CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-515

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Patent Information

Pursuant to 21.C.F.R. §314.53

for

Wellbutrin XL™ (buproprion hydrochloride) Extended-Release Tablets

NDA 21-515

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	Wellbutrin XL™
Active Ingredient:	bupropion hydrochloride
Strength:	150mg, 300mg
Dosage Form:	tablet; oral

Applicable Patent Numbers and Expiration Dates:

Patent No:	US 6,096,341
Expires:	30 October 2018
Owner:	Pharma Pass LLC Licensed to Biovail Corporation Sublicensed to GlaxoSmithKline
Type of Patent:	Drug product

Patent No: US 6,143,327

Expiry Date: 30 October 2018

Owner: Pharma Pass LLC
Licensed to Biovail Corporation
Sublicensed to GlaxoSmithKline

Type of Patent: Drug product

The undersigned declares that the above stated United States Patents cover the composition of Wellbutrin XL tablets. This product is the subject of this application for which approval is being sought.

Please address all communications to:

Robert H. Brink
VP - Pharmaceutical Patents - RTP
Five Moore Drive
PO Box 13398
RTP, North Carolina 27709-3398

18 July 2002
Date

/S/
Robert H. Brink
Registration No. 36,094

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-515 SUPPL #

Trade Name Wellbutrin XL

Generic Name bupropion hydrochloride extended release tablets

Applicant Name GlaxoSmithKline HFD-120

Approval Date August 28, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / X /

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO / X /

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      The pivotal study (AK1BioVail2543) on which this approval was based was a bioequivalence (comparative bioavailability) study which evaluated the bioavailability of a once-daily bupropion (HCL) extended-release tablet test formulation relative to reference Wellbutrin tablets under steady-state, fasting conditions.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 18-644 Wellbutrin Immediate Release

NDA # 20-358 Wellbutrin Sustained Release

NDA # 20-711 Zyban Sustained Release

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active

moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the

Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more

investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial

support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
9/23/03 08:20:06 AM

APPEARS THIS WAY
ON ORIGINAL

MARKETING EXCLUSIVITY

Wellbutrin XL (bupropion hydrochloride) Extended-Release Tablets
NDA 21-515

Pursuant to Sections 505 (c)(3)(d)(iii) and 505(j)(4)(d)(iii) of the Federal Food, Drug and Cosmetic Act, and to Section 314.108(b)(4) of Title 21 of the Code of Federal Regulations, GlaxoSmithKline does not request marketing exclusivity as this New Drug Application is supported by a pivotal bioequivalence study along with other supportive bioavailability studies; there are no new clinical investigations included in this application.

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

DA/BLA # : 21-515 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: August 26, 2002 **Action Date:** August 28, 2003

HFD 120 **Trade and generic names/dosage form:** Wellbutrin XL (bupropion hydrochloride extended-release) Tablets

Applicant: GlaxoSmithKline **Therapeutic Class:** Antidepressant of the aminoketone class

Indication(s) previously approved: Major Depressive Disorder

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Major Depressive Disorder

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- X **No: Please check all that apply: ___Partial Waiver __X__Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- X **Other:** Pediatric Rule currently in litigation

Date studies are due (mm/dd/yy): _____

studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

tion D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
1-594-7337

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richardae Taylor
9/9/03 03:42:34 PM

APPEARS THIS WAY ON ORIGINAL

Table of Contents

NDA 21-515

Wellbutrin XL™ (bupropion hydrochloride)

150 and 300 mg Extended-Release Tablets

Approval Package:
Volume 1 of 1

Table of Contents

NDA 21-515

Wellbutrin XL™ (bupropion hydrochloride)

150 and 300 mg Extended-Release Tablets

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-515	Efficacy Supplement Type SE-	Supplement Number	
Drug: Wellbutrin XL (bupropion hydrochloride extended-release) Tablets		Applicant: GlaxoSmithKline	
RPM: Richardae Taylor for Doris Bates		HFD-120	Phone # 301-594-2850
Application Type: (x) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	9/3/03
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(x) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	x

Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
General Information	
❖ Actions	
• Proposed action	(x) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE 6/24/03
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (x) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	8/20/03
• Original applicant-proposed labeling	See AE Package Tab D
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DSRCS/ 7-24-03 DMETS/ 7-29-03
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	7/3/03
• Reviews	See above reviews dated 7/24/03 and 7/29/03
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Resubmission AK letter 7/15/03
❖ Memoranda and Telecons	
❖ Minutes of Meetings	See AE Package Tab S
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	N/A
• Date of Meeting	
• 48-hour alert	
Federal Register Notices, DESI documents, ~~NAS~~, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	TL Memo/ 8-21-03
❖ Clinical review(s) *(indicate date for each review)*	8/21/03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See clinical review 8/21/03
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	See Tab G
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	7/30/03
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	See AE Package
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	8/15/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See AE Package Tab Q
• Review & FONSI *(indicate date of review)*	See AE Package Tab Q
• Review & Environmental Impact Statement *(indicate date of each review)*	See AE Package Tab Q
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: (x) Acceptable- completed 7/31/03 ( ) Withhold recommendation
❖ Methods validation	( ) Completed (x) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

10 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 21, 2003

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for approval action for NDA 21-515 for Wellbutrin XL (an extended release formulation of bupropion), for major depressive disorder

TO: File, NDA 21-515
[Note: This memo should be filed with the 7-3-03 response to our 6-24-03 approvable letter.]

Background

See 6-6-03 memo to file for background information leading up to the approvable action.

In our 6-24-03 approvable letter, we requested the following:
-Risk management plan regarding the name Wellbutrin XL
-Mock-up of container labels to facilitate final evaluation of name and labels
-Full response to CMC deficiencies
-Adoption of proposed dissolution specifications
-Literature search regarding potential drug interactions
-Safety update, including literature update
-Response to our proposed labeling

Risk management plan regarding the name Wellbutrin XL
-We expressed concern about the potential for medication errors, given the 2 different sustained release formulations of Wellbutrin (SR and XL), and for this reason, asked for a risk management plan to educate health care providers and patients.
-The sponsor proposed an educational program as requested. These materials were reviewed by Jeanine Best from ODS/DSRCS, Charles Hoppes from ODS/DMETS, and DDMAC.
-Jeanine Best and DSRCS supervisory staff found the educational materials acceptable, however, had a few minor recommendations for the PPI and some advice for the sponsor to be implemented postapproval; we will convey these comments in the approval letter.

-Charles Hoppes and DMETS supervisory staff found the name and the educational materials acceptable, however, Jerry Phillips still expressed a concern that there may be confusion. The DMETS review included several comments for the sponsor that will be conveyed in the approval letter.
-DDMAC apparently found the name Wellbutrin XL acceptable from a promotional perspective (no independent review, rather, just a note to this effect in the DMETS review).

Mock-up of container labels to facilitate final evaluation of name and labels
-The sponsor provided the mock-up container labels.
-These materials were submitted and found to be acceptable.

Full response to CMC deficiencies
-We provided a list of deficiencies and the required responses.
-It is my understanding that GSK has fully and satisfactorily responded to all CMC deficiencies, and CMC staff have recommended final approval.

Adoption of proposed dissolution specifications
-We proposed a dissolution method and specifications.
-The sponsor provided justification for broadening the specification at 4 hours, and OCPB has agreed with this change.

Literature search regarding potential drug interactions
-We noted that there are recent in vitro data suggesting that certain SSRIs and antiretroviral drugs may be inhibitors and/or substrates for CYP2B6, the enzyme involved in the hydroxylation of bupropion. Thus, we requested a literature search regarding this issue, and noted that labeling may need modification, depending on what was found.
-The sponsor conducted a literature search and presented the results, and an argument that clinically significant interactions are unlikely. Sally Usdin and OCPB supervisory staff agree that literature reports do not confirm clinically significant interactions, nor do they rule them out. Thus, they argue that some statement is needed in Drug Interactions to at least note the possibility of such interactions. We have asked the sponsor to adopt such a statement, and they have agreed.

Safety update, including literature update
-We requested a safety update, including an update on worldwide use of Wellbutrin XL and a literature update on this product.
-The sponsor provided a safety update including safety data from 6 ongoing or completed studies (1 pk, 2 comparing effects on sexual functioning, 2 in seasonal affective disorder, and 1 in adult ADHD). There were 3 SAEs, however, none could be reasonably attributed to drug. There were 19 discontinuations for adverse events; while for 15 of these the specific event was not listed, we know they did not represent SAEs. There was no indication of any important new safety findings that would impact on the approvability of this product or on labeling.
-Wellbutrin XL is not approved anywhere at this time, and no published references regarding this product were found.

Response to our proposed labeling
-We provided draft labeling and asked the sponsor to either accept our proposal, or propose alternative language.
-The sponsor [redacted] We negotiated final labeling with the sponsor, and reached agreement on 8-20-03.

DSI

Although the pivotal equivalence study was done in Toronto, it was not possible to inspect this site due to travel restrictions. Thus, the records were shipped to a Chantilly, VA facility, and they were inspected there between June 9th and 13th by DSI staff. While there were minor deficiencies, in particular, incorrect reporting of data for 1 patient and inadequate SOPs, overall, the data were deemed to be acceptable for review. The data were reanalyzed by OCPB staff, with corrected values for the patient in question, and the result was unchanged.

Conclusion
-All issues in our approvable letter have been addressed, and this application can now be approved, with the mutually agreed upon final labeling.

cc:
Orig NDA 21-515
HFD-120/DivFile
HFD-120/TLaughren/RKatz/PAndreason/RLevin/DBates/RTaylor

DOC: NDA21515.02

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/s/

Thomas Laughren
8/21/03 01:06:49 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

7 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*: HFD-420/ S. Beam, P. Guinn			FROM: HFD-120 / D. Bates	
DATE July 14, 2003	IND NO. 28,686	NDA 21-515	TYPE OF DOCUMENT trademark review	DATE OF DOCUMENT Jun 24, 2003 (FPL mockups received 7-14-2003)
NAME OF DRUG bupropion HCl **(WELLBUTRIN XL)**	PRIORITY: NDA 3S		CLASSIFICATION OF DRUG Antidepressant	DESIRED COMPLETION DATE: Action Date is 9/3/2003 need consult by 8/15/2003 this is patient info plus trademark – 2nd consult

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE—NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: TRADEMARK REVIEW, PPI REVIEW< PATIENT EDUCATION MATERIALS

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This package contains four full size mockups of the package insert. It is intended to accompany the consult sent on July 8, 2003 for this NDA.

The labeling can also be found in the EDR at:
\\Cdsesub1\n21515\N_000\2003-07-03\labeling
Please contact Dr. D. Bates at 301-594-5536 or via email at batesd@cder.fda.gov if there are questions or further information is needed.

SIGNATURE OF REQUESTER (SEE DFS SIGNATURE PAGE)	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
7/14/03 11:11:04 AM
also being entered in DFS for trademark review

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/s/

Doris Bates
7/14/03 11:14:18 AM
also sent to DFS for DMETS - Med Errors consult

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**			
TO *(Division/Office)*: HFD-420/ S. Beam, P. Guinn			FROM: HFD-120 / D. Bates	
DATE July 8, 2003	IND NO. 28,686	NDA 21-515	TYPE OF DOCUMENT trademark review	DATE OF DOCUMENT Jan 24, 2003
NAME OF DRUG bupropion HCl **(WELLBUTRIN XL)**	PRIORITY: NDA 3S		CLASSIFICATION OF DRUG Antidepressant	DESIRED COMPLETION DATE: Action Date is 9/3/2003 need consult by 8/15/2003 this is patient info plus trademark – 2nd consult
NAME OF FIRM: GlaxoSmithKline				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE—NDA MEETING
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- ☐ RESUBMISSION
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- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: TRADEMARK REVIEW, PPI REVIEW< PATIENT EDUCATION MATERIALS

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The attached information includes both clean and marked up copies of the firm's reproposed package insert, including patient information (clean copy includes changes, marked up copy accentuates them).
Also included are full size color mockups of all container labeling. A full-size mockup of the PI was not provided by the firm and has been requested for courier delivery ASAP.
Also included are the Agency AE letter with the FDA proposed draft labeling, and the reference document on which the Wellbutrin XL labeling is based, which is the Wellbutrin SR current approved labeling. (These materials accompany hard copy of the consult form only.)
Finally, the firm's proposed patient educational program is included

The labeling can also be found in the EDR at:
\\dsesub1\n21515\N_000\2003-07-03\labeling
Please contact Dr. D. Bates at 301-594-5536 or via email at batesd@cder.fda.gov if there are questions or further information is needed.

SIGNATURE OF REQUESTER (SEE DFS SIGNATURE PAGE)	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
7/9/03 11:52:52 AM
Firm has sent one copy of labeling which is being forwarded for both the trademark and medication errors reviews. I can request additional copies but did not want to delay this further by waiting for them.

APPEARS THIS WAY
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-420/ S. Beam (S. Dallas)			FROM: HFD-120 / D. Bates	
DATE Feb. 27, 2003	IND NO. 28,686	NDA NO. 21-515	TYPE OF DOCUMENT trademark review	DATE OF DOCUMENT Jan 24, 2003
NAME OF DRUG bupropion HCl **(WELLBUTRIN XL)**	PRIORITY: NDA 3S		CLASSIFICATION OF DRUG Antidepressant	DESIRED COMPLETION DATE: NDA Action Date is 6/26/2003 need consult by 3/26/2003 this is patient info – 2nd consult

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
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- ☐ SAFETY/EFFICACY
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- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: TRADEMARK REVIEW

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

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- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
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- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The attached information includes both clean and marked up copies of the patient information (clean copy includes changes, marked up copy accentuates them). Also included is the cover letter to the submission of this information and the reference document on which the revisions are based, which is the Wellbutrin SR current approved labeling. (These materials accompany hard copy of the consult form only.)

The labeling can also be found in the EDR at:
http://edr/loadfile.asp?PATH=FILE://\\CDSESUB1\N21515\N_000\2002-08-26&DOCUMENT_ID=2315766&APPL_NO=021515&APPL_TYPE=N

Please contact Dr. D. Bates at 301-594-5536 or via email at batesd@cder.fda.gov if there are questions or further information is needed.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)

	■ MAIL □ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
2/28/03 02:06:01 PM
courtesy copy of e-mail sent to Ms. Phelan

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ON ORIGINAL

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 29, 2003

NDA NUMBER: 21-515

NAME OF DRUG: Wellbutrin XL (Bupropion Hydrochloride Extended-Release Tablets) 150 mg and 300 mg

NDA HOLDER: GlaxoSmithKline

I. INTRODUCTION:

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) for a re-review of the proprietary name, "Wellbutrin XL" as well as a labeling review of the revised proposed professional and patient package insert, container labels, and carton labeling for "Wellbutrin XL". "Wellbutrin XL" is a new extended-release formulation that is given once daily. DMETS previously reviewed the proposed proprietary name "Wellbutrin XL" (ODS Consult 02-0031) and found it acceptable on August 31, 2002. Comments were also provided by DMETS regarding the "Wellbutrin XL" container labels and carton labeling (ODS Consult 02-0031-1) on December 20, 2002 and again on April 2, 2003 (ODS Consult 02-0031-2 and 02-0031-03). At DMETS' request, the sponsor has also provided a communication plan, "...to educate healthcare professionals and patients on the appropriate use of Wellbutrin XL with respect to other marketed dosage forms of bupropion hydrochloride." The sponsor commits to submit any reported actual or potential domestic medication error reports associated with Wellbutrin XL to the Agency within 15 days of receipt.

Other bupropion hydrochloride formulations already exist in the U.S. market. The immediate-release formulation (Wellbutrin), was approved by the Agency on December 30, 1985. The extended-release formulations, Wellbutrin SR and Zyban, were approved by the Agency on October 4, 1996 and May 14, 1997, respectively.

PRODUCT INFORMATION

"Wellbutrin XL" is the proposed proprietary name for bupropion hydrochloride extended-release tablets. It is indicated for the treatment of major depressive disorder. "Wellbutrin XL" is available as a 150 mg and 300 mg tablet. The usual adult target dose of "Wellbutrin XL" is 300 mg/day, given once daily in the morning. However, dosing with "Wellbutrin XL" should begin at 150 mg/day given as a single daily dose in the morning. If the 150 mg initial dose is adequately tolerated by day 4, then an increase to the target dose of 300 mg/day may be given. The maximum dose of "Wellbutrin XL" is 450 mg/day, which can be given as a single or divided dose.

II. RISK ASSESSMENT:

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Wellbutrin XL". Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Since the completion of the initial review of the proprietary name Wellbutrin XL (ODS consult 02-0031), the Expert Panel has not identified any proprietary names, thought to have the potential for confusion with Wellbutrin XL. However, the Expert Panel raised concerns regarding the confusion of the "XL" product with the "SR" product and the immediate-release product currently in the marketplace.

2. DDMAC did not have concerns the name Wellbutrin XL with regard to promotional claims.

B. SAFETY EVALUATOR RISK ASSESSMENT

For reasons explained in earlier reviews (ODS Consults 02-0031, 02-0031-1, -2, and -3) of the proprietary name, "Wellbutrin XL", DMETS still has concerns with potential medication errors occurring between "Wellbutrin XL", Wellbutrin SR, Wellbutrin, and Zyban. However, DMETS believes that the risk of introducing an entirely new proprietary name for this once-a-day bupropion hydrochloride tablet would be greater than the addition of the name modifier "XL".

The sponsor has taken the following steps to minimize the potential for medication errors between "Wellbutrin XL" and other approved dosage forms of bupropion hydrochloride:

1. The sponsor has provided a risk management plan to educate patients and healthcare providers on the appropriate use of this once daily extended release formulation with respect to the other approved dosage formulations of bupropion hydrochloride. Key messages will be directed to physicians, pharmacists, and patients to educate these groups on the appropriate use of Wellbutrin XL.

2. The sponsor has addressed comments from the Division of Surveillance, Research, and Communication Support (DSRCS) regarding the patient information labeling from a March 24, 2003, Memo and DSRCS has provided the Division with additional comments (Memo of July 24, 2003) for the sponsor's latest submission.

3. The sponsor has satisfactorily addressed DMETS' labeling comments and submitted draft labels and labeling. With regard to DMETS' concerns for a proposed Patient Sample Kit [one bottle of 150 mg strength (7 tablets) and one bottle of 300 mg strength (7 tablets)], the sponsor has decided not to develop a patient kit at this time.

In addition, the sponsor has made a commitment to submit all domestic actual medication error reports and potential medication error reports associated with Wellbutrin XL to the Agency as expedited reports (within 15 days).

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the professional and patient package insert labeling, carton labeling, and the container labels of "Wellbutrin XL", DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified areas of possible improvement, which may minimize potential user error.

1. Since there is a potential for confusion between the SR and XL product, the sponsor should be encouraged to include the text "twice-a-day" on container labels and carton labeling of the marketed product Wellbutrin SR (NDA 20-358). Due to the 150 mg daily initiation dosing for Wellbutrin SR, DMETS recommends that this labeling statement be accompanied by a reference to full dosing information, e.g., "* See package insert for full dosage information."

2. PATIENT INFORMATION

   Information about not taking Zyban or other bupropion containing products is buried in the patient information and does not stand out. The sponsor should take measures to increase the prominence of this message by bolding or some other means.

IV. RISK MANAGEMENT PLAN

DMETS requested the firm create and implement a risk management plan to educate healthcare professionals and patients on the appropriate use of this once daily extended-release formulation with respect to the other approved dosage formulations of bupropion hydrochloride. This plan should be executed before and after product launch. In addition, the sponsor was requested to submit any medication error reports (potential and actual) associated with "Wellbutrin XL" to the Agency within 15 days of receipt.

In correspondence dated July 3, 2003, the sponsor responded to this request by proposing a communication program to educate healthcare professionals and patients on the appropriate use of Wellbutrin XL with respect to other marketed dosage forms of bupropion hydrochloride. The sponsor wanted to communicate the following key messages to healthcare professionals and patients.

- Healthcare providers need to be informed that a new once-daily extended release formulation of bupropion will be available in the US marketplace.
- Healthcare providers need to be informed that there will be a 150 mg strength tablet for Wellbutrin SR, Zyban, and Wellbutrin XL, but that Wellbutrin XL is the only once-daily formulation of bupropion.
- Healthcare providers need to be educated regarding how the new extended release formulation should be administered to both new and established patients, and under what circumstances the Wellbutrin or Wellbutrin SR formulations can be switched to the extended-release product.

The general components of this plan are summarized in Appendix One. However, specific education materials were not submitted for review. DMETS has no objections to the risk management plan proposed by the sponsor. The sponsor should submit "Dear Health Professional" letters and educational materials to the Agency for review and comment when they become available. The Division of Surveillance, Research, and Communication Support reviewed the communication program and forwarded their comments to the Division in a July 24, 2003, memorandum.

V. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name "Wellbutrin XL".

2. DMETS has no objections to the risk management plan proposed by the sponsor. The sponsor should submit "Dear Health Professional" letters and educational materials to the Agency for review and comment when they become available.

3. DMETS recommends the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

   We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Charlie Hoppes, R.Ph., M.P.H.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

APPEARS THIS WAY
ON ORIGINAL

Appendix 1. Summary of Sponsor's Risk Communication Plan*

Activities Directed to Physicians

- Dear Healthcare Professional Letters
- Physician Speaker Training
- Wellbutrin XL Dose Card to instruct physicians on proper dosing
- Prescription Pad Ink Stamp which includes name and dosing instructions
- Physician Website

Activities Directed to Pharmacists

- Dear Healthcare Professional Letters
- Pharmacy Shelf Sheet (with information on proper dosing)
- One-page Educational Sheet from Sales Representatives
- Communication in Pharmacy Journals
- Trade Container Labeling and Carton

Activities Directed to Patients

- Patient Education Available from Physician
- Patient Package Insert
- Tear-Off Pads of Patient Package Insert
- Consumer Website
- Sample Container Labeling

Other Activities

- Sales Representative Training
- Training for use by Sponsor's Customer Response Center
- Medication Error Reporting

* Detailed information appears in the sponsor's submission dated July 3, 2003.

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/s/

Charles Hoppes
8/14/03 09:13:19 AM
PHARMACIST

Denise Toyer
8/14/03 12:57:59 PM
PHARMACIST

Carol Holquist
8/14/03 01:09:15 PM
PHARMACIST

Jerry Phillips
8/14/03 01:41:25 PM
DIRECTOR
I am quite uncomfortable with the approval of this name and predict practitioner confusion and resultant errors. A name such as [redacted] would more closely convey a once a day dosage. Jerry Phillips

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

ATE RECEIVED: 7/11/03	DESIRED COMPLETION DATE: 8/15/03	ODS CONSULT #: 02-0031-4

TO:

Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH:

Doris Bates
Project Manager, Division of Neuropharmacological Drug Products
HFD-120

PRODUCT NAME:	**NDA SPONSOR:** GlaxoSmithKline
Wellbutrin XL (Bupropion Hydrochloride Extended-Release Tablets) 150 mg and 300 mg **NDA #:** 21-515	

SAFETY EVALUATOR: Charlie Hoppes, R.Ph., M.P.H.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) conducted a re-review of the proprietary name "Wellbutrin XL" as well as a labeling review of the revised package insert, carton labeling, and container labels for the Wellbutrin XL" patient sample kit.

RECOMMENDATIONS:

1. DMETS has no objection to the use of the proprietary name, "Wellbutrin XL".
2. DMETS has no objections to the risk management plan proposed by the sponsor. The sponsor should submit "Dear Health Professional" letters and educational materials to the Agency for review and comment when they become available.
3. DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
4. DDMAC finds the proprietary name, "Wellbutrin XL", acceptable from a promotional perspective.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Drs. Uppoor and Yasuda, HFD-860			FROM: Dr. Bates, HFD-120 (for Dr. Andreason)	
DATE July 8, 2002	IND NO. 28,676	NDA NO. 21-515	TYPE OF DOCUMENT NDA resubmission	DATE OF DOCUMENT July 3, 2003
NAME OF DRUG Wellbutrin XL (bupropion HCl)	PRIORITY CONSIDERATION 3S		CLASSIFICATION OF DRUG antidepressant	DESIRED COMPLETION DATE: August 15, 2003

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
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- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☒ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Consult is preceded by a hard copy of the firm's resubmission received and delivered by the DDR on July 8, 2003. Note that this is most likely to be a two month response, due on September 3. We are meeting on July 15 at 10:00 a.m. to determine the completeness of response and the resubmission class.

The EDR version was posted on July 7, 2003, and was immediately forwarded to the review team on that date. A copy of the link is below.

\\CDSESUB1\N21515\N_000\2003-07-03

SIGNATURE OF REQUESTER See DFS	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Doris Bates
7/9/03 11:06:51 AM

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

August 28, 2003

RECEIVED
AUG 2 9 2003
DDR-120 / CDER

GlaxoSmithKline

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398
Tel. 919 483 2100
www.gsk.com

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

RECEIVED
AUG 2 9 2003
MEGA/CDER

Re: NDA 21-515; Wellbutrin XL (bupropion hydrochloride) Extended-Release Tablets
Response to FDA Request: Updated Educational Communication Plan for Wellbutrin XL

Dear Dr. Katz:

NEW CORRESPONDENCE
N(C)

Reference is made to our pending New Drug Application for WELLBUTRIN XL™ Extended-Release Tablets, 150 mg and 300 mg, a new extended release formulation of bupropion hydrochloride for the treatment of major depressive disorder. Reference is also made to the letter from the agency dated June 24, 2003 stating the NDA was approvable and included specific requests that needed to be addressed by GlaxoSmithKline (GSK) before the application may be approved. GSK submitted a complete response to the approvable letter on July 3, 2003.

Included in the response to the NDA approvable letter was a proposed Educational Communication Plan directed to healthcare providers and patients describing the appropriate use of Wellbutrin XL™ and a commitment for reporting medication errors associated with Wellbutrin XL™. As requested by the FDA, the Communication Plan focuses on the potential for confusion between the various formulations of bupropion: Wellbutrin Tablets, Wellbutrin SR Sustained-Release Tablets, Wellbutrin XL Extended-Release Tablets, and Zyban Sustained-Release Tablets (as an aid to smoking cessation).

This Educational Communication program was discussed in a telephone conversation on August 27, 2003 with Richardae Taylor and Robbin Nighswander of the Division. In the discussion, it was requested that GSK provide an updated version of the communication plan and the timeline for the implementation of the proposed educational activities.

The purpose of this correspondence is to provide the updated version of the Communication Plan provided in the July 3rd correspondence (included in Attachment 1). This plan is similar to that outlined previously with additional information describing

each tactic being developed. It is important to note GSK did not distribute the "Coming Soon" letters to physicians and pharmacists as described in the original proposal as we had not received feedback from the Division that this strategy was appropriate.

GSK commits to having all components of the attached Educational Communication Plan in place by December 15, 2003. On or before that time, the components of this program will be provided to the Division. As part of this overall commitment, all domestic medication error reports or potential medication error reports associated with Wellbutrin XL will be sent to the Agency as expedited reports (within 15 days).

Many components of this Educational Communication program will be ongoing throughout the duration of marketing for Wellbutrin XL. The implementation of this plan reinforces GSK's commitment to providing clear direction to healthcare professionals and patients through education and instruction in the package inserts, products and samples packaging, educational and promotional materials, and patient information leaflets, regarding the availability of multiple bupropion formulations.

If there are any questions regarding this submission please contact me at 919-483-3763 or James Murray at 919-483-5119. Thank you.

Sincerely,

Mary E. Martinson

Mary E. Martinson
Director
Regulatory Affairs, Psychiatry

cc: Dr. Richardae Taylor (HFD-120)

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
SmithKline Beecham Corporation d/b/a GlaxoSmithKline	August 28, 2003
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(919) 483-2100	(919) 483- 5756
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-515

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Bupropion hydrochloride	WELLBUTRIN XL™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	150 mg, 300 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to FDA Request: Updated Educational Communication Plan for Wellbutrin XL

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*

☒	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* : Response to FDA Request : Updated Educational Communication Plan for Wellbutrin XL

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Jan E Martinson /for	**Mary E. Martinson, Director, Regulatory Affairs, Psychiatry**	28 Aug 2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Five Moore Drive **Research Triangle Park, NC 27709**	**(919) 483-3763**

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

7 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

N-000-SL

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AUG 2 2 2003
CDR/CDER

August 21, 2003

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398
Tel. 919 483 2100
www.gsk.com

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

RECEIVED
AUG 2 5 2003
DDR-120 / CDER

DUPLICATE

Re: NDA 21-515; Wellbutrin XL (bupropion hydrochloride) Extended-Release Tablets
Response to FDA Comment: Labeling

ORIGINAL AMENDMENT
N(EL)

Dear Dr. Katz:

Reference is made to our pending New Drug Application for WELLBUTRIN XL™ Tablets, 150 mg and 300 mg, a new extended release formulation of bupropion hydrochloride. Reference is also made to the email communication received August 19, 2003 from Richardae Taylor, Project Manager for Wellbutrin XL, that included revised wording for the package insert and Patient Information leaflet for WELLBUTRIN XL.

We have reviewed the proposed changes and find them acceptable. The purpose of this correspondence is to submit a draft revised package insert and Patient Information leaflet that includes the following changes as requested by FDA:

Package insert:

[redacted]

[redacted]

[redacted]

We are providing a pdf version of the labeling that uses as the base copy all accepted changes from the August 19, 2003 email communication from FDA. The addition of the website and toll-free number are depicted in the line-revisioned version. A clean copy of the labeling in pdf and WORD97 version as a review aid are also provided.

This submission is being provided electronically in accordance with the *Guidance for Industry, Providing Regulatory Submissions in Electronic Format-NDAs, January 1999.* Please see Guide to Reviewers for detailed information about this electronic submission.

If you have any questions concerning this submission, please contact me at (919) 483-3763. Thank you.

Sincerely,

Mary E. Martinson

Mary E. Martinson
Director
Regulatory Affairs, Psychiatry

cc: Richardae Taylor, HFD-120 (cover letter only)

NDA 21-515

WELLBUTRIN™ XL (bupropion hydrochloride) Extended-Release Tablets

GUIDE TO FDA REVIEWERS

1. Electronic Submission

All documents included in this submission are provided as electronic files in Portable Document Format (PDF). The submission has been organized into a folder-based structure in compliance with the guidance for providing regulatory submissions in electronic format (IT3 January 1999). All components of this submission have likewise been organized into the folder-based structure that was described in the guidance document. An electronic table of contents (amendtoc.pdf), located in folder ' N021515' allows the reviewer to access any report or summary within the submission. The reviewer will be able to view the information, copy and paste the information to a review commentary, and/or print the information, if needed.

2. Electronic Description

Contents of the media: one copy of one CD as the electronic archive copy and labeled ELECTRONIC REGULATORY SUBMISSION FOR ARCHIVE.

Total size of the submission (Approx.1.15mb)

3. Virus Verification

This submission is virus-free and confirmed via McAfee VirusScan w/SP v4.5.0.534 (4287).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338.
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
SmithKline Beecham Corporation d/b/a GlaxoSmithKline	August 21, 2003
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number *(Include Area Code)***
(919) 483-2100	(919) 483-5756

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-515

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
bupropion hydrochloride	WELLBUTRIN XL™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* | CODE NAME (If any)

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	150 mg, 300 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of depression

APPLICATION INFORMATION

APPLICATION TYPE (check one) [X] NEW DRUG APPLICATION (21 CFR 314.50) [ ] ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) [ ] BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE [X] 505 (b) (1) [ ] 505 (b) (2)

IF AN ANDA, OR 505(B) (2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug | Holder of Approved Application

TYPE OF SUBMISSION *(check one)*
(check one) [ ] ORIGINAL APPLICATION [ ] AMENDMENT TO A PENDING APPLICATION [ ] RESUBMISSION
[ ] PRESUBMISSION [ ] ANNUAL REPORT [ ] ESTABLISHMENT DESCRIPTION SUPPLEMENT
[ ] EFFICACY SUPPLEMENT [ ] LABELING SUPPLEMENT [ ] CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT [X] OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY [ ] CBE [ ] CBE-30 [ ] Prior Approval (PA)

REASON FOR SUBMISSION Response to FDA Comment: Labeling

PROPOSED MARKETING STATUS *(check one)* [X] PRESCRIPTION PRODUCT (Rx) [ ] OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 | THIS APPLICATION IS [ ] PAPER [X] PAPER AND ELECTRONIC [ ] ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Drug Product Manufacturer – Ready for inspection
Biovail Corporation, Manufacturing Division
100 LifeSciences Parkway
Steinbach, MB, Canada
Contact: Hanif Sachedina, Director, Corporate Compliance
(416) 285-6000 x217

GlaxoSmithKline Contact (All other sites)
Steve Moss, Compliance Manager, Europe/International
Harmire Road
Barnard Castle, County Durham, DL128DT, UK
+44 (0) 183 369 0600

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

RECEIVED
AUG 2 2 2003
CDR/CDER

This application contains the following items: *(Check all that apply)*	
E	1. Index
E	2. Labeling (check one) [x] Draft Labeling [ ] Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d) (1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods Validation Package (e.g., 21 CFR 314.50 (e) (2) (i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d) (2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d) (3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g., 21 CFR 314.50 (d) (5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50 (d) (5) (vi) (b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50 (d) (6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50 (f) (1); 21 CFR 601.2)
	12. Case reports forms (e.g., 21 CFR 314.50 (f) (2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
	20. OTHER (Specify) Communication Program for Healthcare Professionals and Patients

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Mary E. Martinson	**Mary E. Martinson** **Director** **Regulatory Affairs, Psychiatry**	**August 21, 2003**

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
Five Moore Drive **Research Triangle Park, NC 27709**	**(919) 483-3763**

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

July 3, 2003

GlaxoSmithKline

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709

Tel. 919 483 2100
www.gsk.com

Re: NDA 21-515; Wellbutrin XL (bupropion hydrochloride) Extended-Release Tablets
Response to Approvable Letter: Clinical Pharmacology, CMC, Labeling, Safety

Dear Dr. Katz:

Reference is made to our pending New Drug Application for WELLBUTRIN XL™ Tablets, 150mg and 300mg, a new extended-release formulation of bupropion hydrochloride. This once-daily formulation will provide greater convenience to patients currently being treated with WELLBUTRIN SR® (bupropion hydrochloride) Sustained-Release Tablets or WELLBUTRIN® (bupropion hydrochloride) Tablets for the treatment of major depressive disorder. Reference is also made to the letter from the agency dated June 24, 2003 that stated the application is approvable and included specific requests that must be addressed by GlaxoSmithKline (GSK) before the application may be approved. The purpose of this submission is to provide a complete response to the June 24, 2003 Approvable letter.

The requests from the June 24th letter are stated below in bold type and our response follows:

Proposed Trademark Wellbutrin XL

The Wellbutrin XL trademark has been reviewed by the Office of Drug Safety / Division of Medical Errors and Technical Support and by the Division of Drug Marketing, Advertising, and Communications, which have no objections to the proposed trademark. DMETS does, however, have concerns regarding potential medication errors occurring among Wellbutrin XL, Wellbutrin SR, Wellbutrin, and Zyban.

DMETS recommends the creation and implementation of a risk management plan to educate healthcare professionals and patients on the appropriate use of Wellbutrin XL with respect to other marketed dosage forms of bupropion hydrochloride.

The plan should be implemented both before and after product launch. In addition, once this NDA is approved, you should submit any medication error reports associated with Wellbutrin XL to the Agency within 15 days of their receipt by your firm, whether the error is actual or potential.

Item 20 contains a proposed communication plan to educate healthcare professionals and patients on the appropriate use of Wellbutrin XL with respect to other marketed dosage forms of bupropion hydrochloride. Included is a list of key messages to provide clear directives and a table of proposed communication vehicles along with a proposed timeline for these communications. The document also describes GSK's commitment to report any medication errors associated with Wellbutrin XL to the Agency within 15 days of their receipt, whether the error is actual or potential.

It is CDER policy that proposed proprietary names and their associated labels must be evaluated approximately 90 days prior to the anticipated approval of the NDA. Full re-evaluation of the trademark will be necessary prior to final approval of the NDA. Please assure that a complete set of mock-up container labels and labeling are provided, featuring the proposed trademark.

Item 2 contains the labeling for the containers and cartons, featuring the proposed trademark.

Chemistry, Manufacturing and Controls (CMC)

1. Please provide a description of the bulk packaging process for the drug product.

A description of the bulk packaging process is included in Item 4, Section P7.1.5.

2. In your sampling plan for the drug product, you indicate that representative samples of the drug product will be taken at the end of the manufacturing process to serve as a source of samples for testing. Please be advised that samples should be taken throughout the manufacturing process and not just at the end. Please provide an updated sampling plan which adequately tests samples of product from the beginning, middle, and end of the process.

The sampling plan has been revised to verify that samples of the drug product are taken at the beginning, middle, and end of the manufacturing process. The updated sampling plan is provided in Item 4, Section P6.1.

3. The relative response factors associated with each impurity / degradant should be incorporated into the formulas used for calculating the impurity / degradant levels. The impurity / degradant levels should be recalculated using the relative response factors. In addition, the impurity / degradant limits should be recalculated for the drug product.

The updated analytical method incorporating the relative response factors is included in Item 4, Section P6.4. The primary stability data for the drug-related i [redacted] have been recalculated and are presented in Item 4, Section P9.3. Updated drug product specifications that reflect the revised specifications are provided in Item 4, Section P6.2.

4. Provide a complete and detailed description of the secondary packaging systems for the [redacted] bottles [redacted] Your response should include specifications and in-process controls.

[redacted]

5. Please provide updated drug product stability information.

Included in this amendment is the recalculated stability data (Item 4, Section P9), the updated drug product specifications (Item 4, Section P6.2), and the updated statistical analysis of the stability data (Item 4, Section P9.4). SAS Transport files are also provided.

We have also incorporated the revised storage statement (previously agreed upon between yourselves and our chemistry review team) into the overall revised labeling (package insert) appended to this letter. Please address this change in all labeling elements, including container and carton labeling as well as the package insert, when submitting your complete response.

Item 2 contains the revised product labeling (package insert) and labeling for the containers and cartons. Additionally, the revised storage statement is provided in Item 4, Section P9.4.4.

CMC: Methods Validation
We have not completed validation of the regulatory methods for this application. We will expect your continued cooperation to resolve any problems that may be identified.

GSK commits to continue its cooperation with the Agency to resolve any problems associated with confirming the validation of the analytical methods contained in NDA 21-515 for Wellbutrin XL Tablets.

CMC: Categorical Exclusion
We have completed our review of the Environmental Assessment information provided by your firm, and we agree with your request for a Categorical Exclusion from the requirement to perform a full Environmental Assessment for this application.

Thank you for completing this review.

Clinical Pharmacology and Biopharmaceutics

1. Please adopt the following dissolution method and specifications for both strengths of Wellbutrin XL tablets. Note change in specifications at 4 and 8 hours:

Apparatus:	**USP Apparatus 1 (Basket) at 75 RPM**
Medium:	**900 mL of 0.1N hydrochloric acid at 37±0.5°C**
Specifications:	**2 hours:** [redacted]
	4 hours:
	8 hours:
	16 hours: [redacted]
Sample size:	**12 tablets for each time point in the dissolution profile.**

Item 6 contains the dissolution method and proposed specifications for both Wellbutrin XL Tablets, 150mg and 300mg.

2. Bupropion is hydroxylated by CYP2B6. Recently, in vitro studies have identified more substrates and inhibitors of CYP2B6, and the results of recent in vitro studies suggest that several SSRIs and antiretroviral drugs may inhibit the hydroxylation of bupropion by CYP2B6. It would be useful to characterize the requirement for dosing modifications, if necessary, when such drugs are given concomitantly with

bupropion. Therefore we recommend that you conduct a thorough search of the literature, as well as searching adverse event reports for bupropion, to evaluate the potential for pharmacokinetic and/or pharmacodynamic (adverse event) drug interactions with bupropion and inhibitors/substrates such as paroxetine, sertraline, fluvoxamine, norfluoxetine, efavirenz, ritonavir, and nelfinavir. Based on these literature results, an in vivo drug interaction study may be necessary.

In addition, we have made specific changes in the revised labeling appended to this letter. Please address these changes in your complete response.

Item 6 contains the results of a search of the literature and of GSK's adverse event database to evaluate the potential for pharmacokinetic and/or pharmacodynamic drug interactions with buproprion and inhibitors/substrates such as paroxetine, sertraline, fluvoxamine, norfluoxetine, efavirenz, ritonavir, and nelfinavir. Item 2 contains the revised product labeling.

Clinical / Clinical Safety

We have completed our review of the clinical safety information and proposed package insert as provided in your NDA. Our comments are incorporated into the revised labeling appended to this letter, as bracketed comments, text insertions [underlined], or deletions [strikethrough]. Please address these changes specifically in your complete response.

Item 2 contains the revised package insert.

Request for Safety Update

In your complete response to this letter, please include a safety update as described in 21 CFR 314.50(d)(5)(vi)(b).

A safety update report is included in Item 9.

Literature Update

Wellbutrin XL is not a marketed product nor is it approved for use in any country worldwide at this time.

A search of GSK's internal published literature database [redacted]) was conducted which covers GSK's major marketed products, devices and compounds in full development. It is sourced from [redacted] and abstracts from the conference literature not covered by these commercial databases. The search was conducted against title, abstract and controlled vocabulary terms of the world's literature.

The search was conducted by an Information Scientist in GSK's Information Management department. The Scientist has a BSPH and MSLS from University of North Carolina and has worked with GSK's [redacted] since 1996. The search strategy used included:

- GSK Drug - bupropion
- Title, abstract, indexing terms - XL or extended release or extended-release or once daily dosing.

There were no publications relating to Wellbutrin XL identified from this search.

Additional Pertinent Information

Also, GSK has recently obtained data from a comparative bioavailability study of buproprion 300mg extended release tablets versus bupropion sustained release tablets 150mg in healthy normal volunteers. This pharmacokinetic study was conducted by Biovail Technologies Ltd. of Chantilly, VA, with whom GSK is collaborating in the development of the extended-release formulation of bupropion. The results of the study demonstrate the bioequivalence of once daily bupropion 300mg extended release tablets and twice-daily bupropion sustained-release tablets 150mg under steady-state fasting conditions. A final study report is currently being written and these results will be the subject of a future labeling supplement to Wellbutrin XL.

Labeling (Package Insert and Container Labeling)

1. In addition to responding to the points listed above, it will be necessary for you to submit draft labeling revised as shown in the attachment to this letter.

Item 2 contains the revised product labeling.

2. In addition, we have the following comments with respect to the container labeling for the new drug product:

A. Container Labeling (150 and 300 mg tablets, packages of 7 and of 30 tablets)

1. The phrase "extended-release tablets" should be included within the brackets of the established name so that it reads: (bupropion hydrochloride extended-release tablets)

2. The phrase "extended-release tablets" should appear in the same font as "bupropion HCl" and should be at least ½ the size of the proprietary name.

3. The [redacted] " is distracting and should be deleted, or moved to a less prominent location. The strengths, "150 mg" and "300 mg", on the lids of the cartons that contain 12 bottles of 7 tablets should be made more prominent by, for example, increasing the font size.

Item 2 contains the revised container and carton labeling.

B. Carton Labeling (carton containing 12 bottles of 7 tablets)

1. Please see comments A.1. through A. 3. above.

Item 2 contains the revised container and carton labeling.

C. Patient Sample Kit (1 bottle of 150 mg strength (7 tablets) and one bottle of 300 mg strength (7 tablets))

GSK has decided not to develop a patient kit at this time.

D. Shipping Carton (Contains 4 Sample Kits)

1. See comments C.1. through C.4., above.

Item 2 contains the revised container and carton labeling.

Promotional Materials

In your complete response to this letter, please also submit three copies of the introductory promotional materials that you propose to use for this product. Please submit all material in draft or mock-up form rather than final printed format. Please send one copy to this Division and two copies of both the promotional material and the package insert directly to the Division of Drug Marketing, Advertising, and Communications.

Introductory promotional materials are currently under development and are not yet available. However, it is our understanding from discussions with DDMAC that FDA review of promotional materials prior to use is optional. As required by regulation, all promotional pieces will be filed to the NDA via Form FDA 2253 at the time of initial dissemination.

NDA Amendment Organization

This amendment is provided in accordance with the *Guidance for Industry, Providing Regulatory Submissions in Electronic Format-NDAs (January 1999)* and subsequent agreements. Please see Guide to Reviewers for detailed information about this electronic submission.

Review Aids/Copies

Three paper "Review" copies will be provided of this amendment to Dr. Doris Bates for use by the review team; the paper copies are labeled REVIEW COPY - NOT FOR ARCHIVE. The literature references included as pdf files in Item 6 of the electronic submission have not been included in the review copies. The contents of the paper review copies were printed from the electronic archive pdf files, and are therefore identical to the contents of the electronic archive copies.

Field Copy

In accordance with 21 CFR 314.50(1)(3), GlaxoSmithKline will provide a Field Copy of this Amendment to the FDA Atlanta District. The Field Copy is a true copy of this application.

Closing Information

So that we can be accessible and responsive to your requests during the review process, please note that I can be reached at the following numbers at any time to discuss this application:

Phone: (919) 483-3763
FAX: (919) 315-8319

In my absence, please contact Mr. James Murray, VP Regulatory Affairs, Psychiatry and Neurology (Phone: 919-483-5119) concerning this application.

If there are any questions about the Chemistry, Manufacturing and Controls Section of this application, please contact Mr. Leo Lucisano, CMC Regional Director, Regulatory Affairs, at (919) 483-5848.

We look forward to working with your team as we progress through the review of this New Drug Application. Thank you.

Sincerely,

Mary E. Martinson

Mary E. Martinson
Director
Regulatory Affairs, Psychiatry

cc: Dr. Doris Bates (HFD-120)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved OMB No. 0910-0338.
Expiration Date March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
SmithKline Beecham Corporation d/b/a GlaxoSmithKline	July 3, 2003
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number *(Include Area Code)***
(919) 483-2100	(919) 483-5756

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued)*:

One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued): 21-515

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
bupropion hydrochloride	WELLBUTRIN XL™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: CODE NAME (If any):

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	150 mg, 300 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of depression

APPLICATION INFORMATION

APPLICATION TYPE (check one)
[X] NEW DRUG APPLICATION (21 CFR 314.50) [ ] ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
[ ] BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE [X] 505 (b) (1) [ ] 505 (b) (2)

IF AN ANDA, OR 505(B) (2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Holder of Approved Application:

TYPE OF SUBMISSION (*check one*)
(check one) [ ] ORIGINAL APPLICATION [ ] AMENDMENT TO A PENDING APPLICATION [ ] RESUBMISSION
[ ] PRESUBMISSION [ ] ANNUAL REPORT [ ] ESTABLISHMENT DESCRIPTION SUPPLEMENT
[ ] EFFICACY SUPPLEMENT [ ] LABELING SUPPLEMENT [ ] CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT [X] OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY [ ] CBE [ ] CBE-30 [ ] Prior Approval (PA)

REASON FOR SUBMISSION: Response to Approvable Letter: Clinical Pharmacology, CMC, Labeling, Safety

PROPOSED MARKETING STATUS (*check one*) [X] PRESCRIPTION PRODUCT (Rx) [ ] OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1 THIS APPLICATION IS [ ] PAPER [ ] PAPER AND ELECTRONIC [X] ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Drug Product Manufacturer – Ready for inspection
Biovail Corporation, Manufacturing Division
100 LifeSciences Parkway
Steinbach, MB, Canada
Contact: Hanif Sachedina, Director, Corporate Compliance
(416) 285-6000 x217

GlaxoSmithKline Contact (All other sites)
Steve Moss, Compliance Manager, Europe/International
Harmire Road
Barnard Castle, County Durham, DL128DT, UK
+44 (0) 183 369 0600

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
E	1. Index
E	2. Labeling (check one) [x] Draft Labeling [ ] Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
E	4. Chemistry section
E	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d) (1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods Validation Package (e.g., 21 CFR 314.50 (e) (2) (i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d) (2); 21 CFR 601.2)
E	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d) (3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g., 21 CFR 314.50 (d) (5); 21 CFR 601.2)
E	9. Safety update report (e.g., 21 CFR 314.50 (d) (5) (vi) (b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50 (d) (6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50 (f) (1); 21 CFR 601.2)
	12. Case reports forms (e.g., 21 CFR 314.50 (f) (2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
E	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
E	20. OTHER (Specify) Communication Program for Healthcare Professionals and Patients

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Mary E. Martinson	**Mary E. Martinson** **Director** **Regulatory Affairs, Psychiatry**	**July 3, 2003**

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
Five Moore Drive **Research Triangle Park, NC 27709**	**(919) 483-3763**

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-515

GlaxoSmithKline
Attention: Mary E. Martinson
Director, Psychiatry Regulatory Affairs, 5.5206
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Martinson:

We acknowledge receipt on July 3, 2003 of your July 3, 2003 resubmission to your new drug application for Wellbutrin XL (bupropion) extended-release Tablets.

We consider this a complete, Class 1 response to our June 24, 2003 approvable action letter. Therefore, the user fee goal date for this submission is September 3, 2003.

If you have any questions, please call the undersigned, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Doris Bates
7/15/03 03:58:41 PM

APPEARS THIS WAY
ON ORIGINAL

Minutes of Meeting
NDA 20-515, Wellbutrin XL Extended Release Tablets
GSK / Biovail: Major Depressive Disorder
Resubmission Filing Meeting Minutes

DATE: July 15, 2003
INPUT RECEIVED FROM: R. Katz, T. Laughren, R. Levin, S. Yasuda, T. Oliver, S. McLamore, D. Bates

Background: The NDA for Wellbutrin XL extended-release tablets was submitted on August 26, 2002 and was the subject of an approvable action on June 24, 2003.

Note that the original submission predated the court set-aside of the Pediatric Rule. The firm's requests for

- deferral of pediatric studies pending approval of the adult indication and
- exemption of infants and children under age 7 from pediatric studies (partial waiver)

were granted by the Division in correspondence issued October 16, 2002 (which also predates court set-aside).

A resubmission in response to the action letter was received on July 3, 2003. The subject meeting was scheduled to determine the completeness and class of said resubmission.

Summary:

- The resubmission was agreed to be a **Class 1, 2-month** response by all members of the review team. The action due date for this submission is therefore **September 3, 2003.**
- All consults were forwarded prior to this meeting.
- Disciplines conducting reviews of the resubmission are CMC, OCPB, and Clinical (labeling) as well as consult reviews for the trademark, container labeling, and patient education proposals submitted by the firm (ODS/DMETS, DSURCS).
- Reviews are due to be completed by mid-August.

Post Meeting Notes: The firm was informed of the resubmission class and due date by telephone voice mail immediately following the meeting. An acknowledgement letter was signed and sent later the same day (July 15, 2003).

Please see electronic signature page

Doris J. Bates, Ph.D.
Regulatory Project Manager
For the attendees

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Doris Bates
8/3/03 04:09:47 PM

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