf	0.99	0.99
Cmax	1.01	0.98

1. The bupropion plasma levels peaked at 4 hours for both the test and the reference products under nonfasting conditions and at 5 hours for the test product under fasting conditions.

2. For Impax's bupropion, the mean AUC(0-t), Cmax and AUCinf values were 0.16%, 1.3% and 0.6% higher and lower, respectively, than the reference product values under nonfasting conditions. The ratios of the test arithmetic means to the reference arithmetic means are within the acceptable range of 0.8-1.25 for the above parameters. Also, the ratios of the geometric means are within the acceptable 0.8-1.25 range for AUC(0-t), AUCinf and Cmax. The reviewer's calculations are similar to those submitted by the firm.

3. For the test product, the mean AUC(0-t), AUCinf and

3. For the test product, the mean AUC(0-t), AUCinf and Cmax values were increased by about 15.1%, 14.0% and 37.6%, respectively, when dosed under nonfasting conditions compared to fasting conditions.

TABLE VIII
FED/FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99232
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 26 SUBJECTS
HYDROXYBUPROPION

TIME (HR)	TEST FAST TREATMENT A		TEST FED TREATMENT B		REFERENCE FED TREATMENT C	
0	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
0.5	10.86	(103.6)	7.54	(253.2)	4.79	(153.4)
1	63.37	(46.7)	34.96	(137.1)	29.49	(70.9)
1.5	100.02	(44.0)	70.67	(89.1)	67.02	(59.0)
2	127.56	(44.7)	107.60	(68.0)	103.61	(51.2)
3	176.53	(44.8)	171.29	(50.8)	170.83	(51.6)
4	210.08	(39.6)	229.73	(43.8)	225.07	(45.0)
5	239.03	(37.8)	255.11	(41.5)	253.34	(39.8)
6	241.74	(41.6)	250.80	(38.1)	253.13	(41.7)
8	233.59	(40.8)	241.37	(41.0)	242.77	(39.9)
10	223.53	(42.1)	237.80	(43.5)	232.76	(43.3)
12	207.50	(42.0)	219.33	(45.0)	216.91	(40.2)
16	188.18	(42.0)	208.59	(47.8)	194.28	(43.1)
24	169.93	(43.8)	187.12	(48.9)	176.03	(42.6)
36	122.63	(45.2)	132.11	(51.1)	120.17	(46.0)
48	88.20	(53.0)	91.36	(57.3)	84.76	(49.7)
60	64.86	(64.6)	65.75	(64.6)	57.97	(53.0)
72	46.62	(68.4)	46.60	(73.5)	40.70	(62.8)
96	23.39	(93.4)	23.11	(89.3)	19.76	(81.9)
120	10.92	(121.7)	11.02	(117.3)	7.89	(114.9)
144	5.51	(171.9)	4.04	(171.5)	3.47	(174.9)
168	2.02	(225.7)	1.17	(307.1)	1.21	(248.9)

Pharmacokinetic Parameters

AUC(0-t) (ng.hr/mL)	10575.6(48)	11048.4(53)	10263.7(47)
AUCinf (ng.hr/mL)	10860.2(48)	11084.7(53)	10542.2(46)
Cmax (ng/mL)	254.8(40)	270.8(39)	271.4(41)
Tmax (hr)	6.2	5.5	6.6
Kel(1/hr)	0.033	0.033	0.033
t1/2 (hr)	22.11	22.04	22.05

	B/C Arithmetic Mean	B/C Geometric Mean
AUC(0-t)	1.07	1.05
AUCinf	1.05	1.05
Cmax	1.00	1.00

1. The hydroxybupropion plasma levels peaked at 5 hours for both the test and the reference products under nonfasting conditions and at 6 hours for the test product under fasting conditions.

2. For Impax's hydroxybupropion, the mean AUC(0-t), AUCinf and Cmax values were 7.6%, 5.1% and 0.2% higher and lower, respectively, than the reference product values under nonfasting conditions. The ratios of the test arithmetic means to the reference arithmetic means are within the acceptable range of 0.8-1.25 for the above parameters. Also, the ratios of the geometric means are within the acceptable 0.8-1.25 range for AUC(0-t), AUCinf and Cmax. The reviewer's calculations are similar to those submitted by the firm.

3. For the test product, the mean AUC(0-t), AUCinf and Cmax values were increased by about 4.5%, 2.1% and 6.2%, respectively, when dosed under nonfasting conditions compared to fasting conditions.

TABLE IX
FED/FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99232
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 26 SUBJECTS
THREO-BUPROPION

TIME (HR)	TEST FAST TREATMENT A		TEST FED TREATMENT B		REFERENCE FED TREATMENT C	
0	0.00	(0.0)	0.00	(0.0)	0.00	(0.0)
0.5	0.70	(153.7)	2.52	(272.0)	0.82	(161.5)
1	17.36	(47.7)	16.62	(157.3)	13.54	(78.5)
1.5	35.23	(39.0)	32.72	(99.7)	30.18	(61.1)
2	47.56	(39.0)	50.99	(69.8)	46.71	(52.5)
3	67.08	(40.5)	75.72	(49.5)	71.66	(38.9)
4	80.61	(38.9)	96.91	(41.4)	96.15	(38.5)
5	99.78	(35.7)	114.59	(35.3)	114.58	(30.8)
6	99.90	(36.2)	104.22	(37.2)	108.13	(34.0)
8	89.99	(37.8)	92.05	(42.1)	93.35	(33.2)
10	80.04	(38.4)	83.00	(40.5)	83.43	(35.2)

12	70.93	(45.8)	74.67	(45.7)	74.58	(37.8)
16	62.08	(44.6)	66.18	(46.7)	66.24	(46.9)
24	51.87	(48.2)	54.02	(49.4)	51.53	(45.8)
36	41.56	(57.2)	42.59	(59.3)	37.91	(34.5)
48	33.35	(53.4)	33.87	(64.1)	31.63	(39.4)
60	27.97	(66.9)	28.67	(74.3)	25.21	(40.4)
72	24.26	(62.0)	23.91	(65.9)	22.20	(46.4)
96	16.72	(62.3)	16.52	(75.0)	14.96	(43.0)
120	12.31	(70.8)	11.83	(81.9)	10.69	(48.6)
144	9.36	(74.0)	8.34	(87.1)	7.41	(44.5)
168	6.18	(73.0)	6.29	(91.4)	5.10	(54.4)

Pharmacokinetic Parameters

AUC(0-t) (ng.hr/mL)	4581.4(52)	4658.8(56)	4411.1(39)
AUCinf (ng.hr/mL)	5084.7(54)	5086.1(59)	4789.8(39)
Cmax (ng/mL)	105.5(34)	120.0(38)	119.4(31)
Tmax (hr)	5.8	4.9	4.9
Kel(1/hr)	0.015	0.016	0.016
t1/2 (hr)	49.63	48.15	47.35

	B/C Arithmetic Mean	B/C Geometric Mean
AUC(0-t)	1.06	1.01
AUCinf	1.06	1.02
Cmax	1.02	0.99

1. The threo-bupropion plasma levels peaked at 5 hours for both the test and the reference products under nonfasting conditions and at 6 hours for the test product under fasting conditions.

2. For Impax's threo-bupropion, the mean AUC(0-t), AUCinf and Cmax values were 5.6%, 6.2% and 0.5 higher, respectively, than the reference product values under nonfasting conditions. The ratios of the test arithmetic means to the reference arithmetic means are within the acceptable range of 0.8-1.25 for the above parameters. Also, the ratios of the geometric means are within the acceptable 0.8-1.25 range for AUC(0-t), AUCinf and Cmax. The reviewer's calculations are similar to those submitted by the firm.

reviewer's calculations are similar to those submitted by the firm.

3. For the test product, the mean Cmax value was increased by about 13.7% when dosed under nonfasting conditions compared to fasting conditions.

VII. Study #99076, Multiple-dose Bioequivalence study of Bupropion HCl ER Tablets, 150 mg

Clinical site:	[redacted]
Analytical site:	[redacted]
Study design:	The study was designed as an open-label, randomized, steady-state, 2-way crossover bioavailability study performed on 32 healthy non-smoking adult male volunteers.
Dosing date:	Period I January 15, 2000 Period II February 19, 2000
Analytical date:	Samples were analyzed between April 21 to May 1, 2000.
Dose and Treatments:	Treatment A: 1x150 mg Bupropion HCl ER Tablet (Impax), lot #R99026-100-2, followed by 240 mL of water twice daily for a total of twenty-seven (27) doses. Treatment B: 1x150 mg Wellbutrin SR^{R} Tablet (Glaxo Wellcome), lot #8L2475, Exp. 08/00, followed by 240 mL of water twice daily for a total of twenty-seven (27) doses.
Food and fluid intake:	Subjects fasted for ten hours prior to the morning dosing on day 1 and 13. On day 14, the subjects continued to fast through 4 hours following drug administration, at which time a standard clinical lunch was provided. Water was allowed *ad lib* during the

study, except for 1 hour prior through 1 hour post dose.

Blood samples: Blood samples were collected before the first dose on Days 1, 11, 12 and 13 and at the following times after the 27^{th} dose on Day 14: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours. Blood samples were cooled in an ice bath and separated by refrigerated centrifugation as soon as was possible.

Data Analysis

ANOVA was performed with subjects within sequence, period, drug (i.e. formulations), and sequence as factors for AUC(0-tau), Cmax and Tmax. Area under the curve was determined using linear trapezoidal method.

VIII. In Vivo Results:

Of the 32 subject who began this study, 31 completed both phases. Subject No. 27 dropped from the study for personal reasons. A total 58 adverse events were experienced by 19 subjects during the study. No serious adverse events occurred during the study. A summary of adverse events is presented in page 004622, Vol. 1.15.

The plasma concentrations and pharmacokinetic parameters for Bupropion, Hydroxybupropion and Threo-bupropion are summarized below.

TABLE X
FASTING MULTIPLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99076
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 31 SUBJECTS
BUPROPION

TIME DAY HR	TEST TREATMENT A		REFERENCE TREATMENT B	
Day 1 0	0.15	(392.9)	0.05	(547.7)
Day 1 12	21.7	(33.1)	21.0	(34.3)
Day 11 0	41.8	(32.7)	43.0	(28.9)
Day 11 12	39.9	(34.5)	41.6	(24.5)
Day 12 0	46.9	(31.9)	45.7	(27.0)
Day 12 12	41.5	(27.1)	42.7	(31.4)
Day 13 0	42.0	(26.5)	44.1	(33.9)

Day 13 12	38.3	(27.8)	41.7	(35.5)
Day 14 0	42.4	(27.1)	42.2	(23.2)
0.5	44.9	(24.7)	44.1	(27.7)
1	85.5	(27.3)	84.0	(30.0)
2	107.8	(23.4)	112.8	(23.0)
3	110.6	(27.0)	118.1	(21.4)
4	100.5	(26.5)	110.7	(18.8)
5	100.4	(27.7)	101.9	(16.8)
6	84.2	(26.0)	85.7	(21.7)
7	71.5	(23.3)	72.2	(20.2)
8	63.1	(25.1)	59.9	(21.9)
10	43.1	(27.7)	44.0	(22.8)
12	35.3	(30.6)	35.0	(23.5)

Pharmacokinetic Parameters			T/R	90% CI
AUC(0-τ) [ng.hr/mL]	888.3 (23)	910.0 (18)	0.98	
Cmax [ng/mL]	119.1 (24)	124.3 (19)	0.96	
Cmin [ng/mL]	34.6 (31)	34.6 (24)		
Tmax [hr]	2.7	3.0		
Fluct [%]	115.0	118.9		
LnAUC(0-τ)				91.9-101.7%
LnCmax				88.4-101.3%

1. The mean bupropion plasma levels peaked at 339 hours for both the test and the reference products.

2. For bupropion, the mean values for the AUC(0-tau) and Cmax for the test product were 2.4% and 4.2% lower, respectively, than were those for the reference product. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

3. Regression analysis indicated that plasma concentrations of bupropion were at steady state before sampling for AUC(0-τ) and Cmax.

TABLE XI

FASTING MULTIPLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99076
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 31 SUBJECTS
HYDROXYBUPROPION

TIME DAY HR	TEST TREATMENT A		REFERENCE TREATMENT B	
Day 1 0	0.00	(0.0)	0.00	(0.0)
Day 1 12	213.5	(44.0)	227.1	(42.3)
Day 11 0	964.0	(37.0)	1053.0	(37.0)
Day 11 12	898.0	(39.0)	964.0	(37.0)
Day 12 0	955.0	(40.0)	1015.0	(39.0)
Day 12 12	948.0	(41.0)	955.0	(40.0)
Day 13 0	1015.0	(40.0)	992.0	(39.0)
Day 13 12	916.0	(37.0)	903.0	(39.0)
Day 14 0	964.0	(40.0)	972.0	(43.0)
0.5	989.0	(40.0)	989.0	(44.0)
1	1067.0	(39.0)	1028.0	(40.0)
2	1095.0	(41.0)	1142.0	(45.0)
3	1094.0	(38.0)	1157.0	(42.0)
4	1097.0	(36.0)	1152.0	(41.0)
5	1105.0	(36.0)	1123.0	(37.0)
6	1068.0	(35.0)	1085.0	(41.0)
7	1036.0	(36.0)	1047.0	(35.0)
8	1050.0	(37.0)	1019.0	(36.0)
10	898.0	(40.0)	926.0	(37.0)
12	860.0	(39.0)	894.0	(37.0)

Pharmacokinetic Parameters			T/R	90% CI
AUC(0-τ) [ng.hr/mL]	12262.1(37)	12490.1(38)	0.98	
Cmax [ng/mL]	1203.1(36)	1240.0(40)	0.97	
Cmin [ng/mL]	830.0(40)	850.9(39)		
Tmax[hr]	4.2	4.1		
Fluct [%]	37.8	38.0		
LnAUC(0-τ)				90.0-103.8%
LnCmax				88.9-103.3%

1. The mean hydroxybupropion plasma levels peaked at 339 and 341 hours for the reference and the test products, respectively.

2. For hydroxybupropion, the mean values for the AUC(0-tau) and Cmax for the test product were 1.8% and 2.3% lower, respectively, than were those for the reference product. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

TABLE XII
FASTING MULTIPLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #99076
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 31 SUBJECTS
THREO-BUPROPION

TIME DAY HR	TEST TREATMENT A		REFERENCE TREATMENT B	
Day 1 0	2.39	(426.2)	1.81	(391.3)
Day 1 12	72.3	(45.4)	70.5	(44.5)
Day 11 0	476.0	(47.0)	476.0	(33.0)
Day 11 12	459.0	(39.0)	467.0	(34.0)
Day 12 0	481.0	(35.0)	491.0	(34.0)
Day 12 12	451.0	(32.0)	469.0	(36.0)
Day 13 0	482.0	(38.0)	483.0	(33.0)
Day 13 12	461.0	(37.0)	464.0	(35.0)
Day 14 0	467.0	(36.0)	473.0	(33.0)
0.5	462.0	(36.0)	468.0	(35.0)
1	494.0	(34.0)	494.0	(33.0)
2	531.0	(36.0)	543.0	(32.0)
3	539.0	(36.0)	564.0	(32.0)
4	545.0	(33.0)	573.0	(34.0)
5	560.0	(32.0)	582.0	(35.0)
6	561.0	(33.0)	561.0	(30.0)
7	546.0	(35.0)	562.0	(35.0)
8	535.0	(34.0)	532.0	(34.0)
10	483.0	(40.0)	499.0	(34.0)
12	452.0	(36.0)	463.0	(34.0)

Pharmacokinetic Parameters			T/R	90% CI
AUC(0-τ) [ng. hr/mL]	6221.1(35)	6366.4(33)	0.98	
Cmax [ng/mL]	594.8(32)	611.0(33)	0.97	
Cmin [ng/mL]	429.9(38)	437.6(35)		
Tmax[hr]	5.0	5.0		

Fluct [%]	34.3	33.4	
LnAUC(0-τ)			92.3-101.8%
LnCmax			92.3-103.0%

1. The mean threo-bupropion plasma levels peaked at 341 and 342 hours for the reference and the test products.

2 For threo-bupropion, the mean values for the AUC(0-tau) and Cmax for the test product were 2.3% and 2.7% lower, respectively, than were those for the reference product. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

3. The pre-dose samples for subject #8 in period I and period II, Day 1, contained 54 ng/mL and 38.80 ng/mL of threo-bupropion, respectively. Additional analysis of variance was performed by the reviewer after excluding this subject. Since this subject's predosing values are greater than 5% of his Cmax, it is considered acceptable to exclude this subject by the DBE. The 90% confidence intervals for log-transformed AUC(0-tau) and Cmax remained within the acceptable range of 80-125% for threo-bupropion.

IX. Formulation:

Impax's formulations for its Bupropion HCl ER Tablets, 100 and 150 mg mg, is shown below:

(NOT FOR RELEASE UNDER FOI)

Ingredient	Strength 100 mg	Strength 150 mg
BUPROPION HYDROCHLORIDE	100	150
HYDROXPROPYL CELLULOSE NF	[redacted]	[redacted]
[redacted]		
MICROCRYSTALLINE CELLULOSE NF	[redacted]	[redacted]
COLLOIDAL SILICON DIOXIDE NF	[redacted]	[redacted]
MAGNESIUM STEARATE, NF	[redacted]	[redacted]
Total	[redacted] mg	[redacted] mg

X. In Vitro Dissolution Testing:

Dissolution Method: USP <724>
Dissolution Media: Water, SGF/W enzyme, acetate buffer pH 4.0, phosphate buffer pH 6.0 and phosphate buffer pH 7.5.
Volume: 900 ML
Dissolution Apparatus: 2 (paddle) at 50 rpm and at 75 rpm
Dissolution results are shown in Table XIII.

The firm proposes a dissolution method using 900 mL of water, apparatus 2 at 50 rpm.

	TEST Lot No.: R99026-100-2 Strength: 150MG TABLET No. of Units: 12			REFERENCE Lot No.: 8L2475 Strength: 150MG TABLET No. of Units: 12		
Time(hr)	Mean	Range	%CV	Mean	Range	%CV
1	44.90		9.6	43.64		7.4
2	64.10		6.8	65.00		5.5
4	82.54		4.1	89.59		3.5
6	89.61		2.5	99.17		1.9
12	90.72		1.2	101.33		1.6

	TEST Lot No.: R99040 Strength: 100MG TABLET No. of Units: 12			REFERENCE Lot No.: 9H1752 Strength: 100MG TABLET No. of Units: 12		
Time(hr)	Mean	Range	%CV	Mean	Range	%CV
1	44.10		5.9	42.00		2.9
2	63.00		4.4	63.00		2.9
4	81.90		3.2	87.90		2.7
6	88.50		2.6	98.20		2.0
12	89.80		2.2	101.10		1.7

X1. Comments:

1. The firm's single-dose bioequivalence study #99266 under fasting conditions, conducted on its 100 mg Bupropion HCl ER Tablet is acceptable. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% for Bupropion, Hydroxybupropion and Threo-Bupropion.

2. The firm's single-dose bioequivalence study #99231 under fasting conditions, conducted on its 150 mg Bupropion HCl ER Tablet is acceptable. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% for Bupropion, Hydroxybupropion and Threo-Bupropion.

3. The firm's single-dose bioequivalence study #99232 under fasting and nonfasting conditions, conducted on its 150 mg Bupropion HCl ER Tablet is acceptable. The ratios of the test mean to the reference mean for AUC(0-t), AUCinf and Cmax are within the acceptable range of 0.8-1.25 for Bupropion, Hydroxybupropion and Threo-Bupropion under nonfasting conditions.

4. The firm's multiple-dose bioequivalence study #99076 under fasting conditions, conducted on its 150 mg Bupropion HCl ER Tablet is acceptable. The 90% confidence intervals for LnAUC(0-τ) and LnCmax are within the acceptable range of80-125% for Bupropion, Hydroxybupropion and Threo-Bupropion.

5. The dissolution testing conducted by the firm on its Bupropion Hydrochloride ER Tablets, 100 mg and 150 mg, is acceptable.

XII. Recommendations:

1. The bioequivalence study under fasting conditions conducted by Impax Pharmaceuticals, Inc., on its Bupropion HCl ER Tablet, 100 mg, lot #R99040-60, comparing it to Glaxo Wellcome's Wellbutrin SR^R Tablet, 100 mg, has been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions Impax's Bupropion HCl ER Tablet, 100 mg, is bioequivalent to the reference product, Wellbutrin SR^R Tablet, 100 mg, manufactured by Glaxo Wellcome.

2. The bioequivalence study under fasting conditions conducted by Impax Pharmaceuticals, Inc., on its Bupropion HCl ER Tablet, 150 mg, lot #R99026-100-2, comparing it to Glaxo Wellcome's Wellbutrin SR^R Tablet, 150 mg, has been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions Impax's Bupropion HCl ER Tablet, 150 mg, is bioequivalent to the reference product, Wellbutrin SR^R Tablet, 150 mg, manufactured by Glaxo Wellcome.

3. The bioequivalence study under fasting and nonfasting conditions conducted by Impax Pharmaceuticals, Inc., on its Bupropion HCl ER Tablet, 150 mg, lot #R99026-100-2, comparing it to Glaxo Wellcome's Wellbutrin SR^R Tablet, 150 mg, has been found acceptable by the Division of

Bioequivalence. The study demonstrates that under nonfasting conditions Impax's Bupropion HCl ER Tablet, 150 mg, is bioequivalent to the reference product, Wellbutrin SR^{R} Tablet, 150 mg, manufactured by Glaxo Wellcome.

4. The multiple-dose steady-state bioequivalence study conducted by Impax Pharmaceuticals, Inc., on its Bupropion HCl ER Tablet, 150 mg, lot #R99026-100-2, comparing it to Glaxo Wellcome's Wellbutrin SR^{R} Tablet, 150 mg, has been found acceptable by the Division of Bioequivalence. The study demonstrates that under steady-state conditions Impax's Bupropion HCl ER Tablet, 150 mg, is bioequivalent to the reference product, Wellbutrin SR^{R} Tablet, 150 mg, manufactured by Glaxo Wellcome.

5. The dissolution testing conducted by the firm on its Bupropion HCl ER Tablets, 100 mg and 150 mg, lot #R99040 and lot #R99026-100-2, respectively, is acceptable. The formulation of the 100 mg strength is proportionally similar to the 150 mg strength of the test product which underwent complete acceptable bioequivalence testing. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37^{o}C using USP 23 apparatus II (paddle) at 50 rpm. Based on the submitted data, the test product should meet the following tentative specifications:

Between ——— % in 1 hour.
Between ——— % in 2 hours.
Between ——— % in 4 hours.
NLT ——— % in 6 hours

The firm should be informed of the above recommendations.

Moheb H. Makary
Moheb H. Makary, Ph.D. Date: 9/5/00
Review Branch III
Division of Bioequivalence 9.1.00

RD INITIALLED BDAVIT bnd
FT INITIALLED BDAVIT Barbara Davit Date: 9/5/00

Concur: Dale P. Conner Date: 9/28/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/8-25-00, 9-5-00, 75913SD.600
cc: ANDA #75-913, original, HFD-658 (Makary), Drug File, Division File.

CC: ANDA #75-913
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit

V:\FIRMSAM\IMPAX\LTRS&REV\75913SD.600
Printed in final on 9/5/00

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MMM
HFD-658/ Bio team Leader B. Davit BWD
HFD-650/ D. Conner DR 9/28/00

BIOEQUIVALENCY - ACCEPTABLE submission date: June 22, 2000

OK 1. **FASTING STUDY** (STF) Strengths: 100 mg
Clinical: [redacted] **Outcome: AC**
Analytical [redacted]

OK 2. **FASTING STUDY** (STF) Strengths: 150 mg
Clinical: [redacted] **Outcome: AC**
Analytical [redacted]

OK 3. **FOOD STUDY** (STP) Strengths: 150 mg
Clinical: [redacted] **Outcome: AC**
Analytical: [redacted]

OK 4. **MULTIPLE DOSE STUDY** (STM) Strengths: 150 mg
Clinical: [redacted] **Outcome: AC**
Analytical: [redacted]

OK 5. **STUDY AMENDMENT** (STA) Strengths: 100 mg and 150 mg
Date: August 25, 00 **Outcome: AC**

Outcome Decisions: **AC** - Acceptable

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-913 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion HCl ER Tablets, 100 mg and 150 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm. Based on the submitted data, the test product should meet the following tentative specifications:

Between ——— % in 1 hour.
Between ——— % in 2 hours.
Between ——— % in 4 hours.
NLT — % in 6 hours

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-913 SPONSOR : Impax Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM : Bupropion HCl ER Tablets

STRENGTH(S) : 100 mg and 150 mg

TYPES OF STUDIES : Single-dose fasting, nonfasting, and multiple-dose fasting studies for the 150 mg and Single-dose fasting for the 100 mg

CLINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : Studies are acceptable

DISSOLUTION : Dissolution testing is acceptable

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM DATE : 9/5/00

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : BMD DATE : 9/5/00

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : _____ DATE : 9/28/00

Bupropion HCl ER Tablets
150 mg and 100 mg
ANDA #75-913
Reviewer: Moheb H. Makary
W 75913D.501

Impax Pharmaceuticals, Inc.
Hayward, CA
Submission Date:
May 16, 2001

Review of an Amendment

I. Objective:

In this amendment, the firm proposes to [redacted] the suggested tentative specifications for the above referenced product. The Division of Bioequivalence (letter dated December 20, 2000) previously recommended the following tentative dissolution specifications:

Between [redacted] % in 1 hour
Between [redacted] % in 2 hours
Between [redacted] % in 4 hours
NLT [redacted] % in 6 hours

Following drug release testing at the 78 week (18-month) stability timepoint after storage at 25°C/60% RH and packaged in 100-count glass bottles (stability data page 3, Vol. 3.1), Impax has indicated that it is [redacted] the drug release specifications suggested by the Division of Bioequivalence.

As an alternative, the firm proposes the following drug release specifications:

Between [redacted] % in 1 hour
Between [redacted] % in 2 hours
Between [redacted] % in 4 hours
NLT [redacted] % in 6 hours

This proposal [redacted] the suggested dissolution specifications by [redacted] the top end of the specification range by [redacted] % at the 1-, 2-, and 4-hour timepoints. The 6-hour specification remains unchanged.

II. Comment:

Based on a re-evaluation of the initial dissolution data submitted by the firm on the biobatches and production lots, the Division of Bioequivalence concurs with Impax's proposed dissolution specifications.

III. Recommendations:

1. The Division of Bioequivalence concurs with the firm's proposed dissolution specifications.

2. The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Between ——% in 1 hour
Between ——% in 2 hours
Between ——% in 4 hours
NLT —% in 6 hours

The firm should be informed of the above recommendations

Moheb H Makary
Moheb H. Makary, Ph.D. Date: 7/10/01
Review Branch III
Division of Bioequivalence

RD INITIALLED BDAVIT BNA 7/10/01
FT INITIALLED BDAVIT Barbara N Davit Date: 7/6/01

Concur: for Dale P. Conner Date: 7/31/2001
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/6-19-01, 7-10-01, 75913D.501
cc: ANDA #75-913, original, HFD-658 (Makary), Drug File, Division File.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-913 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion HCl ER Tablets, 100 mg and 150 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm. Based on the submitted data, the test product should meet the following specifications:

Between ——% in 1 hour
Between ——% in 2 hours
Between ——% in 4 hours
NLT —% in 6 hours

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #75-913
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit

V:\FIRMSAM\IMPAX\LTRS&REV\75913D.501
Printed in final on 7/10/01

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MMM 7/16/01
HFD-658/ Bio team Leader B. Davit
HFD-650/ D. Conner for DWC 7/31/2001

BIOEQUIVALENCY - ACCEPTABLE submission date: May 16, 2001

1. **STUDY AMENDMENT** (STA) Strengths:100 mg and 150 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-913 SPONSOR : Impax Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM : Bupropion HCl ER Tablets

STRENGTH(S) : 100 mg and 150 mg

TYPES OF STUDIES : Amendment

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : **N/A**

STUDY SUMMARY :

DISSOLUTION : Dissolution testing is acceptable

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM DATE : 6/19/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : BMD DATE : 7/10/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

for

INITIAL : N Galwaith DATE : 7/31/2001

4

Bupropion HCl ER Tablets
150 mg and 100 mg
ANDA #75-913
Reviewer: Moheb H. Makary
W 75913SD.N01

Impax Pharmaceuticals, Inc.
Hayward, CA
Submission Date:
November 27, 2001

Review of an Amendment

I. Objective:

The firm submitted this amendment to its ANDA #75-913 for Bupropion HCl ER Tablets, 150 mg and 100 mg. This amendment provides for the addition of film-coating to both product strengths (to mask the bitter taste of the active drug substance), and a ——— manufacturing process, whereby [ ] This revised process was applied only to the 150 mg strength to better control the finished tablet drug release profile.

To support the revised manufacturing process, the firm submitted a single-dose fasting study on its Bupropion HCl Extended Release (ER) Tablet, 150 mg, and a single-dose fasting on its Bupropion HCl Extended Release (ER) Tablet, 100 mg, comparing them with RLD Wellbutrin SR^{R} Tablets (Glaxo Wellcome), 150 mg and 100 mg, respectively.

II. Background:

On June 22, 2000, the firm submitted three acceptable *in vivo* bioequivalence studies (single-dose fasting, nonfasting, and multiple-dose fasting studies) on its Bupropion HCl Extended Release (ER) Tablet, 150 mg, and an acceptable single-dose fasting study on its Bupropion HCl Extended Release (ER) Tablet, 100 mg, comparing them with RLD Wellbutrin SR^{R} Tablets (Glaxo Wellcome), 150 mg and 100 mg, respectively.

III. Study #R01-365 for Single-Dose, two-way Crossover Study of Bupropion HCl ER Tablets, 100 mg, Under Fasting Conditions

Clinical site: ———

Analytical site: [redacted]

Study design: Open-label, single-dose, fasted, randomized, two-period crossover.

Dosing date: Period I July 14, 2001
Period II July 28, 2001

Analytical date: Samples were analyzed between August 7 to August 20, 2001.

Subjects: Thirty-six (36) male subjects enrolled in the study. Thirty-five completed the clinical portion of the study. Subject #35 elected to withdraw prior to period II dosing. Subject Nos. 14, 17, 20, 22, 24, 28, 30, 32, 34 and 36 were excluded from the statistical analysis due to pre-dose plasma concentrations greater than 5% of Cmax for bupropion.

Demographic profile of subjects in Study #R01-365

ANDA #75-913

CRO : [redacted]

Age

Mean:	23.6 years
SD:	4.1
Range:	18-40 years

Groups	
< 18	0%
18 - 40	100.0%
41 - 64	0%
65 - 75	0%
> 75	0%
Gender	
Male	100%
Female	00%

Race	
Asian	0%
African American	2.9%

Hispanic	0%
Caucasian	97.1%
Other	0%

Dose and Treatments: After a supervised overnight fast (at least 10 hours) subjects received an oral dose of the assigned formulation with 240 mL of water.
Treatment A: 1x100 mg Bupropion HCl ER Tablet (Impax), lot #R01014-100B-2, manufacturing date: 06/19/01, Exp. N/A, batch size [redacted] Tablets, potency 100.8%, content uniformity 98.2% (%CV=1.5).
Treatment B: 1x100 mg Wellbutrin SR^{R} Tablet (Glaxo Wellcome), lot #1ZP0452, Exp. 8/02, potency 100.1%, content uniformity 96.3% (%CV=2.6).

Washout period: Three weeks

Food and fluid intake: Standardized, caffeine-free meals or snacks were served at 4.5, 10 and 14 hours after dosing. Water was not allowed from 1 hour before until 1 hour after dosing, except for the dosing water (240 mL).

Blood samples: Blood samples were collected at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 96, 120, 144 and 168 hours after dosing. Plasma samples were immediately frozen.

Assay Methodology:

Determination of Bupropion, Hydroxybupropion and Threo-bupropion plasma concentrations was performed by [redacted] method.

Sensitivity: [redacted]

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW (OF 11/27/01 SUBMISSION)

hydroxybupropion were stable after three freeze-thaw cycles in human whole plasma.

Statistical Methods

AUC(0-t), AUCinf, Cmax, Tmax, Ke and T1/2 were calculated from the individual concentration versus time data for bupropion, hydroxybupropion and threo-bupropion. Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure.

IV. In Vivo Results

Nineteen adverse events were reported by twelve of thirty-six subjects dosed in the study. A summary of adverse events is presented in page 221, Vol. 4.2.

The plasma concentrations and pharmacokinetic parameters for bupropion are summarized below.

TABLE I
FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #R01-365
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 25 SUBJECTS
BUPROPION

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B	
0	0.13	(497)	0.04	(505)
0.5	4.35	(213)	2.01	(145)
1	23.47	(40.3)	16.81	(42.9)
1.5	37.40	(40.4)	30.20	(34.9)
2	46.43	(35.6)	39.76	(33.4)
3	53.19	(35.4)	51.76	(33.1)
4	49.19	(37.9)	49.55	(33.1)
5	44.86	(37.7)	50.07	(36.4)
6	35.87	(34.4)	38.55	(33.8)
8	23.05	(30.1)	23.10	(33.1)
10	16.19	(31.3)	17.78	(33.5)
12	12.48	(62.8)	14.07	(67.0)
16	8.08	(122)	10.12	(135)
24	4.75	(152)	6.58	(204)
36	3.25	(247)	4.94	(303)
48	2.19	(337)	4.16	(413)
60	1.36	(422)	3.41	(431)
72	0.83	(448)	1.75	(470)
96	0.00	(0.0)	0.04	(490)

120	0.00	(0.0)	0.00	(0.0)
144	0.00	(0.0)	0.00	(0.0)
168	0.00	(0.0)	0.00	(0.0)

Pharmacokinetic Parameters

	Test	Reference	T/R
AUC(0-t) (ng.hr/mL)	558.5(72)	683.5(133)	0.94
AUCinf (ng.hr/mL)	607.1(87)	705.1(129)	0.95
Cmax (ng/mL)	58.5(27)	58.3(28)	1.01
Tmax (hr)	3.56	5.64	
Kel(1/hr)	0.067	0.071	
t1/2 (hr)	12.76	11.20	

	RMSE	90% CI
LnAUC(0-t)	0.182	85.7-102.3%
LnAUCinf	0.164	87.4-102.5%
LnCmax	0.175	92.5-109.7%

1. The mean bupropion plasma levels peaked at 3 hours for both the test and the reference products following their administration under fasting conditions.

2. For Impax's bupropion, the mean AUCT, AUCI and Cmax values were 18.2%, 13.9% and 0.34% lower and higher, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCT, AUCI and Cmax.

3. After including subject Nos. 14, 17, 20, 22, 24, 28, 30, 32, 34 and 36 with pre-dose plasma concentrations greater than 5% of Cmax, the 90% confidence intervals remained within the acceptable range of 80-125% for log-transformed AUCT, AUCI and Cmax.

4. The results of the active metabolite, hydroxybupropion, are shown below for additional information only.

Pharmacokinetic Parameters

	Test	Reference	T/R
AUC(0-t)	6873.5(40)	7421.7(46)	0.95

(ng.hr/mL)			
AUCinf	7143.3(40)	7681.7(45)	0.95
(ng.hr/mL)			
Cmax	190.5(31)	190.8(36)	1.02
(ng/mL)			
Tmax (hr)	6.19	7.44	
Kel(1/hr)	0.036	0.037	
t1/2 (hr)	20.87	20.12	

	RMSE	90% CI
LnAUC(0-t)	0.139	89.2-100.4%
LnAUCinf	0.134	89.5-100.3%
LnCmax	0.134	96.0-107.6%

V. Study #R01-328 for Single-Dose, two-way Crossover Study of Bupropion HCl ER Tablets, 150 mg, Under Fasting Conditions

Clinical site: [redacted]

Analytical site: [redacted]

Study design: Open-label, single-dose, fasted, randomized, two-period crossover.

Dosing date: Period I June 9, 2001
Period II June 30, 2001

Analytical date: Samples were analyzed between July 13 to October 19, 2001.

Subjects: Thirty-six (36) male subjects enrolled and completed the clinical portion of the study. Subject Nos. 10, 14, 18, 20, 22, 24, 32, 34 and 36 were excluded from the statistical analysis due to pre-dose plasma concentrations greater than 5% of Cmax for bupropion.

Demographic profile of subjects in Study #R01-328

ANDA #75-913

CRO : [redacted]

Age

Mean:	27.0 years
SD:	10.3
Range:	18-68 years

Groups	
< 18	0%
18 - 40	88.9%
41 - 64	8.3%
65 - 75	2.8%
> 75	0%
Gender	
Male	100%
Female	00%

Race	
Asian	2.8%
African American	8.3%
Hispanic	0%
Caucasian	88.9%
Other	0%

Dose and Treatments: After a supervised overnight fast (at least 10 hours) subjects received an oral dose of the assigned formulation with 240 mL of water.
Treatment A: 1x150 mg Bupropion HCl ER Tablet (Impax), lot #R01011-100B-2, manufacturing date: 05/21/01, Exp. N/A, batch size [redacted] Tablets, potency 102.1%, content uniformity 100.6% (%CV=1.5).
Treatment B: 1x150 mg Wellbutrin SR^{R} Tablet (Glaxo Wellcome), lot #0J1579, Exp. 5/02, potency 99.7%, content uniformity 98.8% (%CV=0.74).

Washout period: Three weeks

Assay Methodology:

Determination of Bupropion, Hydroxybupropion and Threo-bupropion plasma concentrations was performed by [redacted]

Sensitivity:

Linearity:

Interday precision:

Precision and Accuracy:

Recovery:

VI. In Vivo Results

Nineteen adverse events were reported by twelve of thirty-six subjects dosed in the study. A summary of adverse events is presented in page 221, Vol. 4.2.

The plasma concentrations and pharmacokinetic parameters for bupropion are summarized below.

TABLE II

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #R01-328
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 27 SUBJECTS
BUPROPION

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B	
0	0.07	(219)	0.55	(212)
0.5	9.19	(131)	4.88	(135)
1	44.49	(57.5)	40.56	(91.9)
1.5	66.73	(50.8)	58.94	(49.3)
2	73.32	(45.6)	73.98	(51.7)
3	81.71	(39.0)	87.10	(43.8)
4	73.94	(40.3)	87.06	(42.5)
5	72.89	(40.3)	79.47	(48.8)
6	60.27	(44.8)	65.80	(47.3)
8	45.04	(53.6)	36.52	(46.4)
10	29.35	(54.5)	23.86	(66.5)
12	19.56	(47.5)	15.87	(56.1)
16	10.51	(43.2)	9.76	(66.0)
24	5.80	(48.2)	5.28	(55.2)
36	2.92	(48.8)	2.76	(56.1)
48	1.48	(79.5)	1.35	(100)
60	0.78	(105)	0.63	(136)
72	0.33	(180)	0.30	(198)
96	0.00	(0.0)	0.16	(400)
120	0.00	(0.0)	0.00	(0.0)
144	0.00	(0.0)	0.00	(0.0)
168	0.00	(0.0)	0.00	(0.0)

Pharmacokinetic Parameters

	Test	Reference	T/R
AUC(0-t) (ng.hr/mL)	820.1(40)	794.8(46)	1.04
AUCinf (ng.hr/mL)	853.9(39)	828.4(129)	1.04
Cmax (ng/mL)	90.5(39)	98.2(39)	0.91
Tmax (hr)	3.24	3.28	
Kel(1/hr)	0.056	0.058	
t1/2 (hr)	16.33	16.16	

	RMSE	90% CI
LnAUC(0-t)	0.208	94.5-114.7%
LnAUCinf	0.207	94.2-114.2%
LnCmax	0.249	81.2-102.4%

1. The mean bupropion plasma levels peaked at 3 hours for both the test and the reference products following their administration under fasting conditions.

2. For Impax's bupropion, the mean AUCT, AUCI and Cmax values were 3.2%, 3.1% and 7.8% higher and lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCT, AUCI and Cmax.

3. After including subject Nos. 10, 14, 18, 20, 22, 24, 32, 34 and 36 with pre-dose plasma concentrations greater than 5% of Cmax, the 90% confidence intervals remained within the acceptable range of 80-125% for log-transformed AUCT, AUCI and Cmax.

4. The results of the active metabolite, hydroxybupropion, are shown below for additional information only.

Pharmacokinetic Parameters

	Test	Reference	T/R
AUC(0-t) (ng.hr/mL)	11705.7(50)	11377.1(51)	1.03
AUCinf (ng.hr/mL)	11982.5(49)	11650.4(50)	1.03
Cmax (ng/mL)	310.4(38)	321.2(41)	0.97
Tmax (hr)	8.58	6.71	
Kel(1/hr)	0.033	0.033	
t1/2 (hr)	23.09	22.60	

	RMSE	90% CI
LnAUC(0-t)	0.229	93.6-114.1%
LnAUCinf	0.222	93.6-114.1%
LnCmax	0.193	89.4-105.6%

VII. Formulations:

Impax's formulations for its Bupropion HCl ER Tablets, 100 and 150 mg mg, are shown below:

(NOT FOR RELEASE UNDER FOI)

Ingredient	Strength 100 mg	Strength 150 mg

	100	150
BUPROPION HYDROCHLORIDE		
HYDROXPROPYL CELLULOSE NF		
MICROCRYSTALLINE CELLULOSE NF		
COLLOIDAL SILICON DIOXIDE NF		
MAGNESIUM STEARATE, NF		
Yellow		
Total	295.3 mg	442.9 mg

VIII. In Vitro Dissolution Testing:

The firm proposes the same dissolution method and specifications that were recommended by the Division of Bioequivalence following the original submission.

Medium: 900 mL of water
Aapparatus: 2 at 50 rpm
Specifications: Between — % in 1 hour
Between — % in 2 hours
Between — % in 4 hours
NLT — % in 6 hours

The dissolution results are shown below:

TEST
Lot No.: R01011
Strength: 150MG TABLET
No. of Units: 12

REFERENCE
Lot No.: OJ1579
Strength: 150MG TABLET
No. of Units: 12

Time(hr)	Mean	Range	%CV	Mean	Range	%CV
1	39.72		2.2	42.70		3.3
2	57.23		3.6	63.29		2.6
4	76.26		1.8	87.00		1.9
6	85.84		1.6	97.22		1.2

TEST
Lot No.: R01014
Strength: 100MG TABLET
No. of Units: 12

REFERENCE
Lot No.: 1ZP0452
Strength: 100MG TABLET
No. of Units: 12

Time(hr)	Mean	Range	%CV	Mean	Range	%CV
1	41.55		5.3	34.48		2.1
2	60.04		4.6	52.33		1.7
4	78.55		4.0	75.98		1.6
6	85.84		3.1	90.12		1.4

IX. Comments:

1. The firm's single-dose bioequivalence study #R01-365 under fasting conditions, conducted on its 100 mg Bupropion HCl ER Tablet is acceptable. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% for bupropion.

2. The firm's single-dose bioequivalence study #R01-328 under fasting conditions, conducted on its 150 mg Bupropion HCl ER Tablet is acceptable. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% for bupropion.

3. The dissolution testing conducted by the firm on its Bupropion Hydrochloride ER Tablets, 100 mg and 150 mg, is acceptable.

4. All inactive ingredients were reviewed and found to be present in the formulations at or below the levels cited in the FDA Inactive Ingredient Guide (1996) for approved drug products.

5. A DSI inspection is requested due to the high percentage of study subjects with predose concentrations. In prior studies done by the same firm no predose concentrations were detected.

X. Recommendations:

1. The bioequivalence study under fasting conditions conducted by Impax Pharmaceuticals, Inc., on its bupropion HCl ER tablet, 100 mg, lot # R01014-100B-2, comparing it to Glaxo Wellcome's Wellbutrin SR^{R} Tablet, 100 mg, has been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions Impax's bupropion HCl ER tablet, 100 mg, is bioequivalent to the reference product, Wellbutrin SR^{R} Tablet, 100 mg, manufactured by Glaxo Wellcome.

2. The bioequivalence study under fasting conditions conducted by Impax Pharmaceuticals, Inc., on its bupropion HCl ER tablet, 150 mg, lot # R01011-100B-2, comparing it to Glaxo Wellcome's Wellbutrin SR^{R} Tablet, 150 mg, has been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions Impax's bupropion HCl ER tablet, 150 mg, is bioequivalent to the

reference product, Wellbutrin SR[R] Tablet, 150 mg, manufactured by Glaxo Wellcome.

3. The dissolution testing conducted by the firm on its bupropion HCl ER tablets, 100 mg and 150 mg, lot #R01014 and lot #R01011, respectively, is acceptable. The formulation of the 100 mg strength is proportionally similar to the 150 mg strength of the test product which underwent complete acceptable bioequivalence testing. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 24 apparatus II (paddle) at 50 rpm. Based on the submitted data, the test product should meet the following specifications:

Between ——% in 1 hour.
Between ——% in 2 hours.
Between ——% in 4 hours.
NLT —% in 6 hours

The firm should be informed of the above recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D. Date: 12/7/01
Review Branch III
Division of Bioequivalence

BMD 12/7/01

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT Barbara N Davit Date: 12/10/01

Concur: Dale Conner Date: 12/31/2001
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/12-6-01, 12-7-01, 75913SD.N01
cc: ANDA #75-913, original, HFD-658 (Makary), Drug File, Division File.

CC: ANDA #75-913
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit

V:\FIRMSAM\IMPAX\LTRS&REV\75913SD.N01
Printed in final on 12/7/01

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MMM 12/6/01
HFD-658/ Bio team Leader B. Davit
HFD-650/ D. Conner for 12/31/2001

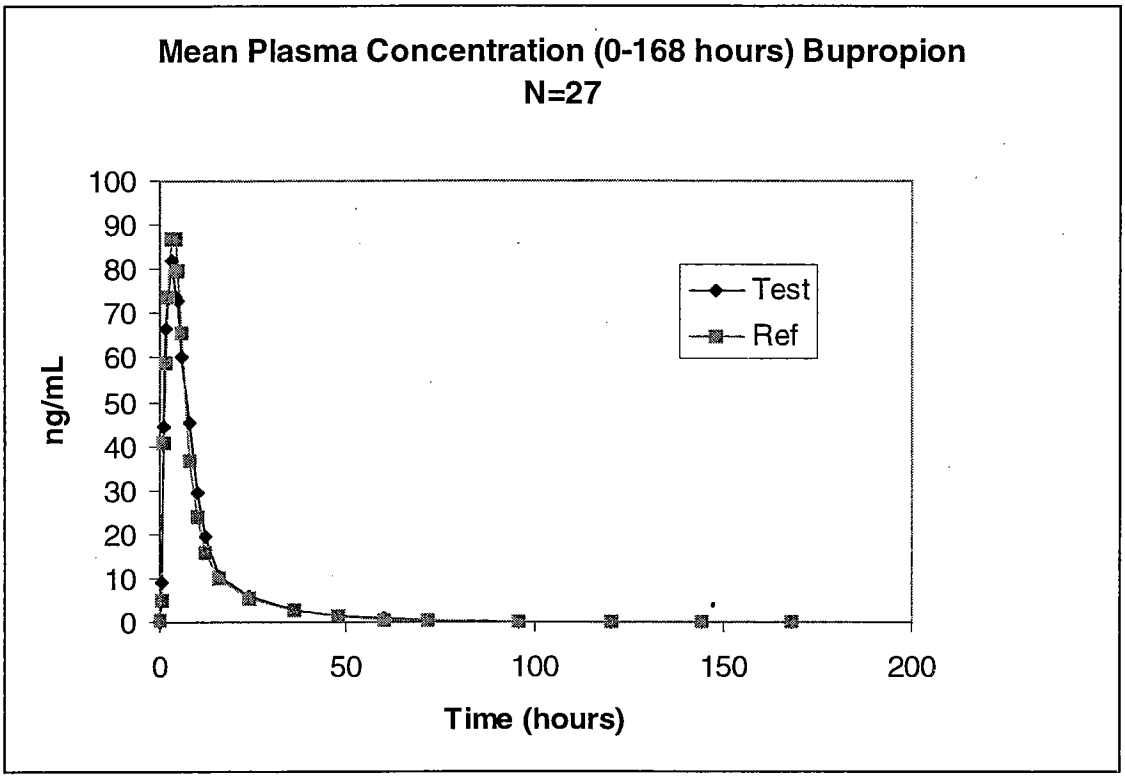
BIOEQUIVALENCY - ACCEPTABLE submission date: November 27, 2001

1. **FASTING STUDY** (STF) Strengths: 100 mg
Clinical: [redacted] **Outcome: AC**
Analytical: [redacted]

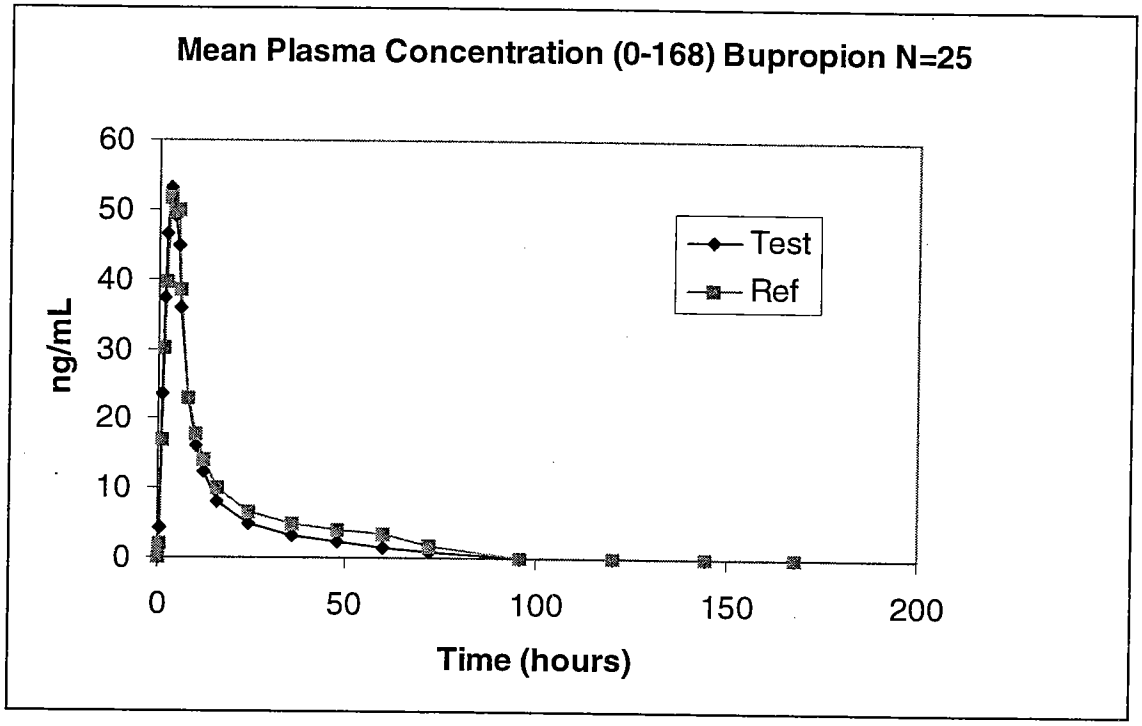
2. **FASTING STUDY** (STF) Strengths: 150 mg
Clinical: [redacted] **Outcome: AC**
Analytical: [redacted]

Outcome Decisions: **AC** - Acceptable

Study #R01-328 for Single-Dose, two-way Crossover Study of Bupropion HCl ER Tablets, 150 mg, Under Fasting Conditions



Study #R01-365 for Single-Dose, two-way Crossover Study of Bupropion HCl ER Tablets, 100 mg, Under Fasting Conditions



DEC 11 2002

Bupropion HCl ER Tablets
150 mg and 100 mg
ANDA #75-913
Reviewer: Moheb H. Makary
W 75913OTH1102.doc

Impax Pharmaceuticals, Inc.
Hayward, CA
Submission Date:
November 5, 2002

Review of an Establishment Inspection Report

At the request of the Division of Bioequivalence, the Division of Scientific Investigations conducted audits of the following bioequivalence studies:

Study #R01-328: "A Relative Bioavilability Study of 150 mg Bupropion Hydrochloride Sustained Release Tablets Under Fasting conditions"

Study #R01-365: "A Relative Bioavilability Study of 100 mg Bupropion Hydrochloride Sustained Release Tablets Under Fasting conditions"

The clinical and analytical portions of studies R-01-328 and R01-365 were conducted at [redacted] and [redacted] respectively.

Form 483 was issued following the inspection at [redacted]. No Form 483 was issued at [redacted].

Background:

On June 22, 2000, Impax Pharmaceuticals, Inc., submitted three acceptable *in vivo* bioequivalence studies (single-dose fasting, nonfasting, and multiple-dose fasting studies) on its bupropion HCl extended-release (ER) tablet, 150 mg, and an acceptable single-dose fasting study on its bupropion HCl extended-release (ER) tablet, 100 mg, comparing them with RLD Wellbutrin SR^{R} Tablets (Glaxo Wellcome), 150 mg and 100 mg, respectively.

On November 27, 2001, the firm submitted an amendment to its ANDA #75-913 for bupropion HCl ER tablets, 150 mg and 100 mg. This amendment provided for the addition of film-coating to both product strengths (to mask the bitter taste of the active drug substance), and a [redacted] manufacturing

process, whereby the [redacted]. This revised process was applied only to the 150 mg strength to better control the finished tablet drug release profile.

To support the revised manufacturing process, the firm submitted a single-dose fasting study on its Bupropion HCl Extended Release (ER) Tablet, 150 mg (**Study #R01-328**), and a single-dose fasting on its Bupropion HCl Extended Release (ER) Tablet, 100 mg (**Study #R01-365**), comparing them with RLD Wellbutrin SR^{R} Tablets (Glaxo Wellcome), 150 mg and 100 mg, respectively.

The Division of Bioequivalence (review dated December 31, 2001) found the studies acceptable.

A DSI inspection was requested for **Study #R01-328 and Study #R01-365** (submission dated November 27, 2001) due to the high percentage of study subjects with pre-dose concentrations. In prior studies (submission dated June 22, 2000) done by the same firm no pre-dose concentrations were detected.

Bupropion HCl ER Tablets, 150 mg and 100 mg, ANDA #75-913 is a pending application.

Inspectors' Findings:

Analytical Site: [redacted]

[redacted] analyzed bupropion (BP) and its metabolites, hydroxybupropion (HBP) and threobupropion (TBP) in plasma by [redacted]

1. Reprocessing of data from Run U2-072901a100 was not justified in Study R01-328.

The original processed data for the analytical Run was not acceptable, as the quality controls (QC) failed to meet the run acceptance criteria (the original processed data indicated that 3 out of 6 QCs did not meet the acceptance criteria). The firm reprocessed the data without justification and accepted the run, without documentation regarding acceptable of the run. Therefore, BP and its

metabolites data for Subject #7 in Run U2-072901a100 are unreliable.

The inspector recommends that the data from subject #7 to be excluded from the study.

Reviewer's Comment:

Since the data for subject #7 are unreliable, the reviewer agrees that the subject should be excluded from the statistical analysis of the study. After excluding subject #7 from the statistical analysis of the study the resulting 90% confidence intervals for bupropion are as follows:

	90% CI
LnAUC(0-t)	93.0-112.3%
LnAUCinf	92.7-111.9%
LnCmax	79.5-97.4%

The 90% confidence interval is not within the acceptable 80-125% range for Cmax, and therefore, the previous conclusion to accept the study should be reversed.

2. BP, HBP and TBP in subject predose samples is due to analytical error in studies R01-328 and R01-365.

The calibration standards were interspersed in analytical runs and the subject pre-dose samples were analyzed immediately after calibration standards. Analyte or analyte interference was found in the pre-dose sample when the preceding calibration standard was 50 ng/mL or above. Therefore, the pre-dose plasma concentrations were due to autosampler carryover from the preceding calibration standards during analysis. The inspector indicated that the extent of carryover should not significantly affect the accuracy of subject samples, as the subject samples from each period were analyzed as a set without interruption by standards or QCs.

Reviewer's Comment:

The reviewer agrees with the inspector that the extent of carryover should not significantly affect the accuracy of subject samples. Furthermore, the reviewer has excluded all subjects with pre-dose plasma concentrations greater than 5% of Cmax for bupropion from the statistical analysis of the studies in original study reviews.

3. The analytical precision for BP and TBP was overestimated in study R0-328.

[redacted] excluded values for QCs labeled "Technical Error" (TE) from the precision and accuracy estimation in studies R01-328 and R01-365. Raw data showed no evidence of TE (no processing errors, instrument failures or poor chromatography). Inclusion of all QC values in studies R01-328 and R01-365 indicated that the assays were not precise (%CV > 20%). The inspector stated that this finding does not affect the study results, as the QCs in the analytical runs for studies R01-328 and R01-365 met the run acceptance criteria.

Reviewer's Comment:

The reviewer agrees with the inspector that the inclusion of all QC values in the studies which resulted in precision of > 20% (%CV) does not affect the study results since the QCs in the analytical runs for studies R01-328 and R01-365 met the run acceptance criteria.

4. Inconsistency in integration of HBP peaks.

[redacted] integrated "shoulders" and merging peaks with the HBP peaks. The inspector states that this finding does not significantly affect the estimation of HBP concentrations.

Reviewer's Comment:

For evaluation of bioequivalence studies for bupropion HCl ER tablets, DBE requests that only bupropion data should be analyzed using the confidence interval approach to determine the bioequivalency of the product. The DBE considers hydroxybupropion (HBP) data as supportive information for the study. Therefore, the above mentioned finding does not significantly affect the conclusion of the study.

Recommendations:

1. The Division of Bioequivalence agrees with the audit's report that subject #7 in the bioequivalence study #R01-328, conducted by Impax Pharmaceuticals, Inc., on its bupropion HCl ER tablet, 150 mg, under fasting conditions, should be excluded from the study and bioequivalence should be reestimated. After excluding subject #7 from the statistical analysis of the study, the 90% confidence

interval for Cmax for bupropion was 79.5-97.4%, which is below the acceptable lower limit of 80.0. The test product does not meet the bioequivalence criteria under fasting conditions. Therefore, the recommendation found as acceptable for this study by the Division of Bioequivalence dated December 31, 2001, for Impax Pharmaceuticals' bupropion HCl ER tablet, 150 mg, should be reversed following this audit.

2. The audit of the bioequivalence study #R01-365 conducted by Impax Pharmaceuticals, Inc., on its bupropion HCl ER tablet, 100 mg, under fasting conditions, did not reveal findings which would invalidate the study and therefore, the recommendation by the Division of Bioequivalence dated December 31, 2001, for this study remains unchanged. The study has been reviewed and found acceptable by the Division of Bioequivalence.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED
FT INITIALLED GJP SINGH Date 12-10-02

Concur: Dale P. Conner Date: 12/11/02
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/ 11-26-02, 12-10-02, 75913OTH1102.doc
cc: ANDA #75-913, original, HFD-658 (Makary), Drug File, Division File.

CC: ANDA #75-913
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MHM
HFD-658/ Bio team Leader G. Singh GOPS 12-10-02
HFD-650/ D. Conner AB 12/11/02

V:\FIRMSAM\IMPAX\LTRS&REV\75913OTH1102.doc
Printed in final on 12/10/02

BIOEQUIVALENCY - DEFICIENCIES Submission Date:11-5-02
U.S. Document
1. OTHER (DSI) Strengths: 100 mg and 150 mg
Outcome: UN

Outcome Decisions: UN -Unacceptable

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY DEFICIENCY

ANDA: 75-913 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion Hydrochloride ER Tablets, 100 mg and 150 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

The Division of Scientific Investigations conducted an inspection of the [redacted], for your in vivo study (fasting study #R01-328, bupropion hydrochloride extended-release tablets, 150 mg). Based on that inspection, the acceptance of analytical Run U2-072901a100 was not justified.

The original processed data for the analytical run was not acceptable, as the quality controls (QC) failed to meet the run acceptance criteria. You reprocessed the data without justification and accepted the run. Therefore, bupropion and its metabolites data for subject #7 in Run U2-072901a100 are unreliable.

After excluding subject #7 from the statistical analysis of the study the resulting 90% confidence intervals for bupropion are as follows:

	90% CI
LnAUC(0-t)	93.0-112.3%
LnAUCinf	92.7-111.9%
LnCmax	79.5-97.4%

The 90% confidence interval is not within the acceptable 80-125% range for Cmax. Therefore, the study is unacceptable.

You are advised to conduct another single-dose fasting bioequivalence study on your bupropion hydrochloride extended-release tablets, 150 mg.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm.

Based on the submitted data, the test product should meet the following specifications:

Between —— % in 1 hour.
Between —— % in 2 hours.
Between —————— % in 4 hours.
NLT — % in 6 hours

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA #75-913
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh
HFD-650/ D. Conner

V:\FIRMSAM\IMPAX\LTRS&REV\75913OTH1102.doc
Printed in final on 12/10/02

BIOEQUIVALENCY - DEFICIENCIES Submission Date:11-5-02

1. OTHER (DSI) Strengths: 100 mg and 150 mg
Outcome: UN

Outcome Decisions: UN -Unacceptable

APPEARS THIS WAY
ON ORIGINAL

MAR 14 2003

Bupropion HCl ER Tablets	Impax Laboratories, Inc.
150 mg and 100 mg	Hayward, CA
ANDA #75-913	Submission Date:
Reviewer: Moheb H. Makary	January 17, 2003
W 75913STA0103.doc	

Review of an Amendment

The firm has submitted its response to the following deficiency stated in the Agency letter dated December 16, 2002, which requested a bioequivalence study under fasting conditions to be conducted on the 150 mg bupropion HCl ER tablets.

Deficiency Comment:

Based on the DSI's inspection at [redacted], the acceptance of analytical Run U2-072901a100 was not justified. Therefore, bupropion and its metabolites data for subject #7 in Run U2-072901a100 are unreliable.

After excluding subject #7 from the statistical analysis of the study the resulting 90% confidence intervals for bupropion are as follows:

	90% CI
LnAUC(0-t)	*93.0-112.3%*
LnAUCinf	*92.7-111.9%*
LnCmax	*79.5-97.4%*

The 90% confidence interval is not within the acceptable 80-125% range for Cmax. Therefore, the study is unacceptable.

The firm was advised to conduct another single-dose fasting bioequivalence study on your bupropion hydrochloride extended-release tablets, 150 mg.

Firm's Response

Impax acknowledges that the assay results for subjects #7 in Study R01-328 were not properly documented at the time the data were generated. The firm has considered the Division's recommendation and wishes to present its justification for reassaying plasma samples from subject #7 and including the results in a re-estimation of bioequivalence.

1. Assessment of the long-term stability of bupropion, hydroxybupropion, and threobupropion in human plasma using the Study R01-328 QC plasma samples stored under the same conditions (-80°C) as those of bupropion plasma samples of Study R01-328.

Table 1 summarized the assay results of bupropion QC samples following long-term frozen storage for 18 months at -80°C. This analysis was conducted on the original QC samples and shows that remaining concentration for bupropion relative to its respective nominal values, averaged (N=6) 77.2% for the high QC samples, and 84.5% for the low QC samples.

Table 1

Date Processed	Analyzed		Bupropion HQC (ng/mL)** 180 (Nominal)	Bupropion LQC(ng/mL)** 2 (Nominal)
Day:0	7/12/2001	7/12/2001 1	200	2.39
		2	199	2.33
		3	205	2.32
		Mean	201	2.35
		%CV	1.60	1.61
		%Recovery*	112	118
Day:543	1/6/2003	1/6/2003 1	144	1.64
		2	128	1.85
		3	138	2.01
		Mean	137	1.83
		%CV	5.90	10.3
		%Recovery*	76.1	92.0
Day:548	1/11/2003	1/11/2003 1	135	1.67
		2	143	1.39
		3	144	1.59
		Mean	141	1.55
		%CV	3.50	9.3
		%Recovery*	78.3	77.5
Combination of 1/6/2003 & 1/11/2003		N	6	6
		Mean	139	1.69
		%CV	4.59	12.9
		%Recovery	77.2	84.5

* % Recovery = (mean concentration found)/Nominal X 100.
** All QC samples were prepared on 7/12/01 and stored at -80°C.

The Day 0 data in Table 1 suggest that the QC samples may have high initial concentrations relative to nominal values. Impax stated that it is important to obtain precise estimates of the initial concentrations of the QC samples to better quantify the long-term stability of the study samples. In this regard, the firm examined the assay results of the QC samples determined during the assay runs of Study R01-328 plasma samples. These assays were conducted within the first four months of sample preparation, with the majority of the assays conducted within 2 weeks of QC sample preparation.

The firm indicated that after excluding the questionable QC results associated with the original assay run of subject #7 samples (July 29/2001, sequence file U2-072901a000), the concentrations of bupropion in the remaining QC samples relative to nominal values averaged 98.5% for the high QC and 92.2% for the low QC samples.

The firm combined the Day 0 QC samples and the QC samples of the original study after excluding the QC samples of subject #7 to provide more precise estimates of the initial concentrations of QC samples. Based on the combined data, the initial concentrations (relative to nominal values) for bupropion were determined to be 94.0% for the low QC samples and 99.0% for the high QC samples.

Impax stated that since the initial concentrations of all QC samples were very similar to their respective nominal values, it was appropriate to assess the long-term stability data of the QC samples of bupropion relative to its respective nominal concentrations as presented in Table 1. Averaging the results obtained for high and low concentrations in Table 1, the firm indicated that it can be estimated that the overall concentrations of bupropion in subject #7's plasma samples probably decreased by 19.2%, during the period of storage from the original analysis (7/29/01) to the date of re-analysis (1/13/03).

2. Re-assay of plasma samples for subject #7 from study R01-328.

The firm re-assayed the plasma samples for subject #7 for bupropion, hydroxybupropion, and threobupropion.

3. Bioequivalence Reassessment

The firm indicated that although the concentration of bupropion of the stored study samples probably decreased by 19.2%, this reduction in concentration is expected to occur to the same extent in both test and reference product.

After including the re-assay data from subject #7 in the original report for all subjects of the study, the resulting 90% confidence intervals for bupropion are as follows:

	90% CI
LnAUC(0-t)	94.0-112.9%
LnAUCinf	93.7-112.5%
LnCmax	81.1-101.2%

The 90% confidence intervals are within the acceptable 80-125% range for LnAUC, LnAUCi and LnCmax.

Reviewer's Response

Assessment of the long-term stability data on the original QC samples (Day zero), shows that measured concentrations for bupropion relative to its respective nominal values averaged 77.2% for the high QC samples, and 84.5% for the low QC samples.

The Day 0 data in Table 1 show that the QC samples have high initial concentrations relative to nominal values (112% and 118% for the high and low QC samples, respectively). The firm's practice to combine Day zero QC samples and the QC samples of the original study (after excluding the QC samples of subject #7) to provide more precise estimates of the initial concentrations of QC samples for the long-term stability assessment is not acceptable, for the reason summarized below.

In the original study amendment dated November 27, 2001, the firm assessed the long-term stability based on mean concentrations found at 0 hour and not on the nominal concentrations at 0 hour for the QC samples.

The long-term frozen stability was studied for 18 months. Concentrations for bupropion remaining after that period relative to its respective mean concentrations on Day zero averaged 69.2% for the high QC samples, and 71.9% for the

low QC samples. These values showed that bupropion was not stable for a period of 18 months in human plasma at -80°C. Therefore, re-assay of the plasma samples for subject #7 from study R01-328 is not valid.

Recommendation:

Based on the long-term frozen stability results for 18 months, the remaining concentrations for bupropion relative to its respective mean concentrations on Day zero averaged 69.2% for the high QC samples, and 71.9% for the low QC samples. These values showed that bupropion was not stable for a period of 18 months in human plasma at -80°C. Therefore, re-assay of the plasma samples for subject #7 from study R01-328 is not valid.

The firm should conduct another single-dose fasting bioequivalence study on its bupropion hydrochloride extended-release tablets, 150 mg.

Moheb H. Makary
Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED
FT INITIALLED GJP SINGH Date 3-14-03

Concur: Barbara Mylus Davit Date: 3/14/03
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/ 2-25-03, 3-4-03, 3-12-03, 75913STA1003.doc
cc: ANDA #75-913, original, HFD-658 (Makary), Drug File, Division File.

BIOEQUIVALENCY DEFICIENCY

ANDA: 75-913 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion Hydrochloride ER Tablets, 100 mg and 150 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

Based on the long-term frozen stability results for 18 months, the remaining concentrations for bupropion relative to its respective mean concentrations on Day zero averaged 69.2% for the high QC samples, and 71.9% for the low QC samples. These values showed that bupropion was not stable for a period of 18 months in human plasma at -80°C. Therefore, re-assay of the plasma samples for subject #7 from study R01-328 is not valid.

You are requested to conduct another single-dose fasting bioequivalence study on your bupropion hydrochloride extended-release tablets, 150 mg.

Sincerely yours,

for Barbara Smyth Davis

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #75-913
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh GJPS 3-14-03
HFD-650/ D. Conner 3/14/03

V:\FIRMSAM\IMPAX\LTRS&REV\75913STA0103.doc
Printed in final on 3/12/03

BIOEQUIVALENCY - DEFICIENCIES Submission Date:1-17-03

1. Study Amendment(STA) Strengths: 100 mg and 150 mg
Outcome: UN

Outcome Decisions: UN -Unacceptable

APPEARS THIS WAY
ON ORIGINAL

MAY 22 2003

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	75-913
Drug Product Name	Bupropion HCl ER Tablets
Strength	150 mg and 100 mg
Applicant Name	Impax Pharmaceuticals, Inc.
Address	Hayward, CA
Submission Date(s)	April 3, 2003
Reviewer	Moheb H. Makary
File Location	V:\FIRMSAM\IMPAX\LTRS&REV\75913STA0403.doc

Executive Summary

As recommended by DBE in response to a DSI inspection, this amendment consisted of one fasting BE study conducted on the 150 mg strength. The BE study is a two-way, crossover study in normal males and females (n=47). Statistical analyses of the plasma concentration data for bupropion demonstrate bioequivalence. Bupropion results are (point estimate, 90% CI): $LAUC_t$ of 108, 102.9-113.4%; $LAUC_i$ of 107, 102.9-113.1% and LCmax of 111, 104.3-118.6%. DBE does recommend measurement of the parent drug, bupropion only. The product meets the FDA dissolution specifications. The amendment is acceptable with no deficiencies.

APPEARS THIS WAY
ON ORIGINAL

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product:
Bupropion HCl ER Tablets, 150 mg, are ———, round convex tablets, debossed with "G" on one side and "2444" on the other side.

Reference Product:
Wellbutrin SR[R] tablet, 150 mg, of GlaxoSmithKline was approved under NDA #20358 on 10/4/1996. Lot #2ZP2073 of the Wellbutrin SR[R] tablets was used in the BE study.

Relevant DBE History:
The Division of Scientific Investigations conducted an inspection of the ———, for Impax's in vivo studies (fasting study #R01-328, bupropion hydrochloride ER tablets, 150 mg and a study #R01-365, bupropion hydrochloride ER tablets, 100 mg) submitted on November 27, 2001. For study #R01-328, based on that inspection, the analytical run for subject #7 was not justified. After excluding subject #7 from statistical analysis of the study, the 90% confidence interval was not within the acceptable 80-125% range for Cmax. Therefore, the Division of Bioequivalence found the study unacceptable. The firm was advised to conduct another single–dose fasting bioequivalence study on its bupropion hydrochloride extended-release tablets, 150 mg.

The audit of the bioequivalence study #R01-365 conducted by Impax Pharmaceuticals, Inc., on its bupropion HCl ER tablet, 100 mg, under fasting conditions, did not reveal findings which would invalidate the study and therefore,

the recommendation by the Division of Bioequivalence dated December 31, 2001, for this study remains unchanged. The study has been reviewed and found acceptable by the Division of Bioequivalence.

In this amendment, the firm submitted a new bioequivalence study under fasting conditions on its bupropion hydrochloride ER tablets, 150 mg.

B. Contents of Submission

		How many?
Single-dose fasting study	Yes	1
Single-dose fed study	No	0
Steady-state study	No	0
In vitro dissolution testing	No	0
Waiver requests	No	0
BCS data	No	
Vasocontrictor studies	No	
Clinical endpoints	No	
Failed studies	No	
Amendments	Yes	

C. Bioanalytical Method Validation (Pre-Study, Vol.8.1, Pages 045)

Number of analytes 1

Analyte name Bupropion

[redacted]

Comments on the Analytical Method: The analytical method and data are acceptable.

D. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study No.	# [redacted]-R03-022
Study Design:	A single-dose, two-period, two-treatment, two-sequence crossover
No. of subjects enrolled	48
No. of subjects completing	47
No. of subjects analyzed	47
Sex(es) included (how many?)	Male (26) Female (22)
Test product,	Bupropion HCl ER tablets, 150 mg manufactured by Impax Laboratories, Inc.
Reference product	Wellbutrin SR^{R} (Sustained-Release) tablets, of GlaxoSmithKline.
Strength tested	150 mg
Dose	1 x 150 mg tablet

Summary of Statistical Analysis

Parameter	Point Estimate	90% Confidence Interval
LnAUCt	1.08	102.86 – 113.43
LnAUCi	1.08	102.89 – 113.07
Lncmax	1.11	104.35 – 118.6

The study is acceptable. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCt, AUCi and Cmax for bupropion. The reviewer's calculations are similar to those submitted by the firm.

E. Formulation

The test product formulation was submitted and found acceptable in the amendment dated November 27, 2001.

F. In Vitro Dissolution

The comparative dissolution testing results for the test and reference products were submitted and found acceptable in the amendment dated November 27, 2001. The firm accepted the dissolution specifications that had been recommended by DBE.

G. Waiver Requests

None

H. Deficiency Comment

None

I. Recommendations

1. The bioequivalence study under fasting conditions conducted by Impax Pharmaceuticals, Inc., on its bupropion HCl ER tablet, 150 mg, lot # R01011-100A-2, comparing it to GlaxoSmithKline's Wellbutrin SR^{R} Tablet, 150 mg, has been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions Impax's bupropion HCl ER tablet, 150 mg, is bioequivalent to the reference product, Wellbutrin SR^{R} Tablet, 150 mg, manufactured by GlaxoSmithKline.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37^{O}C using USP apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Between ——% in 1 hour.
   Between —— % in 2 hours.
   Between ———— % in 4 hours.
   NLT— % in 6 hours

From the bioequivalence point of view, the firm has met the requirements of the *in vivo* bioequivalence and the *in vitro* dissolution testing and the amendment is approvable.

The firm should be informed of the above recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED
FT INITIALLED GJP SINGH Date 5-22-03

Concur: Dale P. Conner Date: 5/22/03
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/ 5-6-03, 5-19-03, 75913STA0403.doc
cc: ANDA #75-913, original, HFD-658 (Makary), Drug File, Division File.

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information

Study Number: # [redacted] R03-022
Clinical Site: [redacted]

Dosing Dates: period I: 1/19/2003
period II: 2/9/2003
Analytical Site: [redacted]

Analysis Dates: 2/21/2003-3/12/2003
Storage Period: 71 days

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Bupropion HCl ER Tablets	Wellbutrin SR^{R} Tablet
Manufacturer:	Impax Pharmaceuticals, Inc.	GlaxoSmithKline
Manufacture Date:	5/01	N/A
Expiration Date:	N/A	10/2004
Strength	150 mg	150 mg
Dosage Form	Tablets	Tablets
Bio Batch Size:	[redacted] Tablets	N/A
Batch/Lot Number:	R01011-100A-2 (same lot used in study #R01-365)	2ZP2073
Potency	102.1%	100.6
Content Uniformity	100.6%	99.3
Formulation	Review in study #R01-365	N/A
Dose Administered:	1 x 150 mg tablet	1 x 150 mg tablet
Route of Administration	Oral	Oral
Study Condition:	Fasting	Fasting

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
Washout Period	21 days
Randomization Scheme	AB for subjects #6, 8, 9, 10, 12, 13, 14, 17, 18, 20, 21, 22, 23, 24, 26, 31, 36, 37, 38, 40, 43, 44, 47, 48 and BA for the rest of subjects.
Blood Sampling Times	0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 96, 120 , 144 and 168 hours
Blood Volume Collected/Sample	10 mL

Blood Sample Processing/Storage	Under conditions with minimal UV exposure
IRB Approval	Yes, on 1/15/2003
Informed Consent	Yes, 1/13/2003
Subjects Demographics	See Table #2
Length of Fasting:	10 hours pre-dose and 4.25 hours post-dose.
Length of Confinement	From at least 11 hours pre-dose to 24 hours post-dose.
Safety Monitoring	Vital signs measurements were obtained prior to dosing each period.

Study Results

Clinical: The firm's clinical summary is provided on Page 104, Vol. 8.1.

Dropout Information	
Subject Nos.	19
Reason	Subject #19 elected to withdraw prior to period II dosing.
Period	Prior to period II drug administration
Replacement	No
Adverse Events	A total of 22 adverse events were reported. No serious adverse events occurred during the study. 7 following administration of Treatment A 15 following administration of Treatment B For additional information see Vol. 8.1, page #118
Protocol Deviations	No significant deviations from the protocol were documented.

Comments:
The adverse events occurred more frequently following administration of the reference product than the test product.

DURING STUDY ASSAY VALIDATION (Vol.8.5, page 1472)

Parameter	
QC Conc. (ng/mL)	
Standard Curve Conc. (ng/mL)	
Between-Batch Precision for Standards (%CV)	
Between-Batch Accuracy for Standards (% Actual)	
Between-Batch Precision for QC (%CV)	
Between-Batch Accuracy for QC (% Actual)	

Repeat Assays
A total of two samples were repeated for the study. There were no pharmacokinetic repeats.

Chromatograms: Acceptable

Comments: The analytical method and data for bupropion are acceptable.

Pharmacokinetic/Statistical Analysis for Bupropion

Mean Plasma Concentrations	Table #2, Figure #1

Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

a. Arithmetic Mean Pharmacokinetic Parameters

PK Parameter	Test Treatment A	Reference Treatment B	T/R
AUCt [ng-hr/mL]	887.6 (32%)	826.4 (33%)	1.07
AUCi [ng-hr/mL]	925.9 (31%)	862.9 (33%)	1.11
Cmax [ng/mL]	105.3 (33%)	95.1 (33%)	1.11
Tmax [hr]	3.39	2.92	
K_{el} [1/hr]	0.040	0.041	
$T_{½}$ [hr]	20.92	19.82	

b. 90% Confidence Intervals

Parameter	RMSE	Point Estimate	90% Confidence Interval
LnAUCt	0.141	1.08	102.86 – 113.43
LnAUCi	0.136	1.08	102.89 – 113.07
Lncmax	0.185	1.11	104.35 – 118.6

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for all subjects
- Measurable drug concentrations at 0 hr: None
- First scheduled post-dose sampling time as Tmax: None
- First measurable drug concentration as Cmax: None
- Pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
- The 90% confidence intervals for AUCt, AUCi, Cmax are within the acceptable limits of 80-125%.

Conclusion:

The single-dose fasting bioequivalence study is acceptable.

B. Attachments

Fig I

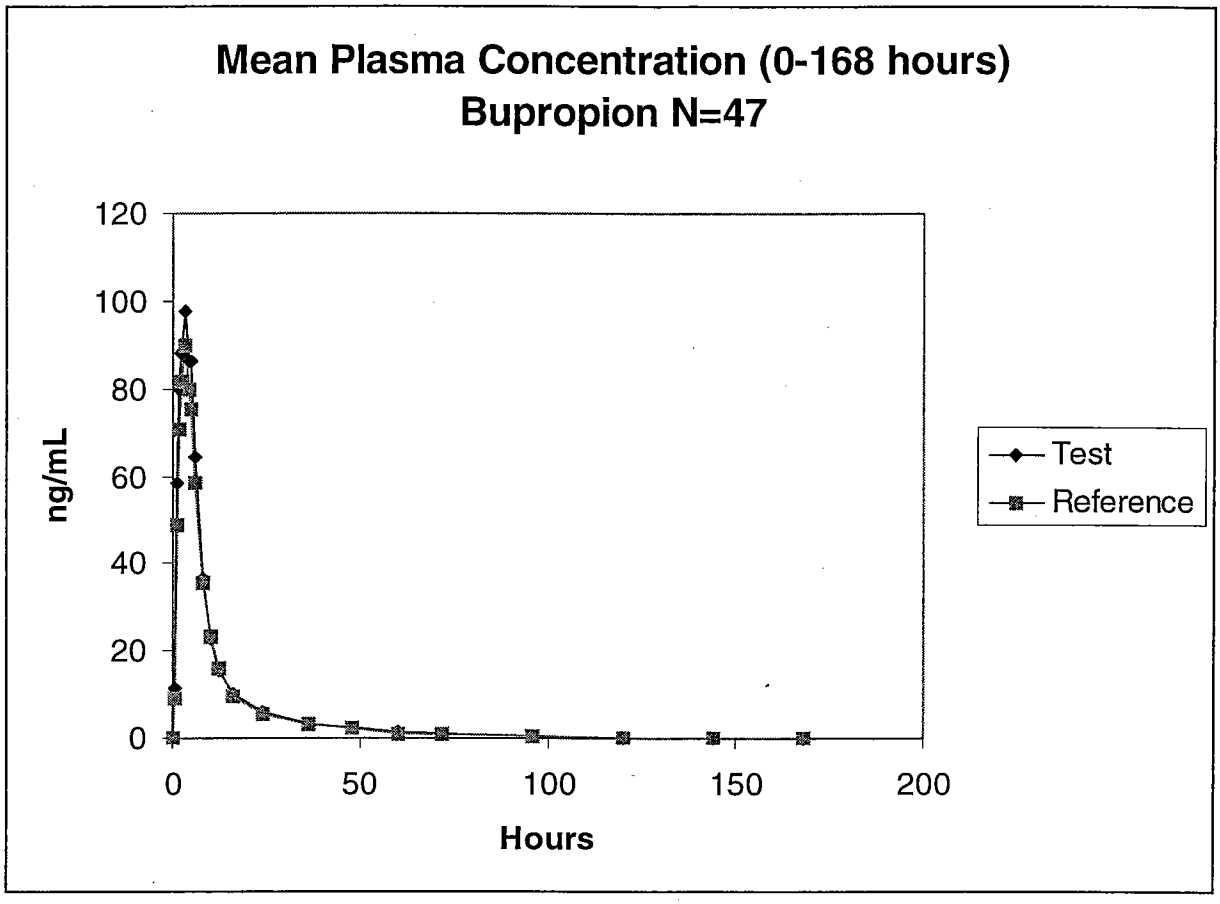


Table 1 : Subject Demographics for Fasting Study									
Age		Age Groups		Gender		Race		Weight (KG)	
		Range	%	Sex	%	Category	%		
		<18	0			Caucasian	98.0		
Mean	25.4	19-40	91.7	Male	54.2	Black.	0	Mean	74.5
SD	10.3	41-64	8.3	Female	45.8	Asian	2.0	SD	10.7
Range	18-62	65-75	0					Range	54-96
		>75	0						

Table 2: Mean Plasma Concentration (ng/mL) of Bupropion – Fasting Study

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B		A/B
0	0.00	(.)	0.00	(.)	.
0.5	11.33	(106)	9.34	(119)	1.21
1	58.52	(58.7)	48.60	(58.6)	1.20
1.5	79.85	(42.5)	70.62	(47.1)	1.13
2	88.03	(38.4)	81.59	(40.1)	1.08
3	97.43	(35.9)	89.66	(32.8)	1.09
4	86.35	(27.5)	79.89	(29.6)	1.08
5	86.42	(25.0)	75.22	(34.6)	1.15
6	64.52	(28.3)	58.23	(30.5)	1.11
8	36.36	(27.3)	35.53	(26.2)	1.02
10	22.63	(28.1)	23.09	(24.9)	0.98
12	15.61	(29.6)	16.01	(25.6)	0.98
16	9.99	(34.3)	9.71	(30.1)	1.03
24	5.96	(34.8)	5.65	(34.2)	1.05
36	3.37	(44.4)	3.14	(44.2)	1.07
48	2.37	(52.4)	2.25	(55.9)	1.05
60	1.32	(72.7)	1.09	(90.9)	1.21
72	0.80	(118)	0.80	(126)	1.00
96	0.30	(190)	0.29	(197)	1.03
120	0.03	(686)	0.05	(475)	0.60
144	0.00	(0.0)	0.00	(0.0)	.
168	0.00	(0.0)	0.00	(0.0)	.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-913 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion Hydrochloride ER Tablets, 100 mg and 150 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm. Based on the submitted data, the test product should meet the following specifications:

Between ——% in 1 hour.
Between ——% in 2 hours.
Between ——— % in 4 hours.
NLT — % in 6 hours

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #75-913
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh

V:\FIRMSAM\IMPAX\LTRS&REV\75913STA0403.doc
Printed in final on 5/19/03

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MMm
HFD-658/ Bio team Leader G. Singh GSPS 5-22-03
HFD-650/ D. Conner DMC 5/22/03

BIOEQUIVALENCY - ACCEPTABLE submission date: April 3, 2003

1. **FASTING STUDY** (STF)
Clinical: [redacted]
Analytical: [redacted]

Strengths: 150 mg
Outcome: AC

Outcome Decisions: **AC** – Acceptable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-913

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

Mark Shaw called with questions about the deficiency letters issued on December 20, 2000 for these applications.

We discussed the deficiencies noted below.

1. Please submit cGMP certification for all outside Firms.

Mr. Shaw stated that certifications were in the original submissions; pages 6308,6310, 6312, 6214, and 6316 for ANDA 75-913; and pages 4867, 4871, 4873, 4875 and 4877 for ANDA 75-914. I told Mr. Shaw that we had located this information and that the only certification needed now was for the [redacted] firm.

2. Please submit USP <671> Container Permeation testing results for each of the proposed container/closure systems to support the labeling requirement of "tight containers".

Mr. Shaw stated that he understood this to be a requirement for glass not plastic bottles. After conferring with the team leader, I told him that he was correct and was not required to answer this deficiency as the bottles submitted in the application were plastic.

For ANDA 75-914 only:

6. The test batch, lot # R99026 (150 mg), has been used in support of your ANDA 75-913. The current office policy does not allow for the use of the same batch in support of this application (ANDA 75-914). Please manufacture a new test batch and submit all relevant information.

Mr. Shaw stated that the firm has manufactured a second batch, R99038 and submitted the data to the application.

I told Mr. Shaw that the deficiency letter for ANDA 75-914 would be considered a fax deficiency when it was received (rather than a major) due do these errors.

Filename:
V:\FIRMSAM\IMPAX\TELECONS\75913.001.doc

DATE January 4, 2001

APPLICATION NUMBER
75-913 and 75-914

TELECON

INITIATED BY APPLICANT/ FDA
Applicant

PRODUCT NAME
Bupropion Extended-release Tablets, 100 mg and 150 mg; Bupropion Extended-release Tablets, 150 mg

FIRM NAME
IMPAX Pharmaceuticals, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Mark C. Shaw, Director Regulatory Affairs and Compliance

TELEPHONE NUMBER
510-429-5883

SIGNATURE

B. McNeal

B. McNeal
1/4/01

CC: ANDA 75-913 and ANDA 75-914
Division Files

K:\MISC\TAB.DOC

RECORD OF TELEPHONE CONVERSATION

The firm was contacted to discuss the following points: The Drug Substance and Drug Product are now USP. Therefore the Agency will need data to show ensure that the lots made meet the specifications of the USP method, including a list of impurities. The firm stated that the USP standards are not always readily available from USP and that they have attempted to contact USP for the standards. The Agency suggested that the firm submit documentation of their inability to obtain the USP standards in order to perform the necessary comparisons. The Agency is not able to locate data on the container/closure system as it pertains to USP 671, requiring a "tight container". The firm will clarify. Regarding the method used to calculate expiration dating, the firm was asked to please include the language from the 1987 Guidance. In the components/composition , the firm was alerted that they may need to update the grade to indicate that the product is USP now. The firm will revise the page and resubmit. Mark Shaw indicated that Adolph Vezza stated that labeling is acceptable for ANDA 75-913, and that Impax is preparing to send 12 copies of FPL to OGD.	**DATE:** 31-Jul-03 **ANDA NUMBER** 75-913&75-914 **TELECON INITIATED BY AGENCY** **PRODUCT NAME:** Bupropion HCl **FIRM NAME:** Impax Laboratories **FIRM REPRESENTATIVES:** Mark Shaw **TELEPHONE NUMBER:** 510-476-2018 **FDA REPRESENTATIVES** U.Venkataram, Ph.D. M.Selvam, Ph.D. S.Shepperson,Pharm.D., meeting recorder **SIGNATURES:** S. Shepperson

Orig: ANDA 75913 & 75914
Cc: Division File
Chem. II Telecon Binder
V:\firmsam\impax\telecons\75913Jul31

Telecon Record

Date: **January 15, 2004**

ANDA: **75-913**

Firm: **IMPAX**

Drug: **Bupropion ER Tablets, 100 mg and 150 mg**

FDA Participants: Martin Shimer

Industry Participants: Mark Shaw(voice mail)

Phone #: **(510) 476-2018**

Agenda: **Marty called Mr. Shaw and asked that IMPAX revise their patent certification to the re'994 patent to PI. This patent was delisted from the OB and was not subject to litigation with respect to this ANDA. Therefore 21 CFR 314.94(a)(12)(viii)(B) requires that the applicant recertify**

15 Jan 2004

See Impax's 1/15/04 amendment addressing this issue.

1/29/04

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-913 Applicant Impax Laboratories, Inc.
Drug Bupropion HCl Extended Release Tablets Strength(s) 100 mg + 150 mg

APPROVAL / TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

	DRAFT Package	FINAL Package
1. Martin Shimer, Chief, Reg. Support Branch	Date 12/16/03 Initials MMS	Date 1/28/04 Initials AW for

Contains GDEA certification: (Yes) No (required if sub after 6/1/92)
Determ. of Involvement? Yes No
Pediatric Exclusivity System
RLD = NDA# 20-358
Patent/Exclusivity Certification: (Yes) No
Date Checked 1/29/04
If Para. IV Certification- did applicant
Nothing Submitted X
Notify patent holder/NDA holder (Yes) No
Written request issued yes
Was applicant sued w/in 45 days: (Yes) No
Study Submitted No
Has case been settled: Yes (No) Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes (No)
Type of Letter: TA
Comments: 30 month exp for '798 patent on 2/18/03, ImpAp is blocked from final Approval by Andey's 180 day exclusivity for 150 mg. 100 mg may be fully Approved

2. Project Manager, Stanley Sheppard Team 8, Review Support Branch	Date 1/15/04 Initials SMS	Date Initials

Original Rec'd date 6-22-00
Date Acceptable for Filing 6-26-00
Patent Certification (type) Para 4
Date Patent/Exclus.expires 8-12-2013
Citizens' Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☑
Acceptable Bio reviews tabbed Yes ☑ No ☐
EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 11-26-03
Date of Office Bio Review 5-22-03
Date of Labeling Approv. Sum 12-1-03
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☑
MV Commitment Rcd. from Firm Yes ☐ No ☑
Modified-release dosage form: Yes ☑ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☑
Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def./NA Minor issued ☐ Date
Comments:

3. Div. Dir./Deputy Dir. Chemistry Div. I or II		Date 1/27/04 Initials

Comments:
Revise. 1/23/04.
CMC Satisfactory

4. Frank Holcombe, Assoc. Dir. For Chemistry	First Generics Only	Date Initials

Comments: (First generic drug review)
N/A. ANDA 75-932 (Eon Labs, Inc) received final approval for the 100 mg strength and tentative approval for the 150 mg strength on 11/25/03.

REVIEWER: FINAL ACTION

5. Gregg Davis
Deputy Dir., DLPS
Date 1/28/04
Initials [illegible] for

Sustained

RLD= Wellbutrin SR ~~Extended~~ release Tablets 100mg, 150mg NDA 20-358 (002, 003)
GlaxoSmithKline

#6 (continued): Because of the deficiencies in the bio study noted by OSI and agreed with by DBE on 4/3/03 Impax submitted a new bio study (single dose, fasting) on the 150mg strength. Study found acceptable 7/22/03. office-level bio endorsed 8/22/03. PIL found acceptable for approval (100mg and tentative approval (150mg strength) on 12/11/03. CMC found acceptable 1/16/04. Methods validation completed + satisfactory. 1/28/04

6. Peter Rickman
Director, DLPS
Date 1/28/04
Initials [illegible] for

Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable LES dated 11/28/03 (Verified 1/29/04). No OAI alerts noted. Bioequivalence studies (testing on 100mg strength, fasting and non-fasting on 150mg strength) found acceptable. Multiple dose steady-state on 150mg strength also found acceptable. Dissolution testing on both strengths found acceptable. "Interim" dissolution specifications established. Bio studies conducted by _____ (dosing) and by _____ (analytical). These facilities have acceptable OSI inspectional histories. Office-level bio endorsed 9/25/00. "Interim" dissolution specifications revised and found acceptable 7/31/01. Post reformulation bio studies (fasting on both 100mg and 150mg strengths) found acceptable 12/31/01. OSI audit of ~~invalidated~~ study # R01-328.

6. Robert L. West
~~Acting~~ Deputy Director, OGD
Date 1/28/2004
Initials [illegible] for

Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒
Comments: Upon filing, Impax made paragraph IV certifications to the following patents: '970, '798, '900, '493, and '994. Impax was sued within the 45-day period over the following patents: '798 (only). On 12/11/02, the district court granted Impax's motion for summary judgement. On 1/15/04, Impax changed its certification to the '994 patent (not listed in the Orange Book) to a paragraph 1.
The 30-month period for this ANDA (IPE-Hylan drug product) expired on 2/18/03. Thus, OGD can approve this ANDA for the 100mg strength only at this time. Final approval of the 150mg strength is currently blocked by Andrx's eligibility for 180-day generic drug exclusivity.
Recommend approval for 100mg strength. Tentative approval for 150mg strength

7. Gary Buehler
Director, OGD
Date 1/28/04
Initials GB
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

8. Project Manager, Team Stan Sheppersen
Review Support Branch
Date 1/28/04
Initials SMS
NHI Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
1/15 am Time notified of approval by phone 1150 ~~Time~~ approval letter faxed
FDA Notification:
1/28/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
1/28/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Ltr: On 11/21/01, Impax submitted a major amendment providing for a revised manufacturing process and the addition of a film coat.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-913

CORRESPONDENCE

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

ack for filing 8/9/00
5. Middleton
505(j)(2)(A)

June 22, 2000

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA for Bupropion Hydrochloride Extended-Release Tablets, 100 and 150 mg

Dear Mr. Buehler:

In accordance with Section 505 (j) of the Federal Food, Drug and Cosmetic Act, IMPAX Laboratories, Inc hereby submits an Abbreviated New Drug Application (ANDA) for bupropion hydrochloride tablets, 100 and 150 mg. The reference listed drug, Wellbutrin SR® (bupropion hydrochloride) tablets, 100 and 150 mg, is the subject of Glaxo Wellcome Inc.'s approved NDA 20-358. The drug product, which is the subject of this ANDA, differs from the listed product in that the formulation contains different excipients.

This application meets the criteria for an ANDA in that 1) the conditions of use, active ingredient, route of administration, dosage form, and strength are identical to those of the listed drug, 2) bioequivalence has been demonstrated, and 3) patent certification is provided. The labeling complies with all labeling requirements. This application lists IMPAX Laboratories, Inc. as the manufacturing site for the drug product. The submission contains 21 volumes, organized and jacketed in accordance with FDA-OGD guidelines.

Also included with this ANDA is an electronic submission of the package insert word processor file, prepared in Microsoft Word. Two (2) write-protected diskettes are included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission. Four (4) copies of the draft labeling, bearing the same page numbers as the single copy appearing in volume 1 of this ANDA, are also provided in a separate, labeled, blue binder.

Two (2) write-protected diskettes containing the pharmacokinetic data resulting from the bioequivalence studies are also included in the archival copy of this submission, in a plastic insert.

Should you have any additional questions regarding this ANDA, please contact me by telephone (510-471-3600; ext 305) or by telefax (510-471-3200).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-913

Impax Pharmaceuticals, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

AUG 14 2000

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated August 9, 2000 and your amendment dated August 9, 2000.

NAME OF DRUG: Bupropion Hydrochloride Extended-release Tablets, 100 and 150 mg

DATE OF APPLICATION: June 22, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 26, 2000

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

> Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Nasser Mahmud, Chief, Regulatory Support Branch, at (301) 827-5862.

In addition, to be in compliance with 314.94(a)(8)(ii), you must provide four copies of the draft labeling in the archival copy of the application. Please provide two additional copies of the container labeling and draft package insert for the archival copy. In the future please include four copies of the draft labels and labeling in **both** the archival and review copies of the application

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

Nasser Mahmud
for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-913
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/NMahmud, Chief, RSB _____ date 8/11/00
HFD-615/SMiddleton, CSO _____ date 8/10/00
Word File
V:\FIRMSAM\IMPAX\LTRS&REV\75913.ACK
FT/mjl/8/9/00
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

August 25, 2000

TELEPHONE AMENDMENT
Via FAX: (301) 594-0181
Hardcopy to Follow

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

CMC AMENDMENT
N/A
BIOAVAILABILITY

Attn: Jennifer Fan

Re: ANDA 75-913 (Bupropion HCl Extended-Release Tablets, 100 mg and 150 mg)
Long-Term Stability in Frozen Plasma

Dear Mr. Buehler:

This correspondence follows a August 25, 2000 request from Ms. Jennifer Fan of the Division of Bioequivalence for data supporting the long-term stability of bupropion, hydroxybupropion, and threo-bupropion in frozen human plasma.

Pages 000259 and 000260 were inadvertently not included in the original ANDA submission. These pages support the long-term stability of bupropion, hydroxybupropion, and threo-bupropion in frozen human plasma for 113 days when stored at –80°C.

If you have any questions regarding this amendment please contact me by telephone (510-471-3600; ext 321) or by telefax (510-471-3200).

Sincerely,
IMPAX Laboratories, Inc.

Michele Anderson

Michele Anderson
Senior Regulatory Affairs Associate

Enclosure

CENTER FOR DRUG
REC'D
AUG 29 2000
OGD
EVALUATION AND RESEARCH

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

August 28, 2000

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP

Re: ANDA 75-913 (Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg)
Documentation of Paragraph IV Patent Notification and Receipt of Notice

Dear Mr. Buehler:

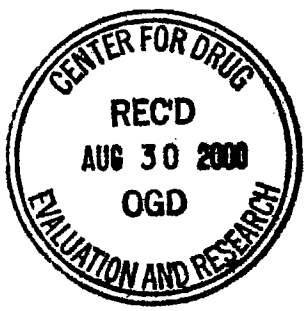
In accordance with 21 CFR 314.95(b), IMPAX Laboratories, Inc. (IMPAX) hereby certifies that it has provided a Notice of Legal and Factual Basis of Non-Infringement for the above-referenced ANDA to the following parties and that the Notice met the content requirements specified in 21 CFR 314.95(c):

Legal Department
Glaxo Wellcome, Inc. (as NDA Holder)
5 Moore Drive
Research Triangle Park, NC 22709
FEDEX tracking number: 8204-8252-1599

Patent Counsel
Glaxo Wellcome, Inc. (as patent owner)
5 Moore Drive
Research Triangle Park, NC 22709
FEDEX tracking number: 8204-8252-1603

Glaxo Wellcome, Inc. (as patent owner)
c/o Donald Brown
130 Water Street
Boston, MA 02109-4280
FEDEX tracking number: 8204-8252-1588

As required by 21 CFR 314.95(e), IMPAX is amending this application to provide documentation of receipt of the Notice of Legal and Factual Basis of Non-Infringement by the above-listed parties. A copy of the FEDEX tracking report documenting the delivery of the Notice accompanies this correspondence.



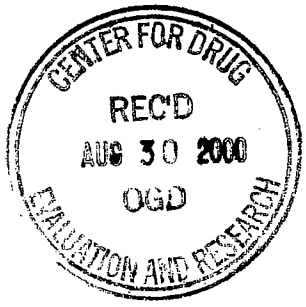
The Notice and documentation of receipt was provided using FEDEX. The acceptability of this form of documentation was agreed to in a July 26, 2000 telephone conversation between the undersigned and Lt. Greg Davis (Regulatory Support Branch), following a July 18, 2000 FAX to the Regulatory Support Branch requesting approval to use FEDEX for Notice delivery.

If you have any questions regarding this amendment please contact me by telephone (510-471-3600; ext 305) or by telefax (510-471-3200).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

Enclosure



IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

October 4, 2000

PATENT AMENDMENT

NEW CORRESP
NC

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 75-913 (Bupropion HCl Extended Release Tablets, 100 and 150 mg)
Documentation of Litigation/Settlement Outcome

Dear Mr. Buehler:

Reference is made to the Office of Generic Drug's August 14, 2000 letter documenting the acceptance for filing of the above-referenced ANDA. The letter requested that IMPAX notify your office in the event that litigation occurred within the 45-day period following notification of the NDA Holder and Patent Owner.

IMPAX hereby confirms that Glaxo Wellcome Inc. initiated a lawsuit within the 45-day period as provided for in section 505(j) (4)(B)(iii) of the Act. Accordingly, IMPAX is enclosing with this correspondence a copy of the complaint, filed September 28, 2000 in the United States District Court for the Northern District of California (San Jose Division).

If you have any questions regarding this amendment please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

Enclosure (Civil Complaint C00-21009)

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT - 6 2000
OGD

FAX AMENDMENT

ANDA 75-913

DEC 20

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: IMPAX Laboratories, Inc. TEL: 510-471-3600

ATTN: Mark C. Shaw FAX: 510-471-3200

FROM: Bonnie McNeal PROJECT MANAGER: 301-827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg.

Reference is also made to your amendment dated: August 25, 2000.

Attached are 6 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FAX AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS:

Enclosed are CMC and labeling deficiencies and bioequivalence comments.

B. McN
12/20/00

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

12/20/2000 FDA FAX

systems to be tested in the formal protocol. Please revise and resubmit the protocol to indicate testing of at least the smallest and largest container/closure systems.

6. Please submit available room temperature stability data accrued to date.

7. We request you to provide data comparing your Drug Product impurity/degradant profile with the innovator's impurity/degradant profile.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Methods validation will be performed on the drug substance and drug product by the FDA field Laboratory.

2. A satisfactory compliance evaluation for the Firms referenced in the ANDA is required for approval. The Establishment Evaluation Request (EER) is pending for two out of four Firms.

Sincerely yours,

for Florence S. Fang

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-913** Date of Submission: **June 22 and August 9, 2000**

Applicant's Name: **Impax Pharmaceuticals, Inc**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

Labeling Deficiencies:

1. CONTAINER 100s and [redacted] (100 mg and 150 mg)

   a. We encourage you to further differentiate your product strengths by boxing, contrasting colors, or some other means.

   b. WARNING: Do not use in combination with Zyban® or any other medicines that contain bupropion hydrochloride.

   c. We encourage you to include the disclaimer "Zyban® is a registered trademark of Glaxo Wellcome.".

2. INSERT

   a. GENERAL COMMENTS

      i. "*in vitro*" and "*in vivo*" (*italics*) throughout the insert labeling

      ii. Delete the hyphen between the number and the units when expressing a dose (e.g., "150 mg" rather than "150-mg").

      iii. "Zyban®" and "ZYBAN®" rather than "Zyban" and "ZYBAN" throughout the insert labeling.

      iv. Replace "sustained" with "extended" throughout the insert labeling except in association with "Zyban®".

      v. Replace "Bupropion ER" with "bupropion hydrochloride extended-release tablets" throughout the insert labeling.

   b. DESCRIPTION

      There is no need to list "NF" with the inactive ingredients.

   c. CLINICAL PHARMACOLOGY

      Pharmacokinetics, eighth paragraph, last sentence - "(±10)" and "(±13)" (delete hyphens)

   d. INDICATIONS AND USAGE

      i. Add a blank line space before this section to be consistent with your formatting.

      ii. Penultimate paragraph - ... previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, ...

e. WARNINGS

"Patient factors:" rather than "Patients factors:"

f. PRECAUTIONS

i. General: Agitation and Insomnia, first sentence - "experienced" rather than "experiences"

ii. Cardiovascular Effects, second paragraph

A). First sentence - ... "extended-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of extended-release bupropion and NTS. In this study ..."

B). Penultimate sentence - "treated" rather than "treted"

iii. Renal or Hepatic Impairment, first sentence - "... kidney and metabolites ..." (delete "the")

iv. Drug Interactions

A). Second paragraph, first sentence - "Because bupropion ..." (delete "of")

B). Drugs Metabolized By ..., second paragraph, first sentence - "coadministration" (delete hyphen)

v. Geriatric Use, last sentence - Delete "(see Use in Patients with Systemic Illness)".

g. ADVERSE REACTIONS

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials

i. Add "Observed" to the title.

ii. First sentence - "... below for the 300 and ..." (add "the")

h. HOW SUPPLIED

Your tablet descriptions as seen in your Specification and Quality Assurance Reports do not agree with those seen in this section. Please revise and/or comment.

i. INFORMATION FOR THE PATIENT (PATIENT PACKAGE INSERT)

i. How many will accompany each container size and how will they accompany the drug product?

ii. See GENERAL COMMENTS 2(a)(ii), (iii), and (v).

Please revise your container labels and physician and patient package insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-913 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion HCl ER Tablets, 100 mg and 150 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm. Based on the submitted data, the test product should meet the following tentative specifications:

Between ——% in 1 hour.
Between ——% in 2 hours.
Between ——% in 4 hours.
NLT —% in 6 hours

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

labeling review
drafted 5/29/01
A. Vezza

mcp

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

May 16, 2001

MINOR AMENDMENT

NDA ORIG AMENDMENT
N/AP 1

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 18 2001
OGD

Re: ANDA 75-913: Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg
Attn: Bonnie McNeal, fax 301-827-4337

Dear Mr. Buehler:

This letter responds to your December 20, 2000, facsimile, naming deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter. IMPAX also references a January 3, 2001 telephone conversation with Ms. Bonnie McNeal of OGD, during which IMPAX addressed several of the deficiencies cited in your facsimile. Since IMPAX required more than 30 days to respond, we have redesignated this response as a "Minor" amendment.

Each deficiency is listed in boldface type followed by IMPAX's response. As required to complete each response, additional data are provided as attachments in this submission. In addition to responding to the Chemistry, Labeling and Bioequivalence comments, IMPAX also acknowledges the following comments:

1. This submission includes a response to the Labeling deficiencies. As requested, a side-by-side comparison of the labeling changes and four (4) copies of the Draft Labeling are provided in the archival copy of the amendment. Also included with this amendment is an electronic submission of the package insert word processor file, prepared in Microsoft Word. Two (2) write-protected diskettes are included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission.

2. IMPAX notes that a satisfactory compliance evaluation of the firms referenced in the ANDA is required for approval.

3. IMPAX acknowledges that method validation will be performed on the drug substance and drug product by the FDA field laboratory. Please note that method validation samples were submitted by IMPAX to FDA's Bothell, Washington laboratory on January 18, 2001.

4. This submission also includes updated long-term stability data for lots R99040 (100 mg) and R99026 (150 mg).

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in Attachment 6.

mcp 5/23/01

Should you have any additional questions regarding this response, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

cc: Marshalette Edwards, SFDO

APPEARS THIS WAY
ON ORIGINAL

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

November 27, 2001

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT
1) REVISED MANUFACTURING PROCESS
2) BIOEQUIVALENCY AMENDMENT

ORIG AMENDMENT
N/AC

Re: Amendment to ANDA 75-913
Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg
Revised Manufacturing Process; Addition of Film-Coat

Dear Mr. Buehler:

In accordance with 21 CFR 314.96, IMPAX Laboratories, Inc. hereby submits an amendment to Abbreviated New Drug Application (ANDA) 75-913 for bupropion hydrochloride tablets, 100 mg and 150 mg. This amendment provides for the addition of film-coating to both product strengths, and a ——— manufacturing process, whereby the——————————————————————————— This revised process was applied only to the 150 mg strength to better control the finished tablet drug release profile, which exhibits a ——————————— as determined during ongoing stability studies. IMPAX recognizes that this amendment contains significant data under 21 CFR 314.96(a)(2), and that the submission of such data may extend the review time of the application up to 180 days.

IMPAX generated dissolution profiles and stability data on its bupropion hydrochloride tablets, 100 mg and 150 mg, as originally filed in ANDA 75-913, dated June 22, 2000. The drug release test results from these stability studies showed an ——————— ———, particularly for the 150 mg strength. This was evident not only in the 150 mg strength subject to this ANDA ("generic Wellbutrin®"), but also in data from related ANDA 75-914 ("generic Zyban®"). IMPAX has also amended related ANDA 75-914 with an improved manufacturing process.

The amendment contained herein provides for a revised manufacturing process that results in a more ——————————— , and hence a more consistent tablet-to-tablet drug release as compared to the manufacturing process described in the original ANDA submission. While incorporating this revised and improved manufacturing process, IMPAX also added a film-coat to the tablets to mask the bitter taste of the active drug substance.

IMPAX established the bioequivalence of this revised formulation by conducting a single-dose fasting study for both the 100 mg and 150 mg tablet strengths. This amendment includes study reports describing the results obtained from these single-dose bioequivalence studies located in Section VI.

Also included is complete CMC documentation for the biobatch used in each bioequivalence study. The CMC section includes complete manufacturing documentation for the biobatches used in the bioequivalency studies. Except as otherwise indicated, the CMC information in this amendment replaces the information included in the original ANDA submission and subsequent amendments.

This amendment contains 12 volumes, organized and jacketed in accordance with FDA-OGD guidelines.

Draft labeling has also been modified to follow the Labeling Review Branch's recommendations for bupropion container labels. These recommendations were conveyed to IMPAX in a September 10, 2001 facsimile for related ANDA 75-914 ("generic Zyban®"). IMPAX confirmed with the Labeling Review Branch that it should also incorporate the recommended establishment name typography into the container labels for this application (i.e., buPROPion). The newly revised draft labeling is located in Section V.

An electronic submission of the package insert word processor file, prepared in Microsoft Word has been provided. Two (2) write-protected diskettes are included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission. Four (4) copies of the draft labels and labeling are included in both the archival and review copies of the amendment.

Two (2) write-protected diskettes containing the pharmacokinetic data resulting from the bioequivalence studies are also included in the archival copy of this submission, in a plastic insert.

Should you have any additional questions regarding this ANDA, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

1-26-02

February 20, 2002

EXCLUSIVITY STATEMENT

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

DWY

NEW CORRESP

Re: ANDA 75-913: Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

Dear Mr. Buehler:

This correspondence provides a new exclusivity statement with respect to the Exclusivity Code M-10, assigned to Glaxo Wellcome.

If you have any questions regarding this amendment please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 25 2002
OGD

1 copy

MINOR AMENDMENT

ANDA 75-913

MAY 20 2002

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Impax Laboratories, Inc. TEL: 510-429-5883

ATTN: Marc C. Shaw FAX: 510-429-5886

FROM: Stanley Shepperson PROJECT MANAGER: 301-827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg.

Reference is also made to your amendment(s) dated: August 25, 2000 and May 16 and November 27, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__3__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
CMC comments included.

5/20/02

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

5/20/2002 FDA FAX

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

We will not be submitting your analytical methods for validation until all formulation and manufacturing issues are resolved.

Sincerely yours,

for Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

July 15, 2002

MINOR AMENDMENT

ORIG AMENDMENT
N/A M.

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

cc: Stanley Shepperson

Re: ANDA 75-913: Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

Dear Mr. Buehler:

This letter responds to your May 20, 2002, facsimile, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

Each deficiency is listed in boldface type followed by IMPAX's response. As required to complete each response, additional data are provided as attachments in this submission. In addition to responding to the Chemistry deficiencies, IMPAX also acknowledges the following comments:

1. IMPAX acknowledges that the FDA will not submit IMPAX's analytical methods for validation until all formulation and manufacturing issues are resolved.

2. This submission also includes updated long-term stability data for lots R01014 (100 mg) and R01011 (150 mg).

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 5.**

Should you have any additional questions regarding this response, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

cc: Marshalette Edwards, SFD-D

RECEIVED
JUL 17 2002
OGD / CDER

7/22/02

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

September 5, 2002

PATENT AMENDMENT

NEW CORRESP
NC

Gary Buehler
~~Acting~~ Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 75-913
Bupropion HCl Extended Release Tablets, 100 and 150 mg

Attn.: Stanley Shepperson

Dear Mr. Buehler:

As requested in the August 14, 2000 Acceptance for Filing letter, please find attached a copy of the court order granting IMPAX's Motion for Summary Judgment of Non-Infringement, filed August 21, 2002. The court ruled in favor of IMPAX in deciding that the IMPAX product does not infringe the Glaxo Wellcome, Inc. patent named in the lawsuit.

Should you have any questions regarding this information, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
SEP 0 9 2002
OGD / CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

September 11, 2002

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

DRIG AMENDMENT
N|AM

Re: ANDA 75-913
Bupropion HCl Extended Release Tablets, 100 mg and 150 mg

Attn.: Stan Shepperson (Project Manager, OGD)

Dear Mr. Buehler:

This correspondence follows a September 5, 2002 telephone conversation with Mr. Shepperson and Dr. Selvam of your office concerning ANDA 75-914, Bupropion Hydrochloride Extended-release Tablets, 150 mg. IMPAX confirmed with Stan Shepperson on September 9, 2002 that the information discussed during the September 5, 2002 telephone conversation regarding ANDA 75-914 should also be included in this application (75-913).

Dr. Selvam requested that IMPAX Laboratories, Inc. (IMPAX) revise its ——— specification to ——— to match that of the updated Manufacturer Certificate of Analysis. Dr. Selvam also requested that IMPAX send a revised Stability Protocol to account for changes in the ——— amount (from ——— to ———) in the 100-count proposed packaging configuration.

IMPAX has made these changes and has also provided updates to Section XIII parts 1-3, to account for the change in desiccant quantity. These pages will replace those in the Major Amendment dated November 27, 2001. The revised documents are enclosed in a labeled blue binder.

If you have any questions regarding this amendment please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
SEP 13 2002
OGD / CDER

Labeling review
drafted 1/3/03
A. Vezza

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

December 2, 2002

LABELING AMENDMENT

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

Re: ANDA 75-913
Bupropion HCl Extended-Release Tablets, 100 mg and 150 mg

Attn.: Stan Shepperson (Project Manager, OGD)

Dear Mr. Buehler:

This correspondence follows several facsimiles from OGD Labeling Reviewer Adolph Vezza (dated 10/8/02, 10/9/02, 10/11/02, 11/1/02, and 11/22/02), directing IMPAX to revise its package insert and patient package insert to be in accordance with that of the Reference Listed Drug (RLD), Wellbutrin® SR.

IMPAX has updated its package insert and the patient package insert accordingly. Twelve (12) specimens of Final Printed Labeling, including container labels, are included with this correspondence.

If you have any questions regarding this amendment please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
DEC 0 3 2002
OGD / CDER

labeling review
drafted 1/3/03
A. Vega

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

December 16, 2002

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

N/AFA

Re: ANDA 75-913
Bupropion HCl Extended-Release Tablets, 100 mg and 150 mg

Attn.: Stan Shepperson (Project Manager, OGD)

Dear Mr. Buehler:

Following submission of the December 2, 2002 Labeling Amendment, IMPAX noted errors in the package insert. The errors have been corrected and twelve (12) specimens of Final Printed Labeling (insert only) are included with this correspondence. The container labels in the December 2, 2002 Labeling Amendment do not require revision.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
DEC 18 2002
OGD / CDER

BIOEQUIVALENCY AMENDMENT

ANDA 75-913

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: IMPAX Laboratories, Inc. TEL: 510-471-3600

ATTN: Mark C. Shaw FAX: 510-471-3200

FROM: Aaron Sigler PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on June 22, 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

DEC 16 '10

BIOEQUIVALENCY DEFICIENCY

ANDA: 75-913 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion Hydrochloride ER Tablets, 100 mg and 150 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

The Division of Scientific Investigations conducted an inspection of the [redacted], for your in vivo study (fasting study #R01-328, bupropion hydrochloride extended-release tablets, 150 mg). Based on that inspection, the acceptance of analytical Run U2-072901a100 was not justified.

The original processed data for the analytical run was not acceptable, as the quality controls (QC) failed to meet the run acceptance criteria. You reprocessed the data without justification and accepted the run. Therefore, bupropion and its metabolites data for subject #7 in Run U2-072901a100 are unreliable.

After excluding subject #7 from the statistical analysis of the study the resulting 90% confidence intervals for bupropion are as follows:

	90% CI
LnAUC(0-t)	93.0-112.3%
LnAUCinf	92.7-111.9%
LnCmax	79.5-97.4%

The 90% confidence interval is not within the acceptable 80-125% range for Cmax. Therefore, the study is unacceptable.

You are advised to conduct another single-dose fasting bioequivalence study on your bupropion hydrochloride extended-release tablets, 150 mg.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm.

Based on the submitted data, the test product should meet the following specifications:

Between [redacted] % in 1 hour.
Between [redacted] % in 2 hours.
Between [redacted] % in 4 hours.
NLT [redacted] % in 6 hours

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

January 17, 2003

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCY AMENDMENT

ORIG AMENDMENT
N/AB

Re: ANDA 75-913
Bupropion HCl Extended Release Tablets, 100 mg and 150 mg

Attn.: Aaron Sigler (Division of Bioequivalence)

Dear Mr. Buehler:

This correspondence responds to the December 16, 2002 bioequivalency deficiency in the above-referenced ANDA. The deficiency concerns the reliability of the bioanalytical data associated with Subject #7, who participated in IMPAX Laboratories, Inc.'s (IMPAX) single-dose fasting study #R01-328.

This response includes data from a reanalysis of the plasma samples from Subject #7, demonstration of acceptable long-term frozen stability covering the interval from initial blood draw to this reanalysis, and a re-estimation of the bioequivalence. The raw data used in the bioequivalence calculations are provided with this response in duplicate labeled floppy diskettes, prepared in SAS Transport format.

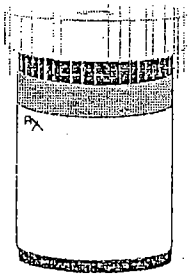
A copy of your December 16, 2002 correspondence accompanies this response. If you have questions or require additional information in connection with this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
JAN 21 2003
OGD / CDER

FAX COVER SHEET



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: January 22, 2003

TO: Michele Anderson - Im PAX

Phone: (510) 476-2010 Fax: (510) 476-2091

From: Adolph Vezza - Labeling Review Branch

Phone: (301) 827-5846 Fax: (301) 443-3847

Number of Pages: 4
(Including Cover Sheet)

Comments:

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-913** Dates of Submission: **December 2 and December 16, 2002**

Applicant's Name: **Impax Pharmaceuticals, Inc**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

Labeling Deficiencies:

1. INSERT

   a. CLINICAL TRIALS

      First paragraph, Sentence beginning "This trial ..." - "450 mg/day dose" (delete the hyphen)

   b. CONTRAINDICATIONS

      Revise so that the following becomes the fourth paragraph:

      "Bupropion hydrochloride extended-release tablets are contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines)."

   c. WARNINGS (Seizures)

      i. First bullet, third line - "0.4%" (add "%")

      ii. Recommendations for Reducing the Risk of Seizure, first bullet - "***not***" (***bold and italics***)

      iii. Hepatic Impairment, second sentence - "... as peak bupropion, as well as AUC, levels are ..."

   d. PRECAUTIONS

      i. General - Cardiovascular Effects

         A). First paragraph, first sentence - "... in some cases severe, requiring acute treatment, has been ..." (add two commas)

         B). Third paragraph, third sentence - "... well tolerated in depressed patients who ..."

      ii. Information for Patients, Physicians are advised to discuss the following issues with patients

         A). Add the following as the second paragraph:

         "Patients should be told that bupropion should be discontinued and not restarted if they experience a seizure while on treatment.

         Patients should be told that any CNS-active ..."

B). Revise the paragraph which discusses alcohol use as follows:

"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 bupropion. Patients should be advised that the consumption of alcohol should be minimized or avoided.

Patients should be advised to ..."

iii. Laboratory Tests - Revise the title ("Tests" rather than "Test").

iv. Drug Interactions

A). Levodopa and Amantadine

1). Retitle this sub-subsection as shown above.

2). Revise this sub-subsection as follows:

"... in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of bupropion to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

B). Add the following sub-subsection immediately after the "Nicotine Transdermal System" sub-subsection:

Alcohol: In post marketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol intolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with bupropion should be minimized or avoided (also see CONTRAINDICATIONS).

f. ADVERSE REACTIONS

Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion, Hemic and Lymphatic - Add the following as the last sentence:

"... thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.."

g. OVERDOSAGE

Human Overdose Experience, first paragraph, second sentence - "vomited" rather than "[redacted]"

h. HOW SUPPLIED

State "[redacted]" rather than "[redacted]" as the color of the 150 mg tablet.

2. PATIENT INFORMATION LEAFLET

a. What is the most important information..., first bullet, second line - Place a space between "bupropion" and "hydrochloride"

b. What should I tell my doctor ...,

i. Delete "hydrochloride extended-release tablets" (three instances). You may retain it in the question if you wish.

ii. "Bupropion passes through your milk."

iii. "anorexia nervosa"

iv. "Tell your doctor about all the medicines you take" ("you" rather than "your")

c. How should I take ..., third line up from the last line

i. "... your next tablet the regular ..." (delete "at")

ii. "It is important ..." rather than "This is important ..."

Please revise your physician and patient package insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

MAJOR AMENDMENT

5-1

ANDA 75-913

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

FEB - 7 2003

TO: APPLICANT: Impax Laboratories, Inc. TEL: 510-476-2018

ATTN: Mark Shaw FAX: 510-476-2091

FROM: Stanley Shepperson PROJECT MANAGER: 301-827-5798

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg.

Reference is also made to your amendment(s) dated: July 15, September 11, December 2 and December 16, 2002; and January 17, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

2/7/03

FEB -7 2003

38. Chemistry Comments to be provided to the Applicant:

ANDA: 75-913 **APPLICANT:** IMPAX Laboratories, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Extended-release Tablets 100 mg and 150 mg

The Deficiency presented below represents a Major Deficiency:

The Division of Chemistry has no further comments regarding the Chemistry, Manufacturing and Controls (CMC) issues. We note that the Division of Bioequivalence (DOB) has requested additional studies in their 12/16/2002 letter. Any changes made to the CMC portion of the ANDA (such as formulation change, manufacturing of a new batch, etc.) in response to the DOB deficiency letter should be submitted for review.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

March 10, 2003

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

CMC AMENDMENT
N/AF

FPL

Re: ANDA 75-913
Bupropion HCl Extended-Release Tablets, 100 mg and 150 mg

Attn.: Stan Shepperson (Project Manager, OGD)

Dear Mr. Buehler:

This correspondence responds to the January 22, 2003 facsimile, listing labeling deficiencies for the above application.

IMPAX has updated its package insert and the patient package insert accordingly. Twelve (12) specimens of Final Printed Labeling (package insert), and 4 artwork proofs of the container labels and patient package inserts are included with this correspondence. The proofs are the true size, color and text of the production container labels and patient package inserts.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

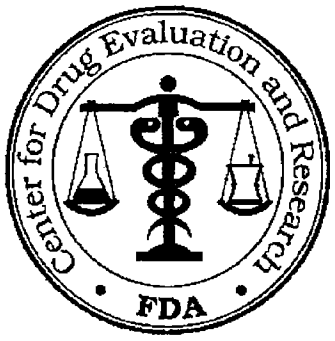
RECEIVED
MAR 12 2003
OGD / CDER

BIOEQUIVALENCY AMENDMENT

ANDA 75-913

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAR 19 2003



APPLICANT: IMPAX Laboratories, Inc. TEL: 510-476-2018

ATTN: Mark Shaw FAX: 510-476-2091

FROM: Aaron Sigler PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on January 17, 2003, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride ER Tablets, 100 mg and 150 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies, which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

MAR 19 2003

BIOEQUIVALENCY DEFICIENCY

ANDA: 75-913 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion Hydrochloride ER Tablets, 100 mg and 150 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

Based on the long-term frozen stability results for 18 months, the remaining concentrations for bupropion relative to its respective mean concentrations on Day zero averaged 69.2% for the high QC samples, and 71.9% for the low QC samples. These values showed that bupropion was not stable for a period of 18 months in human plasma at -80°C. Therefore, re-assay of the plasma samples for subject #7 from study R01-328 is not valid.

You are requested to conduct another single-dose fasting bioequivalence study on your bupropion hydrochloride extended-release tablets, 150 mg.

Sincerely yours,

for Barbara Myers David

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

March 19, 2003

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE:
PATENT CLARIFICATION

NEW CORRESP
NC

Re: ANDA 75-913
Bupropion HCl Extended Release Tablets, 100 and 150 mg

Attn.: Gregory Davis, Branch Chief, Regulatory Support Branch

Dear Mr. Buehler:

This correspondence follows my March 13 and 14 telephone conversations with Lieutenant Commander Gregory Davis of your office regarding the above-referenced ANDA. LCDR Davis and I discussed the patent certifications and the notice of certification of invalidity or noninfringement of a patent, which IMPAX Laboratories, Inc. (IMPAX) provided to Glaxo Wellcome in accordance with the provisions at 21 CFR 314.95.

During our telephone conversation LCDR Davis indicated that IMPAX's ANDA 75-913, covering Bupropion HCl ER Tablets, 100 mg and 150 mg, was presently unapprovable because IMPAX had failed to notify Glaxo following IMPAX's November 27, 2001 Major Amendment, providing for a ——— manufacturing process and the addition of a cosmetic film coating to the finished dosage form.

It was IMPAX's position at the time of the Major Amendment, as well as now, that the changes described did not require that another Notice be sent to Glaxo because the qualitative and quantitative composition of the —— tablets remained unchanged. As described in the Major Amendment, the only change was to ——————— ——————— and other formulation excipients, to provide a ——————— ——————————. This change was only applied to the 150 mg strength. Further, a cosmetic ——— film coating was added to both strengths, which in no way affected the drug release properties of the finished dosage form.

The above-referenced ANDA was the subject of civil litigation (Glaxo v IMPAX, Case No. C00-4403 MHP). IMPAX provided full disclosure to Glaxo of its Major Amendment within 10 days of such submission. This included copies of the amendment that described in complete detail the modified manufacturing process described above.

Provided as attachments to this submission is documentation showing that Glaxo was fully apprised of the Major Amendment. This includes documentation regarding the Major Amendment itself, as well as court documents demonstrating Glaxo's awareness of this amendment. Each such document, and its significance, is described herein.

IMPAX believes that the accompanying documentation clearly shows Glaxo's awareness of the subject amendment, and that the Court, in granting a Motion for Summary Judgment in favor of IMPAX, was also fully aware of this matter.

We respectfully submit this documentation in order to show that IMPAX acted in good faith in advising Glaxo, and the Court, of this modification to the formulation. If FDA has substantial disagreement after reviewing this submission, IMPAX reserves the right to further pursue this matter through other means.

We also request that FDA conduct an expeditious review of this matter in order that IMPAX may obtain a Tentative and/or Final Approval of its application, commensurate with the completion of the technical review of the application. We request your response within ten (10) business days.

Should you have any questions regarding this information, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

Enclosure

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

April 3, 2003

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

1) BIOEQUIVALENCE AMENDMENT
2) CHEMISTRY AMENDMENT

ORIG AMENDMENT
N|AB

ORIG AMENDMENT
N|AC

Re: ANDA 75-913
Bupropion HCl Extended-Release Tablets, 100 mg and 150 mg

Attn.: Stan Shepperson (Project Manager, OGD)

Dear Mr. Buehler:

This correspondence responds to the March 19, 2003 facsimile, requesting another single-dose fasting bioequivalence study. The study has been repeated as requested; the study report describing the results obtained from the single-dose bioequivalence study is located in Section VI.

Two (2) write-protected diskettes containing the pharmacokinetic data resulting from the bioequivalence study are also included in the archival copy of this submission, in a plastic insert.

This correspondence has been designated as both a Bioequivalence Amendment and Chemistry Amendment as per a telephone conversation with Sarah Ho of your office. Ms. Ho requested this designation to assure that both bioequivalence and chemistry issues are resolved during the review. This amendment does not contain any new chemistry information.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

RECEIVED
APR 0 7 2003
OGD / CDER

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-443-3839

FAX TRANSMISSION COVER SHEET

APPLICANT: Impax Labs

TEL: 510-476-2091

ATTN: Mark Shaw

FAX: 510-476-2018

FROM: Stanley Shepperson

PROJECT MANAGER: 301-827-5849

Comments from The Division of Bioequivalence regarding ANDAs 75-913 and 75-914.

2 pages + cover
6/2/03

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-913 APPLICANT: Impax Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion Hydrochloride ER Tablets, 100 mg and 150 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm. Based on the submitted data, the test product should meet the following specifications:

Between ——% in 1 hour.
Between ——% in 2 hours.
Between ——— % in 4 hours.
NLT —% in 6 hours

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

8-1

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-913 SPONSOR : Impax Pharmaceuticals, Inc.
DRUG AND DOSAGE FORM : Bupropion HCl ER Tablets
STRENGTH(S) : 100 mg and 150 mg
TYPES OF STUDIES : A single-dose fasting for the 150 mg tablets
CLINICAL STUDY SITE(S) : ———————
ANALYTICAL SITE(S) : ———————

STUDY SUMMARY : The Study is acceptable.
DISSOLUTION : Dissolution testing is acceptable

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic NO New facility _____ For cause _____ Other X	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM DATE : 5/22/03

TEAM LEADER : GJP SINGH, Ph.D. BRANCH : III

INITIAL : Gurpreet Singh DATE : 5-22-03

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 5/22/03

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

June 27, 2003

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ORIG AMENDMENT
N|AF

Re: ANDA 75-913
Bupropion HCl Extended-Release Tablets, 100 mg and 150 mg

Attn.: Stan Shepperson (Project Manager, OGD)

Dear Mr. Buehler:

This correspondence responds to labeling comments received via telephone on June 23, 2003 from Labeling Reviewer Adolph Vezza.

IMPAX has updated its package insert accordingly. A side-by-side comparison of the labeling changes and twelve (12) specimens of Final Printed Labeling are included with this correspondence.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
JUN 30 2003
OGD/CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

July 9, 2003

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ORIG AMENDMENT
N/A

Re: ANDA 75-913
Bupropion HCl Extended-Release Tablets, 100 mg and 150 mg

Attn.: Stan Shepperson (Project Manager, OGD)

Dear Mr. Buehler:

This correspondence responds to labeling comments received via telephone on June 23, 2003 from Labeling Reviewer Adolph Vezza.

IMPAX has updated its container labels accordingly. A side-by-side comparison of the labeling changes and 4 artwork proofs of the container labels and patient package inserts are included with this correspondence. The proofs are the true size, color and text of the production container labels and patient package inserts.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Michele Odis for

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
JUL 10 2003
OGD/CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

August 1, 2003

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/AC

Re: ANDA 75-913
Bupropion HCl Extended Release Tablets, 100 mg and 150 mg

Attn.: Stan Shepperson (Project Manager, OGD)

Dear Mr. Buehler:

This correspondence follows a July 31, 2003 telephone conference call with Mr. Stan Shepperson and Drs. Venkataram and Selvam of your office concerning the above-referenced ANDA.

Dr. Venkataram requested that IMPAX Laboratories, Inc. (IMPAX) provide data and/or revised documentation to address the following issues:

1. Data to show conformance of the proposed IMPAX drug substance and drug product with the compendial monograph for Bupropion Hydrochloride and Bupropion Hydrochloride Extended-Release Tablets, now official in USP 26.

2. Data demonstrating the conformance of the proposed container/closure system with the requirements in USP General Chapter <671> for Containers—Permeation.

3. Updated expiration-dating statement to conform correctly to FDA's 1987 guidance.

4. Updated components/composition statement indicating the active ingredient as Bupropion Hydrochloride, USP.

Provided herein are the data and updated information addressing each of these requests. A Field Copy certification is provided in **Attachment 6**. If you have any questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
AUG 0 4 2003
OGD/CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

Labelling reviewed 8/12/03

August 01, 2003

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ORIG AMENDMENT
N/AF

FPL

Re: ANDA 75-913
Bupropion HCl Extended-Release Tablets, 100 mg and 150 mg

Attn.: Stan Shepperson (Project Manager, OGD)

Dear Mr. Buehler:

This correspondence follows a recent telephone conversation with Labeling Reviewer Adolph Vezza. Reference is also made to IMPAX's July 9, 2003 Labeling Amendment.

Mr. Vezza requested that IMPAX submit a total of twelve (12) artwork proofs of FPL for each package size of the immediate-container label along with the patient package insert, which is part of the container label.

Accompanying this correspondence are twelve (12) artwork proofs. The proofs are the true size, color, and text of the production container labels and patient package insert. The FPL accompanying this submission differ slightly from the FPL submitted in the July 9, 2003 correspondence as explained herein.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
AUG 0 4 2003
OGD/CDER

IMPAX LABORATORIES, INC.
30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

September 5, 2003

TELEPHONE AMENDMENT

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A

Re: ANDA 75-913
Bupropion HCl Extended Release Tablets, 100 mg and 150 mg

Attn.: Stan Shepperson (Project Manager, OGD)

Dear Mr. Buehler:

This correspondence follows an August 21, 2003 conference call with Mr. Stan Shepperson and Dr. Venkataram of your office concerning the above-referenced ANDA. Reference is also made to IMPAX Laboratories, Inc.'s (IMPAX) August 1, 2003 Telephone Amendment citing its difficulties in demonstrating compliance to the USP monograph for bupropion due to the unavailability from the USP of any of the reference standards, other than bupropion HCl itself.

During the telephone call Dr. Venkataram explained FDA's position as being that data are still required to demonstrate that IMPAX's proposed drug substance and drug product conform to the respective USP monographs. The proposal by IMPAX, that such data be submitted as a post-approval commitment, was not acceptable. Dr. Venkataram further indicated that IMPAX should attempt to obtain the required reference materials from sources other than the USP.

Although the USP does not currently supply any of the required reference standards, other than for the parent compound bupropion HCl, IMPAX was able to obtain samples of the following reference compounds from the following sources:

- [ ]
  - Bupropion Hydrochloride Related Compound A
  - Bupropion Hydrochloride Related Compound B
  - Bupropion Hydrochloride Related Compound F + C
  - Bupropion Hydrochloride Related Compound E

RECEIVED
SEP 0 8 2003
OGD/CDER

- [ ]
  - m-chlorobenzoic acid

A certificate of Analysis for each of these reference compounds is provided in **Attachment 1.**

Following the August 21 teleconference, IMPAX revised and revalidated its proposed analytical test methods in order to adapt them for use in analyzing its proposed drug substance and drug product for all of the related substances cited in the USP monograph for bupropion. The revised test methods and validation reports are provided in **Attachment 2.**

Presented in **Attachment 3A** and **3B,** respectively, are data presenting the test results obtained by IMPAX for its proposed drug substance and for the 100 mg and 150 mg strengths of its proposed drug product. The data presented for both the drug substance and drug product were generated with IMPAX methods and USP methods. Also included in each respective attachment are copies of IMPAX's blank Specification and Quality Assurance (SQAR) reports that establish new specification commitments, in full conformance with the current USP monograph, for the drug substance and drug product that are the subject of this ANDA. Please note that the USP drug substance methods will be implemented on a routine basis when the USP standards are available.

In addition to conducting an analysis of the drug substance using the USP methods, IMPAX also conducted an analysis of its proposed drug product by comparing its revised test methods versus the USP test methods. The data presented in **Attachment 3B** demonstrate that the proposed IMPAX test methods are comparable to the USP methods, with respect to both Assay and Related Compounds, and thus support the use of the IMPAX methods for routine use.

The stability protocol has been updated to reflect the USP specifications; please refer to **Attachment 4.**

IMPAX explained during the August 21 teleconference that the biobatch lots submitted in its November 27, 2001 Major Amendment (Lot R01014 and Lot R01011 for the 100 mg and 150 mg strengths, respectively) are now more than two years old and have exceeded the proposed two-year expiration dating period proposed in this ANDA. Accordingly, and as agreed to by Dr. Venkataram, the analyses presented in Attachment 3B are from recently manufactured, full-scale lots of finished product manufactured in accordance with IMPAX's November 27 Major Amendment.

The blank SQAR presented in Attachment 3B for the 150 mg finished product strength has also been revised to change the tablet color from ——to yellow. This color change was made by removing———————————————— formerly used ————————————). The removal of such an inactive ingredient, intended only to affect the color of the finished dosage form, is a change permitted by regulation (21 CFR 314.70 (d)(4).

This change would have otherwise been reported in the first Annual Report to this ANDA. A copy of the qualitative formula, IMPAX SQAR and manufacturer's C of A for the revised dye component is provided in **Attachment 5**. In addition, the Statement of Components and Comparison between Strengths, provided in **Attachment 6**, have been updated to include information related to the color change.

The color change for the 150 mg tablet also affected the DESCRIPTION and HOW SUPPLIED sections of the drug product labeling. Final Printed Labeling (insert) was last submitted to this application in correspondence dated June 27, 2003. Provided in **Attachment 7** is a side-by-side labeling comparison and twelve (12) copies of the revised prescribing information that reflect the color change for the 150 mg product.

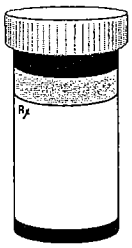
The data accompanying this submission demonstrate that IMPAX's proposed source of bupropion HCl (———————————) and the 100 mg and 150 mg drug products that are the subject of this ANDA meet the current USP monographs for Bupropion HCl and Bupropion HCl Extended-Release Tablets.

A copy of this submission has been sent to the San Francisco District Office. A Field Copy certification is provided in **Attachment 8**. Should you have any questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: September 29, 2003

To: Mark Shaw, Regulatory Affairs

Phone: 510-476-2018 **Fax:** 510-476-2091

From: Postelle Birch

Phone: (301) 827-5846 **Fax:** (301) 443-3847

Number of Pages: 2
(Including Cover Sheet)

Comments:
Attached are labeling deficiencies for ANDA 75-913 per our conversation. Please deliver this fax to the appropriate agent ASAP.

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-913** Dates of Submission: **July 9 and August 1, 2003**

Applicant's Name: **Impax Pharmaceuticals, Inc**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No

Professional Package Insert Labeling:
Satisfactory in FPL as of July 9, 2003 submission

Container Labels and Patient Package Insert Labeling (attached to Container Labels):

Revisions needed PRE-approval:

a. 100s container size

It is unclear how the patient information leaflet will appear on the bottles. Please submit as FPL the actual labeling piece.

b. 500s container size

i. It is difficult to read your insert labeling. Please enhance the readability of your insert labeling. The information on the labels/labeling lacks the conspicuousness required by section 502c of the Act. In order to assure that the computer generated labels/labeling meet this requirement, they must be of true size, color and clarity. Refer to 21 CFR 201.15(a)(6) for guidance.

ii. You have included one patient information leaflet for this bottle size. It is expected that this bottle size is intended for the dispensing of multiple prescriptions. Please describe your plans for supplying the patient information leaflet with your product, e.g., how many leaflets will you supply for each container size and how will these leaflets be supplied.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Wellbutrin SR®
NDA Number: 20-358
NDA Drug Name: Wellbutrin SR® (bupropion hydrochloride extended-release) Tablets
NDA Firm: Glaxo Wellcome
Date of Approval of NDA Insert and supplement #: 10-22-02 (S-029)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

ORIG AMENDMENT
N/A C

October 2, 2003

TELEPHONE AMENDMENT

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 75-913
Bupropion HCl Extended Release Tablets, 100 mg and 150 mg

Attn.: Stan Shepperson (Project Manager, OGD)

Dear Mr. Buehler:

This correspondence follows an October 2, 2003 telephone message from Stan Shepperson of your office, concerning the above-referenced ANDA. Mr. Shepperson indicated that Dr. Venkataram requests the chromatography supporting the drug substance and drug product impurity data provided in the September 5, 2003 Telephone Amendment. The chromatography is included with this submission.

Should you have any questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
OCT 0 3 2003
OGD/ODLR

Fax Cover Sheet

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: October 28, 2003

To: Mark Shaw in c/o Isabel McGann

Phone: 510-476-2000 **Fax:** 510-476-2091

From: Postelle Birch

Phone: (301) 827-5846 **Fax:** (301) 594-1174

Number of Pages: 3
(Including Cover Sheet)

Comments:
Attached are labeling deficiencies for ANDA 75-913 per my conversation with Isabel. Please deliver this fax to the appropriate agent ASAP.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-913** Dates of Submission: **September 5, 2003**

Applicant's Name: **Impax Pharmaceuticals, Inc**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

Labeling Deficiencies:

1. Professional Package Insert Labeling:

   a. DESCRIPTION

      We note that the listing of the inactive ingredients does not include all of the ingredients appearing in your Components and Composition Statements and Raw Materials Controls. Please insert "iron oxide yellow" in the listing of inactive ingredients for the 100mg tablet.

   b. PRECAUTIONS

      i. Your product contains FD & C yellow #5. According to CFR 201.20(b) it is required that you insert the following statement to the PRECAUTIONS section of your insert:

         "This product contains FD & C Yellow No. 5 (tartrazine) which may cause allergic type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD & C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity."

      ii. In the *Cardiovascular Effects* subsection please revise the first sentence of the second paragraph to read, "Data from a comparative study of the extended-release formulation of bupropion...".

   c. DRUG ABUSE AND DEPENDENCE

      In "Animals" subsection please revise the last sentence to read, "In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms...".

2. Container Labels and Patient Package Insert Labeling (attached to Container Labels):

   a. GENERAL COMMENT

      Please add the statement, "Contains FD&C Yellow No. 5 (tartrazine) as a color additive" or "Contains color additives including FD&C Yellow No. 5 (tartrazine).

   b. 100s container size

      It is unclear how the patient information leaflet will appear on the bottles. Please submit as FPL the actual labeling piece.

   c. 500s container size

i. It is difficult to read your insert labeling. Please enhance the readability of your insert labeling. The information on the labels/labeling lacks the conspicuousness required by section 502© of the Act. In order to assure that the computer generated labels/labeling meet this requirement, they must be of true size, color and clarity. Refer to 21 CFR 201.15(a)(6) for guidance.

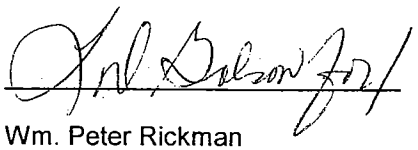
ii. You have included one patient information leaflet for this bottle size. It is expected that this bottle size is intended for the dispensing of multiple prescriptions. Please describe your plans for supplying the patient information leaflet with your product, e.g., how many leaflets will you supply for each container size and how will these leaflets be supplied.

Please revise your labels and labeling, as instructed above, and submit final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

ORIG AMENDMENT

November 14, 2003

M/AE

LABELING AMENDMENT

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 75-913
Bupropion HCl Extended-Release Tablets, 100 mg and 150 mg

Attn.: Postelle Birch (Labeling Reviewer, OGD)

Dear Mr. Buehler:

This correspondence responds to the September 29 and October 28, 2003 facsimiles, as well as the November 4, 2003 telephone conversation between labeling reviewer Postelle Birch of your office and the undersigned.

Included in this amendment are the following:

- Container Label and Patient Information Leaflet
  - 100 mg, 100 count
  - 100 mg, 500 count
  - 150 mg, 100 count

Please note that the labels for the 100 mg product now include the statement regarding FD&C Yellow No. 5. A side-by-side labeling comparison is provided. The text in the 150 mg container labels is identical to the text in the artwork proofs submitted August 1, 2003.

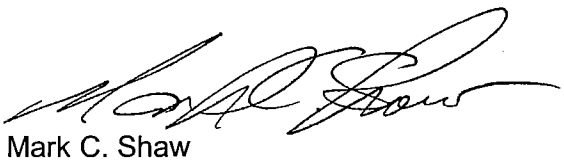
- Physician insert, 100 mg only
- Physician insert, 100 mg and 150 mg

A side-by-side comparison for the 100/150 mg insert is included.

IMPAX has included twelve (12) specimens of the actual labeling piece (container label and patient information leaflet) with this submission. The container label will be adhered to the bottle and the patient information leaflets are "sandwiched" between the adhered bottom label and the top container label. Please note that the 100-count bottle contains 4 patient information leaflets (one patient information leaflet per 30 tablets) and the 500-count bottle contains 10 patient information leaflets (one patient information leaflet per 60 tablets for the 100 mg or 150 mg product). Please note that the Dosing and Administration section instructs the patient to take one 150 mg tablet twice a day, hence the need for at least one patient information leaflet per 60 tablets for a 30-day supply.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.



Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

December 2, 2003

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT
(Post-Approval Commitment)

NEW CORRESP
NC

1/12/04

Re: ANDA 75-913
Bupropion HCl Extended-Release Tablets, 100 mg and 150 mg

Attn.: Lillie Golson (Division of Labeling and Program Support)

Dear Mr. Buehler:

This correspondence follows my December 1, 2003 telephone call with Ms. Lillie Golson of your office regarding labeling for the above-referenced ANDA. IMPAX submitted Final Printed Labeling in correspondence dated November 14, 2003 that included revised container labels and patient information leaflets. The patient leaflets are "sandwiched" between the bottom label, which is adhered to the bottle, and the top container label. The top container label is peeled back to reveal the patient leaflets, which are removed by the pharmacist and dispensed to the patient along with the prescription. This configuration is also known as a "fix-a-form" label.

Ms. Golson requested that IMPAX provide information on its container label alerting the dispensing pharmacist to the patient leaflets contained inside the fix-a-form label. We agreed that IMPAX would revise the text of its container label to incorporate directions for the dispensing pharmacist as a post-approval commitment. As IMPAX has already procured a significant inventory of labeling, we also agreed, as an interim measure, that IMPAX will place a sticker on each bottle of packaged product alerting the dispensing pharmacist to the patient leaflets. IMPAX agrees to submit revised labeling as a post-approval labeling supplement.

If you have any questions regarding this correspondence please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

ORIGINAL

RECEIVED
DEC 0 5 2003
OGD/CDER

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

December 8, 2003

ORIG AMENDMENT
NDA

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT
(Post-Approval Commitment)

Re: ANDA 75-913
Bupropion HCl Extended-Release Tablets, 100 mg and 150 mg

Attn.: Lillie Golson (Division of Labeling and Program Support)

Dear Mr. Buehler:

This correspondence follows my December 8, 2003 telephone call with Ms. Postelle Birch and Ms. Lillie Golson of your office regarding labeling for the above-referenced ANDA.

The Division of Labeling and Program Support advised IMPAX that it is necessary to incorporate the text, "Twice-A-Day," into the immediate-container label of the 150 mg drug product. This change is required in order to minimize any potential dispensing errors and/or confusion with Wellbutrin® XL, which is dosed once per day. IMPAX was advised that this change applies only to the 150 mg container label.

IMPAX has advised its label supplier of this change and we hereby commit to add the required text to the 150 mg product labels prior to market introduction. Revised labeling, incorporating this change as well as the minor labeling change described in IMPAX's December 2, 2003 post-approval commitment, will be submitted as a post-approval labeling commitment.

If you have any questions regarding this correspondence please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
DEC 11 2003
OGD/CDER

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

APIV to PI for RE33994 (delisted) S. Mitchell 3/2/04

January 15, 2004

PATENT AMENDMENT

XP

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 75-913
Bupropion HCl Extended Release Tablets, 100 and 150 mg

Attn.: Martin Shimer

Dear Mr. Buehler:

This amendment provides a revised patent certification to the above-referenced ANDA. This patent revision follows today's telephone message from Martin Shimer of the Regulatory Support Branch regarding a change to the patent certification for the above-referenced ANDA.

The attached correspondence revises the patent certification for patent RE33994 from a paragraph IV to a paragraph I certification.

If you have any questions regarding this amendment please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
JAN 20 2004
OGD/CDER

10-1

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

January 23, 2004

TELEPHONE AMENDMENT

Vilayat Sayeed, Ph.D.
Director, Division of Chemistry III
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

[illegible] CORRESP
NC

Re: ANDA 75-913
Bupropion HCl Extended Release Tablets, 100 mg and 150 mg

Attn.: Stan Shepperson (Project Manager, OGD)

Dear Dr. Sayeed:

This correspondence follows our January 22, 2004 teleconference regarding the above-referenced ANDA. I also reference our January 23, 2004 teleconference, which included participation by Ms. ———————————, Inc. As discussed during the January 22 teleconference, you requested that IMPAX Laboratories, Inc. (IMPAX) address the following application issues, which you identified during your division-level review:

1. Add a specification for ———————— to the proposed commercial batch record following completion of the ————————————————
2. Commit to the Post-Approval submission of a CBE-0 Supplement that provides drug product release results for three full-scale batches of the 100 mg and 150 mg strengths
3. Commit to the Post-Approval submission of a CBE-30 Supplement for any changes IMPAX proposes to the approved container/closure system

This correspondence addresses each of these three requests. Should you have any questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091). A Field Copy of this amendment has been submitted to the San Francisco District Office.

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
JAN 28 2004
OGD/CDER

8.1

ANDA 75-913

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

MAR - 2 2004

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated June 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

Upon further review and reconsideration of the labeling for the 100 mg strength product, we ask the following to reduce potential dosing errors in the market place:

At the time of next printing of the labeling for your 100 mg strength product, please make the following revisions to your container labels and insert labeling. Submit final printed container labels and insert labeling as a "Special Supplement - Changes Being Effected" in accordance with 21 CFR 314.70(c).

1. CONTAINER

   a. Insert "twice-a day *" in parenthesis to appear beneath the product strength.

   b. On the side panel, insert the statement, "See package insert for full dosage information."

In addition,

2. INSERT

   DESCRIPTION- Include the following statement "This product meets USP Drug Release Test #3" as the last paragraph.

Please ensure that the same changes are made to your 150 mg strength when you submit your Supplement-Expedited Review for full approval.

To facilitate review of your submission and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the last approved labeling with all the differences annotated and explained.

Sincerely yours,

3/1/04

William Peter Rickman
Director
Division of Labeling and Program Support

Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-913
Division File

V:\FIRMSAM\IMPAX\LTRS&REV\75913.LO.doc

Endorsements: HFD-613/L.Golson
HFD-613/M. Dillahunt 2/23/04

Letter out