

**CENTER FOR DRUG  
EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**22-108**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 22-108

SUPPL #

HFD # 130

Trade Name Aplenzin

Generic Name Bupropion Hydrobromide

Applicant Name Biovail

Approval Date, If Known April 23, 2008

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)2

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

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 sponsor solely submitted bioequivalence data comparing itself to the innovator, Wellbutrin XL, to support approval.

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

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

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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  NO

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

NDA# 21-515

Wellbutrin XL (bupropion HCl) Extended-Release Tablets

NDA#

NDA#

2. Combination product.

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 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 8:

(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- 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

If you have answered "yes" for one or more investigation, identify the NDA in which a



Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! 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:

---

Name of person completing form: Renmeet Grewal, Pharm.D.  
Title: Senior Regulatory Project Manager  
Date: 4/21/08

Name of Office/Division Director signing form: Thomas Laughren, M.D.  
Title: Division Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

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Thomas Laughren  
4/23/2008 11:57:24 AM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-108 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: 10-23-07 PDUFA Goal Date: 4/23/08

HFD -130 Trade and generic names/dosage form: buprion hydrobromide

Applicant: Biovail Therapeutic Class: antidepressant

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.  
 No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): \_\_\_\_\_

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Major Depressive Disorder

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.  
 No. Please proceed to the next question.

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 (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 0 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 6 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 (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 7 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 17 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): 9/23/08

*If 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 (fill in applicable criteria below):

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.*

NDA 22-108

Page 3

**This page was completed by:**

*{See appended electronic signature page}*

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**Renmeet Grewal, Pharm.D.**  
**Senior Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH  
STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

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**Attachment A**

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

Indication #2: \_\_\_\_\_

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

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 (fill in applicable criteria below)::

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 (fill in applicable criteria below):

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.

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

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

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

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Renmeet Grewal  
4/21/2008 03:57:38 PM

4-11-08

4/11/08

**Grewal, Renmeet**

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**From:** Grewal, Renmeet  
**Sent:** Friday, April 11, 2008 10:44 AM  
**To:** 'Lidia Mostovy'  
**Subject:** NDA 22-108 Tradename

Hi Lidia,

The Division of Medical Errors and Preventions has found your tradename "Aplenzin" acceptable.

We do have the following recommendations regarding the Container Label:

1. Relocate the net quantity so that it is not presented in close proximity to the product strength.
2. Revise the "Dosage" statement
3. Increase the prominence of the "WARNING:                     " by highlighting the warning or using a different color text.
4. Include a "Different Salt" banner on the principal display panel not to exceed six months.

b(4)

Best Regards,  
Rimmy

---

*Renmeet Grewal, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1080  
Email: renmeet.grewal@fda.hhs.gov  
Fax: (301) 796-9838*

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/s/

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Renmeet Grewal  
4/17/2008 02:40:18 PM  
CSO

4/8/08

**Grewal, Renmeet**

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**From:** Grewal, Renmeet  
**Sent:** Monday, April 07, 2008 5:11 PM  
**To:** 'Lidia Mostovy'  
**Cc:** 'Robert Ashworth'  
**Subject:** NDA 22-108/Bupropion HBr/ 522mg strength

**Importance:** High

Dear Lydia,

Based on the 12-month stability data submitted for the 522 mg strength Bupropion HBr XL Tablets, only a 9-month expiration date can be granted at this time for the 522 mg strength. One of the three 522 mg batches in 90 counts bottles did not meet the specification of NLT — (at 8 hours) when measured at the 12-month time point. In addition, the dissolution results at the 8 hour time point exhibit a downward trend as a function of time, and this trend is more pronounced with the higher count packaging.

b(4)

Sincerely,  
Rimmy

---

*Renmeet Grewal, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1080  
Email: renmeet.grewal@fda.hhs.gov  
Fax: (301) 796-9838*

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/s/

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Renmeet Grewal  
4/8/2008 09:04:38 AM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-108

INFORMATION REQUEST LETTER

Keller and Heckman LLP  
US Agent for Biovail Laboratories International SRL  
Attention: John B. Dubeck, Esq.  
1001 G Street NW Suite 500W  
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your September 27, 2006, new drug application (NDA) submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for bupropion hydrobromide extended-release tablets.

We also refer to your submissions dated April 26, 2007, June 6, and June 28, 2007, July 3, and July 10, 2007, and October 23, 2007.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submissions and have the following comments and information requests. We request a written response in order to continue our evaluation of your NDA:

- 1. DMF \_\_\_\_\_ which you are cross-referencing for the drug substance information was found deficient. The approval of the NDA from the CMC standpoint is contingent on the satisfactory resolution of the CMC deficiencies. We have notified the DMF Holder, \_\_\_\_\_ of the deficiencies. b(4)
- 2. We recommend that you apply to USAN to obtain the established name for Bupropion Hydrobromide according to 21 CFR §299.4(c). The application form for USAN name can be found in the USAN Dictionary.
- 3. Include the Relative Retention Time (RRT) instead of Retention Time (RT) for peak of \_\_\_\_\_ in the System Suitability criteria of the HPLC method for this impurity. b(4)
- 4. The specification limit of \_\_\_\_\_ for impurity \_\_\_\_\_ at release and shelf life of the Bupropion Hydrobromide ER Tablets, 174 mg, 348 mg and 522 mg, is not justified based on the stability data obtained for the samples stored at the shelf life conditions. Reduce this limit to \_\_\_\_\_ that is accepted in the USP Monograph for Bupropion Hydrochloride Extended Release Tablets.
- 5. Provide confirmation by reference to the 21 CFR food additive regulations, that \_\_\_\_\_ which are in direct contact with the drug product, are safe for use. b(4)

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**Additional Strength, 522 mg**

6. Provide results of testing the impurity \_\_\_\_\_ in drug substance batch, Biovail Lot No. STN10675 \_\_\_\_\_ Lot No. 06PC0188), using current regulatory method. **b(4)**
7. The submitted 6-month stability data at long term and accelerated conditions for Bupropion HBr XL Tablets, 522 mg do not support \_\_\_\_\_ the requested expiry. Please provide additional stability data to support the requested expiry.
8. With the addition of 522 mg Bupropion HBr Tablets, provide justification that the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion to qualify for the categorical exclusion as per 21 CFR §25.31(b). **b(4)**

**Labeling & Package Insert**

9. Change the chemical name of Bupropion HBr in the Description Section of the Package Insert to (±)-2-(tert-butylamino)-3'-chloropropiophenone Hydrobromide.
10. State in the Description Section of the Package Insert that inactive ingredient Carnauba Wax is absent in the 522 mg dosage strength tablets.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at 301-796-2055.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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Ramesh Sood  
2/26/2008 11:44:10 AM

1/18/08

**MEMORANDUM OF TELECON**

DATE: January 14, 2008

APPLICATION NUMBER: NDA 22-108

**BETWEEN:**

Name: Robert Ashworth, PhD., VP, Regulatory Affairs  
 Lidia Mostovy, Director, Regulatory Affairs  
 Peter Silverstone, M.D., VP, Scientific Affairs  
 Michel Chouinard, COO, Biovail Laboratories International  
 Gilbert Godin, COO, Biovail Corporation

Phone: 1-866-864-1636 conf. code: 2610971046

Representing: Biovail Technologies Ltd.

**AND**

Name: Thomas Laughren, M.D., Division Director, Division of Psychiatry Products (DPP)  
 Mitchell Mathis, M.D., Deputy Director  
 Thomas Oliver, Ph.D., Office of New Drug Quality Assessment  
 Raman Baweja, Ph.D., Office of Clinical Pharmacology  
 Andre Jackson, Ph.D., Office of Clinical Pharmacology  
 Paul David, RPh., Chief Project Manager Supervisor, DPP  
 Renmeet Grewal, Pharm.D., Regulator Project Manager, DPP

**SUBJECT:** The sponsor wanted to discuss the classification of the resubmission of the NDA in response to the agency's July 19, 2007 non-approvable letter.

The agency confirmed the resubmission dated October 23, 2007 is a class 2 submission and the PDUFA date for this submission is April 23, 2008. We also told the sponsor there is a possibility of finishing this prior to the review date, however we can not promise anything.

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Renmeet Grewal, Pharm.D.  
 Regulatory Project Manager

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/s/

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Renmeet Grewal  
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CSO

n/16/z



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 22-108

Biovail Technologies, Ltd.  
Attention: Lidia D. Mostovy  
Director, Regulatory Liaison, CNS and Pain  
700 Route 202/206 North  
Bridgewater, NJ 08807

Dear Ms. Mostovy:

We acknowledge receipt of your resubmission dated and received October 23, 2007, to your new drug application for bupropion hydrobromide extended release tablets.

We consider this a complete, class 2 response to our July 19, 2007 action letter. Therefore, the user fee goal date is April 23, 2008.

Please note that this resubmission was classified as a class 2 response because you amended your NDA, late in the first review cycle, with additional information including a new dosage strength (522mg extended release tablet). As conveyed in our July 19, 2007 action letter, the Agency informed you that these new data would be reviewed when you completely responded to our action letter. These data in conjunction with your response to our deficiencies warrant a class 2 resubmission decision.

If you have any question, call Renmeet Grewal, Pharm.D., Regulatory Project Manager, at (301) 796-1080.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Division Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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Thomas Laughren  
11/16/2007 05:44:17 PM

**Grewal, Renmeet**

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**From:** Grewal, Renmeet  
**Sent:** Friday, October 19, 2007 3:38 PM  
**To:** 'Robert Ashworth'  
**Subject:** RE: NDA 22-108- Question re: Review Status

Hi Bob,  
The Office of Clinical Pharmacology has looked at the PK simulations submitted to NDA 22-108 by Biovail on September 18, 2007, for the Bupropion Hydrobromide NDA and the approach is acceptable. Please include the submitted information as part of the complete response to FDA for NDA 22-108.

Sincerely,  
Rimmy

---

*Renmeet Grewal, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1080  
Email: renmeet.grewal@fda.hhs.gov  
Fax: (301) 796-9838*

---

**From:** Robert Ashworth [mailto:Robert.Ashworth@biovail.com]  
**Sent:** Friday, October 19, 2007 12:55 PM  
**To:** Grewal, Renmeet  
**Subject:** NDA 22-108- Question re: Review Status

Hi Rimmy:

I don't know if you are in the office today, so I am sending this email as a follow-up to an earlier voice mail. We are eager to get an update on the status of the review of the PK simulation data which was submitted last month. Our complete response to the July 19 action letter is dependent upon the timing of the review of the PK data. Andre Jackson telephoned two weeks ago during his review of the submission and we were wondering how things are progressing.

Any information you could glean from the PK group regarding the current review status or anticipated timing for your response to Biovail is greatly appreciated.

Regards,

Bob

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Robert Ashworth  
Biovail Pharmaceuticals, Inc.  
Tel: (908) 927-1748

10/19/2007

Robert.Ashworth@biovail.com

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/s/

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Renmeet Grewal  
10/19/2007 03:42:05 PM  
CSO



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-108

Biovail Laboratories International SRL  
Attention: Lidia D. Mostovy,  
Regulatory Liason, CNS & Pain  
700 Route 202/206 North  
Bridgewater, NJ 08807

Dear Ms. Mostovy:

Please refer to your New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrobromide 174mg & 348mg extended release tablets.

We also refer to the meeting between representatives of your firm and the FDA on August 14, 2007. The purpose of the meeting was to give guidance to the sponsor on how to proceed with the not approvable letter issued by the agency on July 19, 2007.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call LCDR Renmeet Grewal, Pharm.D., Regulatory Project Manager, at (301) 796-1080.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren  
Division Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

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## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** August 14, 2007  
**TIME:** 3:30pm  
**LOCATION:** White Oak Campus  
**APPLICATION:** NDA 22-108  
**DRUG NAME:** bupropion hydrobromide  
**TYPE OF MEETING:** Guidance

**MEETING CHAIR:** Thomas Laughren, M.D.

**MEETING RECORDER:** Renmeet Grewal, Pharm.D.

**FDA ATTENDEES:** (Title and Office/Division)

Thomas Laughren, M.D., Division Director  
Mitchell Mathis, M.D., Deputy Director  
Robert Levin, M.D., Medical Reviewer  
Mehul Mehta, Ph.D., Director, Office of Clinical Pharmacology (OCP)  
Ramana Uppoor, Ph.D., Deputy Director, OCP  
Raman Baweja, Ph.D., Team Leader, OCP  
Andre Jackson, Ph.D., Reviewer, OCP  
Thomas Oliver, Ph.D., Chemistry team Lead, ONDQA  
Renmeet Grewal, Pharm.D., Regulatory Project Manager

**EXTERNAL CONSTITUENT ATTENDEES:**

**Biovail:**

Michel Chouinard, Chief Operating Officer, Biovail Laboratories, International, SRL  
Gilbert Godin, MBA, Executive Vice-President & Chief Operating Officer, Biovail Corp.  
Peter Silverstone, M.D., Senior Vice-President, Medical & Scientific Affairs, Biovail Corp.  
Okpo Eradiri, Ph.D., Vice-President, Pharmacology/Toxicology  
Robert Ashworth, Ph.D.- Vice-President, Regulatory Affairs  
Lidia Mostovy- Director, Regulatory Affairs

**Background:**

Biovail submitted NDA 22-108 on September 27, 2006 for bupropion hydrobromide to treat major depressive disorder. The NDA was submitted with a multiple dose, steady-state bioequivalence study comparing pharmaceutical alternative formulations containing equimolar amounts of the same active moiety. On July 19, 2007 the agency took a non-approvable action regarding this NDA because the sponsor failed to conduct a single dose bioequivalence study. The purpose of this meeting is to provide the sponsor an opportunity to seek further clarification of the basis for FDA's nonapprovable action.

**Questions:**

**Question 1.** Has the CMC review of our April 26 submission been completed?

**Preliminary Comments:** The CMC review of the April 26<sup>th</sup> submission regarding the new dosage strength has not been completed. It will be reviewed in the new review cycle.

Discussion at Meeting: none

Question 2. Has the agency accepted our justification for the multiple dose study supporting the 522mg dosage strength?

Preliminary Comments: As noted, the 522 mg dosage strength is still under review. Thus, our response to this question will focus on the 348 mg dosage strength that has already been reviewed.

Results from the pooled data (studies 3228 & 3229 in NDA 22108 vs. studies 2548 & 2571 in NDA 21515) gave the following CIs for parent:

C <sub>max</sub>	(81.8-97)
AUC <sub>inf</sub>	(86-102)
AUC <sub>inf</sub>	T/R Ratio=(1607.7/1704.9)=0.94
C <sub>max</sub>	T/R Ratio=(133.4/149)=0.89

Results for the MD study (3220) gave the following CIs for parent:

C <sub>max</sub>	(80.2-92)
AUC <sub>t</sub>	(84-93.9)
AUC <sub>t</sub>	T/R Ratio=(1362.44/1541.27)=0.88
C <sub>max</sub>	T/R Ratio=(129.86/151.03)=0.86

- Theory predicts that the range for the C<sub>max</sub> CI should increase from multiple to single dosing. The C<sub>max</sub> CI range is 15 and 12 respectively for the single and multiple dosing studies.
- This increase in the C<sub>max</sub> CI range based upon literature references is to be expected. However, the increase in the lower CI limit following single dosing (i.e., the pooled data) is unexpected.
- The ratio for the fraction of drug which is bioavailable decreases from single to multiple dosing, as defined by the respective T/R AUC ratios, which may be a contributing factor.
- Therefore, these results are difficult to interpret.

These apparent differences in the analyses are difficult to understand if indeed the pooled single dose data is predictive of multiple dose behavior.

The Office of Clinical Pharmacology has consulted with the Office of Biostatistics which has pointed out the following:

The study factor test conducted may address the question related to: [results on HBr salt in first study] vs. [results on HBr in second study], which might give some belief that results from the HBr salt in the two studies are homogeneous. Similarly the study factor for the HCL salt may address [results on HCL salt in first study] vs. [results on HCL salt in second study], which may indicate that results from HCL salt in its two studies are homogeneous. However, there is no test to determine whether results from the two HBr studies are comparable to results from the two HCL studies, unless there was a treatment in common in those studies. Therefore, there is no way of knowing:

1. If there are differences observed between the HBr salt and HCL salt do they really differ or are the differences due to the difference between the studies?

2. If the HBr salt and HCL salt appear to have similar biopharmaceutic properties, this might be due to the fact that they actually differed but the differences were masked by a study effect that went in the opposite direction?

**Discussion at Meeting:**

The discussion at the meeting focused on:

1. Conduct of a single dose study
2. Performing simulations

The purpose of the simulations is to predict the steady-state pharmacokinetics of bupropion hydrobromide based upon the single dose treatment arms of studies which had been conducted by the firm. The simulated results from single dose studies are to be compared with observed data in multiple dose study 3230 to show that single dose and multiple dose bupropion hydrobromide pharmacokinetics are comparable.

Stepwise simulation procedures are outlined in Appendix I, and have been sent to the sponsor.

Question 3. Will the Agency review our submission of our proposed tradename regardless of the timing of a complete response?

**Preliminary Comments:** The agency is currently reviewing the proposed tradenames which you have proposed. Once we have come to a conclusion we will forward you the comments from DMETS.

**Discussion at Meeting:** none

Additional Information discussed at the meeting:

**BUPROPION SIMULATIONS:**

1. Using superposition predict the steady-state concentrations for each individual subject in the fasted leg of single dose study 3229 1x348 mg Bupropion HBr treatment and the 1x348 mg Bupropion HBr fasted treatment arm of study 3228. Plot the single and predicted multiple dose profiles. Also provide a plot of the observed steady-state curves for each subject in study 3230.

2. Compare the mean profiles at steady-state separately from superposition for studies 3229 and 3228 with the results for the 1x348 mg fasted treatment arm for the Bupropion HBr in study 3230.

3. For the superimposed steady-state concentrations for each subject from #1 prepare 200 bootstrap samples which will be the test treatment. Also prepare 200 bootstrap samples for the observed Wellbutin XL formulation at steady-state (i.e., study 3230) as the reference. Calculate AUC<sub>inf</sub> and C<sub>max</sub> for each subject for the 200 bootstrapped test and reference samples.

Analyze the data using a parallel design model and calculate the mean 90% CI for each parameter.

4. Increase the individual concentration values for each subject at each time prior to C<sub>max</sub> (0-6hrs) by 5% then by 10% and finally by 20%. This can be done for either the fasted leg of single dose study 3229 1x348 mg Bupropion HBr treatment or the 1x348 mg Bupropion HBr fasted treatment arm of study 3228, if they both are superimposable with the steady-state study 3230 in step #2.

5. Repeat steps 1-3 on each of the respective per cent changes in the time points from (0-6 hrs). This step should be completed (i.e., each study has had the absorption concentrations increased by 5-20% for each individual subject). When this is completed then the mean curves in # 6 can be estimated.

6. Summarize and provide the mean curves for Bupropion HBr (i.e., increased by 5%, 10% and 20% ) and compare with the mean steady-state curve for the fasting 348 mg arm of study 3230 for Wellbutrin XL. Summarize the 90% CI for each of the simulated Bupropion HBr (i.e., increased by 5%, 10% and 20% respectively) as test vs Wellbutrin XL (ref) 300 mg collected in study 3230.

7. Based upon the simulated single dose curves i.e., 5%, 10% and 20% determine which per cent change in absorption single dose plasma concentrations from 0-6 hrs would result in steady-state ratios close to the observed 0.89 test/reference ratio in study 3230.

8. The PK representative at Biovail should contact OCP at (301)-796-1545 if they have any questions related to the simulation proposal.

The sponsor submitted the information below in a response to our preliminary comments sent to the sponsor on August 10, 2007.

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**ADDENDUM TO BRIEFING PACKAGE SUBMITTED JULY 30, 2007:  
Response To The Agency's Preliminary Comments  
NDA 22-108: Bupropion Hydrobromide Extended-Release Tablets**

Biovail gratefully acknowledges receipt of FDA's preliminary responses and comments to some of the issues discussed in the Briefing Document, which was submitted to the Agency on July 30, 2007. Accordingly, in an effort to further facilitate a collaborative and successful discussion, Biovail wishes to in part directly address the preliminary responses and to clarify the points that we believe are most critical to address at the meeting on August 14, 2007.

In summary, the enclosed comments cover three areas:

- Appropriateness and clinical relevance of the steady-state study as a basis for approval
- Comments on the cross-study comparison
- Discriminatory power of multiple dose (Study 3230) versus single-dose

1. Appropriateness and Clinical Relevance of the Steady-State Study as a Basis for Approval

In developing PK data to support the approval of its 505(b)(2) application for a novel bupropion salt, Biovail does not concur with the FDA that a single dose study focusing on three (3) PK parameters for the parent drug is sufficient to bridge safety and efficacy to the marketed product. Hence, a multiple dose, steady-state study was conducted to evaluate the PK profile of parent drug and metabolites under clinically relevant conditions. This is consistent with previous Agency observations which underscored the importance of metabolite measurement for bupropion since clinically over 90% of the exposure is to metabolites with long half-lives. It is also relevant to the clinical situation given that our data (unpublished) shows that these metabolites also are likely to be the major cause of the grand-mal seizures seen with bupropion. Given the long half-life of the key metabolites (up to 37 hours), a steady-state study provides the best basis for accurately measuring these.

The results of the multiple-dose study submitted in the NDA are robust in that they demonstrate comparable bioavailability of the two pharmaceutical alternatives based on fifteen (15) PK parameters, including parent drug, three major metabolites, and PAWC, when evaluated under the conditions of use.

2. Comments on the cross-study comparison

It should be clarified that while the cross-study statistical analysis provided in the Briefing Document was done to provide additional support and information regarding the pharmacokinetic profile of the dosage form covered by this NDA, it was not intended to serve as the sole, definitive basis on which to determine approvability. In terms of this cross-study comparison, we note comments from both the OCP and the Office of Biostatistics contained within the Division's Preliminary Response to Question 2. We accept the premise outlined in the Preliminary Response that pooled data on bupropion HBr and bupropion HCl from two sets of studies may not be homogeneous. In this case, however, differences in variability between the two sets of data were minimal for the following reasons:

- All four studies were performed in the same clinical facility
- The same validated analytical method was used to assay samples
- All four studies were conducted under the same SOP's

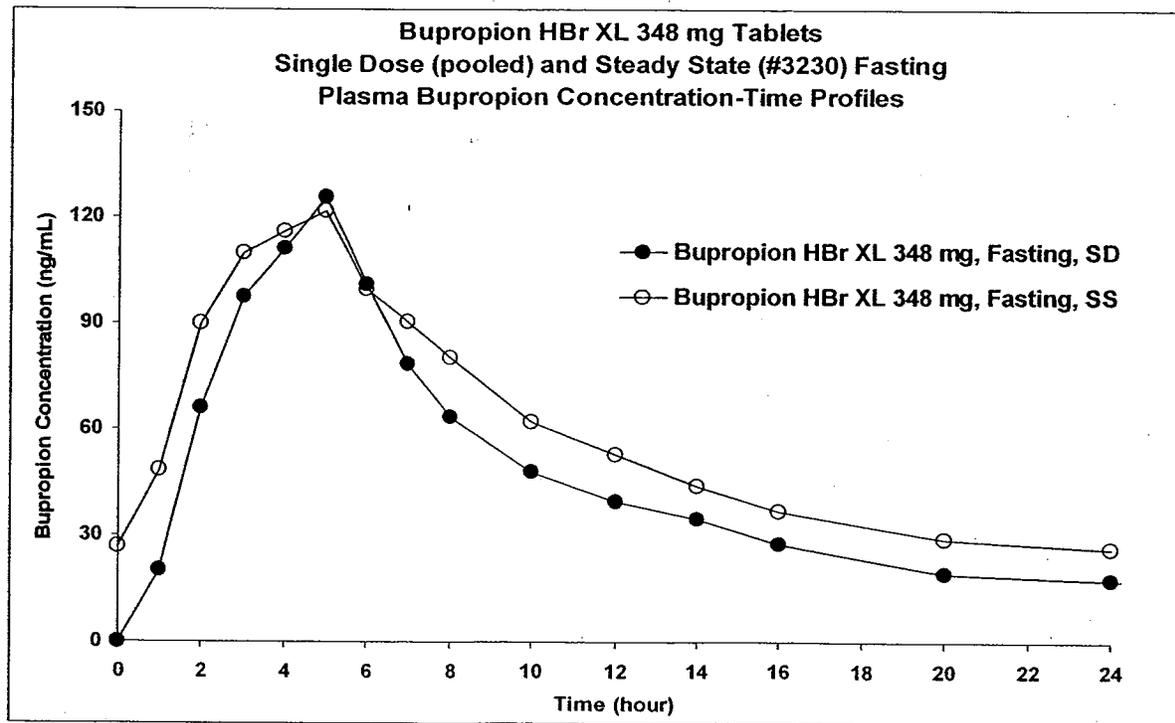
Biovail believes that the above factors make our cross-study comparison more valid than historical data generated from different study sites using different analytical methods. In this context, we are aware of OCPB's prior acceptance of the historical comparison of the PK data of a pharmaceutical alternative (paroxetine mesylate) with multiple dose PK data for a marketed product (paroxetine HCl) in lieu of a head-to-head study.

### 3. Discriminatory Power of Multiple-Dose (Study 3230) versus Single-Dose

While discussing the scientific validity of our steady-state approach with experts in the field, the need to understand the discriminatory power of our steady-state study arose (as it applies to the bupropion drug molecule). This concept, not presented in the Briefing Document, is briefly described.

For bioequivalence studies, in general, single-dose data are more sensitive and, therefore, more discriminatory than multiple-dose data. Of particular relevance is the fact that at steady-state discriminatory power may be lost due to the residual concentration at time zero. The presence of substantial residual concentration, often, reduces the difference between  $C_{max}$  and  $C_{min}$  i.e., the differences in concentration between samples collected during the absorption phase are minimized. This may lead to loss of discriminatory power between subsequent samples. However, in the case of steady-state for bupropion HBr, and indeed bupropion HCl, there is relatively very little residual concentration (concentration at time zero). Indeed, the absorptive phase is as steep as following repeated doses as it is after single doses (Figure 1).

**Figure 1: Comparison of Single- and Multiple-Dose Profiles**



The profiles presented in Figure 1 demonstrate that the difference between  $C_{\max}$  and  $C_{\min}$  is very close for the single and multiple dose studies (assuming  $C_{24h}$  as  $C_{\min}$  in the SD study). The multiple-dose study, therefore, retains the discriminatory power sometimes only seen in the absorption phase following single dose studies.

Biovail therefore believes that conduct of a single-dose study would yield no additional useful data and information beyond that already generated from the multiple-dose study.

Conclusion:

In conclusion, Biovail believes strongly that the information contained in the 505(b)(2) NDA application, as well as the information subsequently supplied to the FDA, are sufficient to obtain your full concurrence on the approvability of our submission. We look forward to discussing this opinion with you in our meeting on August 14<sup>th</sup>, 2007.

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/s/

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Thomas Laughren  
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8/10/07

**Grewal, Renmeet**

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**From:** Grewal, Renmeet  
**Sent:** Friday, August 10, 2007 8:47 AM  
**To:** 'Lidia Mostovy'  
**Subject:** Preliminary Comments for meeting on August 14, 2007

**Attachments:** NDA 22018 PRELIMINARY COMMENTS.pdf

Good Morning Lidia,  
Please find the preliminary comments from our division attached to this email.



NDA 22018  
PRELIMINARY COMMENT

Sincerely,  
Rimmy

---

*Renmeet Grewal, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1080  
Email: renmeet.grewal@fda.hhs.gov  
Fax: (301) 796-9838*

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## FDA Preliminary Responses

NDA 22-108 Bupriopion Hydrobromide

Biovail

Type A meeting

Face-to-Face

The Agency issued a non approvable letter on July 19, 2007 for NDA 22-108 for Bupropion Hydrobromide to treat major depressive disorder. The sponsor requested a meeting on July 20, 2007 and the agency granted the meeting on July 25, 2007 at 3:00pm.

### Participants –

#### **FDA:**

Thomas Laughren, M.D., Division Director

Mitchell Mathis, M.D., Deputy Director

Robert Levin, M.D., Medical Reviewer

Mehul Mehta, Ph.D., Director, Office of Clinical Pharmacology (OCP)

Ramana Uppoor, Ph.D., Deputy Director, OCP

Raman Baweja, Ph.D., Team Leader, OCP

Andre Jackson, Ph.D., Reviewer, OCP

Renmeet Grewal, Pharm.D., Regulatory Project Manager

#### **Biovail:**

Michel Chouinard, Chief Operating Officer, Biovail Laboratories, International, SRL

Gilbert Godin, MBA, Executive Vice-President & Chief Operating Officer, Biovail Corp.

Peter Silverstone, M.D., Senior Vice-President, Medical & Scientific Affairs, Biovail Corp.

Okpo Eradiri, Ph.D., Vice-President, Pharmacology/Toxicology

Robert Ashworth, Ph.D.- Vice-President, Regulatory Affairs

Lidia Mostovy- Director, Regulatory Affairs

#### **Background:**

Biovail submitted NDA 22-108 on September 27, 2006 for bupropion hydrobromide to treat major depressive disorder. The NDA was submitted with a multiple dose, steady-state bioequivalence study comparing pharmaceutical alternative formulations containing equimolar amounts of the same active moiety. On July 19, 2007 the agency took a non-approvable action regarding this NDA because the sponsor failed to conduct a single dose bioequivalence study. The purpose of this meeting is to provide the sponsor an opportunity to seek further clarification of the basis for FDA's nonapprovable action.

#### **Questions:**

Question 1. Has the CMC review of our April 26 submission been completed?

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**Preliminary Comments:** The CMC review of the April 26<sup>th</sup> submission regarding the new dosage strength has not been completed. It will be reviewed in the new review cycle.

**Discussion at Meeting:**

Question 2. Has the agency accepted our justification for the multiple dose study supporting the 522mg dosage strength?

**Preliminary Comments:** As noted, the 522 mg dosage strength is still under review. Thus, our response to this question will focus on the 348 mg dosage strength that has already been reviewed.

Results from the pooled data (studies 3228 & 3229 in NDA 22108 vs. studies 2548 & 2571 in NDA 21515) gave the following CIs for parent:

C <sub>max</sub>	(81.8-97)
AUC <sub>inf</sub>	(86-102)
AUC <sub>inf</sub>	T/R Ratio=(1607.7/1704.9)=0.94
C <sub>max</sub>	T/R Ratio=(133.4/149)=0.89

Results for the MD study (3220) gave the following CIs for parent:

C <sub>max</sub>	(80.2-92)
AUC <sub>τ</sub>	(84-93.9)
AUC <sub>τ</sub>	T/R Ratio=(1362.44/1541.27)=0.88
C <sub>max</sub>	T/R Ratio=(129.86/151.03)=0.86

- Theory predicts that the range for the C<sub>max</sub> CI should increase from multiple to single dosing. The C<sub>max</sub> CI range is 15 and 12 respectively for the single and multiple dosing studies.
- This increase in the C<sub>max</sub> CI range based upon literature references is to be expected. However, the increase in the lower CI limit following single dosing (i.e., the pooled data) is unexpected.
- The ratio for the fraction of drug which is bioavailable decreases from single to multiple dosing, as defined by the respective T/R AUC ratios, which may be a contributing factor.
- Therefore, these results are difficult to interpret.

These apparent differences in the analyses are difficult to understand if indeed the pooled single dose data is predictive of multiple dose behavior.

The Office of Clinical Pharmacology has consulted with the Office of Biostatistics which has pointed out the following:

The study factor test conducted may address the question related to: [results on HBr salt in first study] vs. [results on HBr in second study], which might give some belief that results from the HBr salt in the two studies are homogeneous. Similarly the study factor for the HCL salt may address [results on HCL salt in first study] vs. [results on HCL salt in second study], which may indicate that results from HCL salt in its two studies are homogeneous. However, there is no test to determine whether results from the two HBr studies are comparable to results from the two HCL studies, unless there was a treatment in common in those studies. Therefore, there is no way of knowing:

1. If there are differences observed between the HBr salt and HCL salt do they really differ or are the differences due to the difference between the studies?
2. If the HBr salt and HCL salt appear to have similar biopharmaceutic properties, this might be due to the fact that they actually differed but the differences were masked by a study effect that went in the opposite direction?

**Discussion at Meeting:**

Question 3. Will the Agency review our submission of our proposed tradename regardless of the timing of a complete response?

**Preliminary Comments:** The agency is currently reviewing the proposed tradenames which you have proposed. Once we have come to a conclusion we will forward you the comments from DMETS.

**Discussion at Meeting:**

***General Comments:***

***This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion during the teleconference scheduled for August 14, 2007 between Biovail and the Division of Psychiatry Products. This material is shared to promote a collaborative and successful discussion at the teleconference. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Renmeet Grewal, Pharm.D.). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to [your development plan/the purpose of the meeting/to the questions] (based on our responses herein), we may not be prepared to discuss or reach agreement on such***

*changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact Renmeet Grewal, Pharm.D., at [renmeet.grewal@fda.hhs.gov](mailto:renmeet.grewal@fda.hhs.gov) to discuss the possibility of including these for discussion at the meeting.*

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/s/

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Renmeet Grewal  
8/10/2007 08:54:13 AM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-108

Biovail Technologies, Ltd.  
Attention: Lidia D. Mostovy Director,  
Regulatory Liaison, CNS and Pain  
700 Route 202/206 North  
Bridgewater, NJ 08807

Dear Ms. Motovy:

Please refer to your new drug application (NDA) dated September 27, 2006, received September 28, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for bupropion hydrobromide 174mg & 348mg extended release tablets.

We acknowledge receipt of your submissions dated November 15, 2006, December 22, 2006, April 13, 2007, and May 24, 2007.

We also acknowledge receipt of your submission dated April 26, 2007, June 6, 2007, June 28, 2007, July 3, 2007, and July 10, 2007. These submission were not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

**Nonapproval Deficiencies**

Single dose bioequivalence study

The relative BA study conducted in this NDA, to compare bupropion hydrobromide and bupropion hydrochloride modified release formulations, was a multiple dose study. It should be noted that a multiple dose comparison minimizes differences in formulations and therefore is not the appropriate test. In this case, where both the test (the HBr salt) and reference (HCl salt) are modified release formulations, a single dose bioequivalence study provides the most sensitive conditions for testing similarity of test and reference formulations and therefore, the Agency requires a single dose, fasting bioequivalence study evaluating these two formulations in a minimum of 24 subjects. The parent and only the 4- hydroxybupropion metabolite should be measured and reported with the understanding that bioequivalence consideration will be based only on the parent drug.

Additionally, we have the following comments and requests that will need to be addressed in your resubmission.

**Office of Clinical Pharmacology and Biopharmaceutics**

We ask that you agree to the following final dissolution method and specification for all strengths:

**Dissolution**

Medium: 900 ml 0.1N HCl  
Apparatus I: Basket  
Speed: 75 rpm

**FDA proposed dissolution specifications**

2 hours NMT dissolved  
4 hours dissolved  
8 hours NLT dissolved

b(4)

**Chemistry Manufacturing & Control (CMC)**

1. Please be advised that FDA sent Deficiency Comments to \_\_\_\_\_ holder of DMF \_\_\_\_\_ which you are cross-referencing for the drug substance information.
2. Provide the USAN/INN name for hydrobromide salt of the bupropion. The application form for USAN name can be found in the USAN Dictionary.
3. Include a test and limit for particle size distribution, and limits for bulk and tapped densities in the drug substance specifications, and provide appropriate justification for the proposed limits. Limits for particle size distribution should be based on the results for drug substance batches used in the clinical studies.
4. Provide data to demonstrate that impurity \_\_\_\_\_ with a genotoxic threat, has been adequately tested in appropriate *in vitro* genotoxicity assays, and shown to be non-genotoxic; or limit this impurity in the drug substance to an acceptance criterion that would result in a daily exposure of NMT \_\_\_\_\_ in the drug product, and provide appropriate validation data to demonstrate that the analytical procedure is capable of quantifying this impurity at the revised lower level.
5. Provide information on the level of the photo degradation impurity \_\_\_\_\_ in the drug substance batches.
6. Provide information on the source of the impurity reference standards photo-impurity \_\_\_\_\_ and commercial source of the impurity \_\_\_\_\_; and provide CoAs of these impurity standards. Provide a chemical structure of the photoimpurity \_\_\_\_\_ if available.
7. Include \_\_\_\_\_ statement on the container label for the bulk drug substance Bupropion HBr, and on the container label for the bulk drug product, Bupropion HBr XL Tablets, 174 mg and 348 mg.
8. Justify wide in-process control limits \_\_\_\_\_ for Bupropion HBr XL uncoated Tablets and its impact on the dissolution of the Bupropion HBr XL Tablets.

b(4)

b(4)

b(4)

b(4)

9. Separate description of the 174 mg tablets from that of 348 mg tablets in the same table in the drug product specifications. Send a sample of the imprinted tablets (174 mg and 348 mg) to demonstrate the imprinting of "BR" over "174" or "348" in black ink. Explain when (in what case) the \_\_\_\_\_ ) is planned to be used. **b(4)**
10. The identification test based on retention time in HPLC method is not a specific test. Include an additional identification test in the drug product specifications, that is based on different physico-chemical characteristics of the drug substance (refer to ICH Guidance Q6A).
11. Decrease the limit for impurity \_\_\_\_\_ in the drug product specification to that accepted in the USP Monograph for Bupropion Hydrochloride Extended Release Tablets, i.e., \_\_\_\_\_ or justify the limit of \_\_\_\_\_ that you are proposing. **b(4)**
12. Establish a definite limit for moisture content in the drug product specification.
13. Include a microbial limits in the drug product specification, or, otherwise, provide rationale for not including this parameter in the specification.
14. Provide commitment to optimize HPLC method for Assay and Impurities in order to obtain a distinct separation of the diluent and impurity \_\_\_\_\_ peaks. The usage of the summed peak value for % diluent peak + impurity \_\_\_\_\_ is not acceptable to quantify the impurity \_\_\_\_\_, and to validate HPLC method for this impurity. **b(4)**
15. Provide numeric values for individual unspecified impurities in the drug product batches at the release and stability testing.
16. Provide information on the secondary packaging for \_\_\_\_\_ bottles, if applicable. Provide packaging information for the bulk drug product. **b(4)**
17. We have noticed that only one lot of Bupropion HBr drug substance manufactured \_\_\_\_\_ was used to manufacture all Bupropion HBr XL Tablets of both strengths, 174 mg and 348 mg. The ICH Guidance Q1A(R2) recommends that multiple drug substance batches should be used to manufacture primary stability batches of the drug product. Provide additional stability data generated from drug product batches manufactured using different drug substance batches. **b(4)**
18. Change the chemical name of Bupropion HBr to : (±)-2-(tert-butylamino)-3'- chloropropiophenone Hydrobromide in the Description Section of the Package Insert.
19. Remove \_\_\_\_\_ from the name of excipient ethylcellulose aqueous dispersion in the Description Section of the Package Insert. **b(4)**
20. Provide information on the carton labels (secondary packaging) for Bupropion HBr tablets, if applicable.

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**Nomenclature**

We do acknowledge your submission dated July 12, 2007 asking the agency to retract your request for your initial tradename. The agency also acknowledges your request for a new tradename to be reviewed.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Renmeet Grewal, Pharm.D., Regulatory Project Manager, at (301) 301-796-1080.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Thomas Laughren  
7/19/2007 03:47:44 PM

NDA 22-108  
OND/DMETS Meeting: June 6, 2007

b(4)

Attendees:, Denise Toyer, Carol Holquist, Jinhee Jahng, Todd Bridges, Yana Mille, Robert Levin, Grewal, Renmeet and Angela Robinson

Purpose: Discuss concerns regarding \_\_\_\_\_ and other Wellbutrin products co-existing in the marketplace.

- Discussion points:
- What is the benefit of \_\_\_\_\_ ? None were identified at this meeting.
  - overlapping dosage forms: both are extended release
  - same dosage schedule: once daily in the morning
  - bioequivalent dosing (i.e. \_\_\_\_\_ 174 mg = Wellbutrin XL 50 mg, etc)
    - overlapping indications: Major Depressive Disorder
- Current safety issues with Bupropion (name, strengths, etc.)
- Increase confusion with existing Wellbutrin product line (i.e. Wellbutrin, Wellbutrin SR, Wellbutrin XL). Additionally, there is potential for error in the whole medication use system (i.e prescribing, dispensing, administration).

b(4)



b(4)

- Would allowing this product to enter the marketplace start a precedent of using modifiers to indicate compound, not release?

Action items:

- DMETS will check patent/trademark
- RD will meet with OND team to discuss issues and will f/u with OSE.

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/s/

-----  
Angela Robinson

7/3/2007 12:36:52 PM



NDA 22-108

INFORMATION REQUEST LETTER

Keller and Heckman LLP  
Attention: John B. Dubeck, US Agent for  
Biovail Laboratories International SRL  
1001 G Street NW Suite 500W  
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your September 27, 2006 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for bupropion hydrobromide extended-release tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response in order to continue our evaluation of your NDA:

1. Please be advised that FDA sent Deficiency Comments to \_\_\_\_\_ which you are cross-referencing for the drug substance information. The approval of the NDA from the CMC standpoint is contingent on the satisfactory resolution of the CMC deficiencies. **b(4)**
2. Provide the USAN/INN name for hydrobromide salt of the bupropion. The application form for USAN name can be found in the USAN Dictionary.
3. Include a test and limit for particle size distribution, and limits for bulk and tapped densities in the drug substance specifications, and provide appropriate justification for the proposed limits. Limits for particle size distribution should be based on the results for drug substance batches used in the clinical studies.
4. Provide data to demonstrate that impurity \_\_\_\_\_ with a genotoxic threat, has been adequately tested in appropriate in vitro genotoxicity assays, and shown to be non-genotoxic; or limit this impurity in the drug substance to an acceptance criterion that would result in a daily exposure of NMT \_\_\_\_\_ in the drug product, and provide appropriate validation data to demonstrate that the analytical procedure is capable of quantifying this impurity at the revised lower level. **b(4)**
5. Provide information on the level of the photo degradation impurity \_\_\_\_\_ in the drug substance batches.

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6. Provide information on the source of the impurity reference standards \_\_\_\_\_ photo-impurity \_\_\_\_\_ and commercial source of the impurity \_\_\_\_\_ and provide Certificates of Analysis (CoAs) of these impurity standards. Provide a chemical structure of the photo-impurity \_\_\_\_\_ if available. b(4)
7. Include \_\_\_\_\_ statement on the container label for the bulk drug substance Bupropion HBr, and on the container label for the bulk drug product, Bupropion HBr XL Tablets, 174 mg and 348 mg.
8. Justify wide in-process control limits \_\_\_\_\_ for Bupropion HBr XL uncoated Tablets and its impact on the dissolution of the Bupropion HBr XL Tablets. b(4)
9. Separate description of the 174 mg tablets from that of 348 mg tablets in the same table in the drug product specifications. Send a sample of the imprinted tablets (174 mg and 348 mg) to demonstrate the imprinting of "BR" over "174" or "348" in black ink. Explain when (in what case, \_\_\_\_\_) is planned to be used. b(4)
10. The identification test based on retention time in HPLC method is not a specific test. Include an additional identification test in the drug product specifications, that is based on different physico-chemical characteristics of the drug substance (refer to ICH Guidance Q6A).
11. Decrease the limit for impurity \_\_\_\_\_ in the drug product specification to that accepted in the USP Monograph for Bupropion Hydrochloride Extended Release Tablets, i.e., \_\_\_\_\_ or justify the limit of \_\_\_\_\_ that you are proposing. b(4)
12. Establish a definite limit for moisture content in the drug product specification.
13. Include microbial limits in the drug product specification, or, otherwise, provide rationale for not including this parameter in the specification.
14. Provide commitment to optimize HPLC method for Assay and Impurities in order to obtain a distinct separation of the diluent and impurity \_\_\_\_\_ peaks. The usage of the summed peak value for % diluent peak + impurity \_\_\_\_\_ is not acceptable to quantify the impurity \_\_\_\_\_ and to validate HPLC method for this impurity. b(4)
15. Provide numeric values for individual unspecified impurities in the drug product batches at the release and stability testing.
16. Provide information on the secondary packaging for \_\_\_\_\_ bottles, if applicable. Provide packaging information for the bulk drug product. b(4)
17. We have noticed that only one lot of Bupropion HBr drug substance manufactured \_\_\_\_\_ was used to manufacture all Bupropion HBr XL Tablets of both strengths, 174 mg and 348 mg. The ICH Guidance Q1A(R2) recommends that multiple drug substance batches should be used to manufacture primary stability batches of the drug product. Provide additional stability data generated from drug product batches manufactured using different drug substance batches.

Regarding the Labeling and Package Insert:

18. Change the chemical name of Bupropion HBr to: (±)-2-(tert-butylamino)-3'-chloropropiophenone hydrobromide in the Description Section of the Package Insert.
19. Remove \_\_\_\_\_ from the name of excipient ethylcellulose aqueous dispersion in the Description Section of the Package Insert.
20. Provide information on the carton labels (secondary packaging) for Bupropion HBr tablets, if applicable.

b(4)

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at 301-796-2055.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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Ramesh Sood

6/12/2007 01:52:08 PM

5-31-07

## Grewal, Renmeet

---

**From:** Grewal, Renmeet  
**Sent:** Thursday, May 31, 2007 3:42 PM  
**To:** 'Lidia Mostovy'  
**Cc:** Grewal, Renmeet  
**Subject:** NDA 22-108 Information Request

**Importance:** High

Good Afternoon Lidia,

Regarding your NDA 22-108 we are requesting you to delete the Bupropion Erythoamino Alcohol (BEA) levels for subjects #022 and #023 and the analysis repeated as stated in item #3 on the 483 also copied below. Please submit this information as soon as possible.

3. Concentrations of the quality control samples (QCs) for Bupropion Erythoamino Alcohol (BEA) used in the analytical runs are not relevant to the BEA concentrations observed in plasma samples of study subjects. For example, the mean peak concentrations (C<sub>max</sub>) for BEA from study subjects following drug administration are 103.9±28.4 ng/ml for the test product and 11.4 ± 26.3 ng/ml for the reference product, but the BEA QCs used to monitor performance of analytical runs are 3 ng/ml (low QC), 192 ng/ml (mid QC), and 768 ng/ml (high QC).

Sincerely,  
Rimmy

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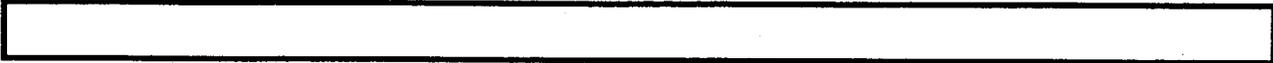
*Renmeet Grewal, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1080  
Email: [renmeet.grewal@fda.hhs.gov](mailto:renmeet.grewal@fda.hhs.gov)  
Fax: (301) 796-9838*

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/s/

-----  
Renmeet Grewal  
5/31/2007 03:48:34 PM  
CSO



**DSI CONSULT**

**Request for Biopharmaceutical Inspections**

**DATE:** October 5, 2006

**TO:** C.T. Viswanathan, M.D.  
Division of Scientific Investigations, HFD-48

**THROUGH:** Thomas Laughren, M.D.  
Director, Division of Psychiatry Products, HFD-130

**FROM:** Renmeet Gujral, Pharm.D., Regulatory Project Manager, HFD-130

**SUBJECT:** **Request for Biopharmaceutical Inspections**  
NDA 22-108  
Bupropion Hydrobromide Extended Release Tablets  
(174mg & 348mg)  
Indication: Treatment of Major Depressive Disorder

**Study/Site Identification:**

As discussed with you, the following sites pivotal to approval have been identified for inspection:

**Clinical sites: Biovail Contract Research**

- 1. 460 Comstock Road, Toronto, Ontario, Canada M1L 4S4
- 2. 689 Warden Ave., Units 1 and 2, Toronto, Ontario, Canada M1L 4R6

**Analytical site: Biovail Contract Research**

- 1. 460 Comstock Road, Toronto, Ontario, Canada M1L 4S4

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  X   Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

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/s/

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Thomas Laughren  
10/6/2006 01:46:36 PM

MEMORANDUM

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

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DATE: May 29, 2007

TO: Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products (DPP)

FROM: Martin K. Yau, Ph.D.  
Pharmacologist  
Division of Scientific Investigations (HFD-48)

THROUGH: *for* C.T. Viswanathan, Ph.D. *Tom Laughren 5/30/07*  
Associate Director - Bioequivalence  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of an EIR Covering NDA 22-108  
Bupropion Hydrobromide Extended Release 174 mg and 348  
mg Tablets Sponsored by Biovail Laboratories  
International SRL, c/o Biovail Technologies, Ltd,  
Chantilly, VA

At the request of the Division of Psychiatry Products (DPP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the following bioequivalence study:

**Study 3230**

**(B06-756PK-10121)**: "A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Comparative Bioavailability Study of Bupropion HBr XL 348 mg Tablets versus Wellbutrin® XL 300 mg Tablets in Normal, Healthy, Non-Smoking Male and Female Subjects".

The clinical portion of Study 3230 was conducted at Biovail Contract Research (BCR), 689 Warden Avenue, Toronto, Ontario, Canada. The analytical portion of the study was conducted at BCR, 460 Comstock Road, Toronto, Ontario, Canada. Please note that BCR also has a clinical unit at 460 Comstock Road, Toronto, Canada and the BCR clinical staff work and support both clinical units at Warden Avenue and at Comstock Road. For Study 3230, the dosing of subjects and processing of blood samples obtained in the study took place at the Warden Avenue clinical unit, which is located within two miles from the Comstock site. Following

the inspection at BCR (May 7 - 10, 2007), a Form FDA-483 was issued (Attachment 1). The evaluation of the significant findings of the inspection follows:

Biovail Contract Research, Toronto, Ontario, Canada:

1. The firm did not include all data in their final pharmacokinetic and statistical analyses. Specifically, data for subjects #019 and #033 were excluded when their bupropion and active metabolite levels were found to be either very low or below the limit of quantitation (LOQ) following drug administration. An investigation by the principal investigator (PI) failed to identify a root cause. During the interview with the PI, both subjects #019 and #033 stated they ingested the study drugs as directed and denied any noncompliance.

During the inspection, the FDA investigators confirmed that the BCR clinical staff conducted a mouth check for all subjects shortly after dose administration to assure each subject swallowed the study drug. The mouth checks conducted for subjects #019 and 033 were negative. However, BCS is still of the opinion that subjects #019 and 033 might have hidden the medication in their mouth and discarded it after the mouth check, thus resulting in the very low levels of bupropion and its active metabolites. Due to the incidence cited in the above 483 observation, BCR is now requiring, in their current studies, a second mouth check within 1 to 5 minutes after dosing when requested by a study sponsor.

When inquired by the FDA investigators, BCR acknowledged that subjects #019 and 033 had participated in BCR studies previously and both subjects did not have a history of non-compliance. Furthermore, as cited in the above 483 observation, subjects #019 and #033 denied any noncompliance. It should also be noted that Study #3230 was a multiple-dose BE study. For subjects 019 (Period 2) and 033 (Period 2), all pre-dose samples collected on Days 10, 11, 12, 13, and all post-dose plasma samples collected on Day 13 were very low relative to other subjects, or below LOQ. The pharmacokinetic profiles observed in subjects #019 (Period 2) and #033 (Period 2) would require dosing non-compliances on multiple occasions (This seems to be a highly unlikely scenario). The FDA investigators also noted that both subjects 019 and 033 ingested the reference drug product and not the test product in Period 2.

To investigate if the unexpected results noted above were due to analytical errors, the analytical runs that analyzed all the plasma samples from subjects #019 (Run name: BUPR3230subj019,020; date of analysis: May 28, 2006) and #033 (Run name: BUPR3230subj032,033; date of analysis: June 1, 2006) were audited carefully. Our audit, however, suggests that the root cause is not due to analytical issues, because the calibration curves and QC results for bupropion and its three active metabolites (bupropion erythroamino alcohol, bupropion threoamino alcohol, and hydroxybupropion) in these two runs met the run acceptance criteria, and no significant interferences were noted in the peaks of all the analytes. Moreover, all the analytes and the internal standard exhibited normal retention times and good chromatograms, and no sample processing errors were reported by BCR.

**2. The firm failed to include in the analytical report all valid precision and accuracy (PA) data generated during a partial assay re-validation in June 2006 following completion of all sample analyses. Specifically, the precision and accuracy of the assay was re-validated by Biovail Bioanalytical Laboratory due to a deviation in the method SOP (i.e., the concentration of the internal standard solution used in all analytical runs was 10 times higher due to a preparation error.) Four PA runs were conducted during the re-validation. PA Runs # 1, 2, and 4 yielded good results and were included in the analytical report. PA Run #3 yielded poor results and was excluded without a valid reason.**

Upon the request of the FDA investigators, BCR recalculated the assay precision and accuracy by including results from all four PA runs conducted during the partial re-validation in June 2006. The results are summarized in Attachment 2. The overall inter-assay inaccuracy for bupropion and its three active metabolites were higher than originally reported, but the assay inaccuracy (i.e., deviations from the nominal values) remained < 15% for all the analytes. The overall inter-assay imprecision for bupropion and its three active metabolites were also higher than originally reported. However, one active metabolite (hydroxybupropion) exhibited unacceptable assay imprecision (i.e. >15% CV). Specifically, the overall inter-assay imprecision for the active metabolite, hydroxybupropion, at LLOQ was 20.1% CV.

**3. Concentrations of the quality control samples (QCs) for Bupropion Erythroamino Alcohol (BEA; a bupropion active**

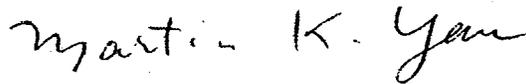
metabolite) used in the analytical runs are not relevant to the BEA concentrations observed in plasma samples of study subjects. For example, the mean peak concentrations (C<sub>max</sub>) for BEA from study subjects following drug administration are 103±28.4 ng/ml for the test product and 111.4±26.3 ng/ml for the reference product, but the BEA QCs used to monitor performance of analytical runs are 3 ng/ml (low QC), 192 ng/ml (mid QC), and 768 ng/ml (high QC).

DSI is concerned that the QCs for BEA employed in the analytical runs are not relevant to BEA concentrations observed in study subjects. Of particular concern is one analytical run conducted on 5/29/2006 (Run BUPR3230subj022,023) where 50% of the QCs in both the low and mid concentrations failed the acceptance criteria. DSI is of the opinion that the BEA data generated in this run for subjects 022 and 023 are not reliable.

Conclusions:

1. The OCP reviewer should decide whether the Period 2 data from subjects 019 and 033 should be excluded from the bioequivalence determination. The FDA inspection at BCR found no evidence of dosing non-compliance, and no analytical problems were identified in the analysis of the plasma samples from Subjects 019 and 033.
2. The BEA data for subjects 022 and 023 are not reliable due to the objectionable finding discussed in 483 Item 3.
3. The assay is not adequately re-validated at LLOQ (1 ng/ml) for the active metabolite, hydroxybupropion. However, this should not have a significant impact on the study results as majority of the hydroxybupropion data are higher than the LLOQ.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

  
Martin K. Yau, Ph.D.

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**DSI Final Classification:**

**VAI - Biovail Contract Research at 460 Comstock Road and 689  
Warden Avenue, Toronto, Ontario, Canada,**

**cc:**

HFD-45/RF

HFD-48/Yau/Himaya/cf

OND/DPP/Grewal

OTS/OCP/Baweja

HFR-NE1500/Steyert

Draft: MKY 5/29/07

DSI:5731; O:\BE\EIRCOVER\22-108biovail.bup

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/s/

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Amalia Himaya  
5/30/2007 10:14:38 AM  
CSO

Jacqueline OShaughnessy  
5/30/2007 01:08:29 PM  
PHARMACOLOGIST  
On behalf of Dr. Viswanathan

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857**FILING COMMUNICATION**

NDA 22-108

Biovail Technologies, Ltd.  
Attention: Lidia D. Mostovy Director,  
Regulatory Liaison, CNS and Pain  
700 Route 202/206 North  
Bridgewater, NJ 08807

Dear Ms. Mostovy:

Please refer to your September 27, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrobromide Extended-Release Tablets 174mg and 348mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 27, 2006 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Renmeet Grewal, Regulatory Project Manager, at (301) 796-1080.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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11/21/06

**From:** Grewal, Renmeet  
**To:** "Lidia Mostovy";  
**CC:** Grewal, Renmeet; Bender, William;  
**Subject:** RE: NDA 22-108; Bupropion Hydrobromide Extended-Release Tablets  
**Date:** Monday, November 27, 2006 1:09:51 PM  
**Attachments:**

---

Hi Lidia,  
The NDA is filable. You will be receiving a letter in the mail shortly.  
Sincerely,  
Rimmy

---

*Renmeet Grewal, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1080  
Email: [renmeet.grewal@fda.hhs.gov](mailto:renmeet.grewal@fda.hhs.gov)  
Fax: (301) 796-9838*

---

**From:** Lidia Mostovy [<mailto:Lidia.Mostovy@biovail.com>]  
**Sent:** Wednesday, November 22, 2006 12:19 PM  
**To:** Grewal, Renmeet  
**Subject:** NDA 22-108; Bupropion Hydrobromide Extended-Release Tablets

Hi Renmeet,

As you know, today was the filing date listed on our acknowledgement letter for the above-listed application. Is there any way that you can tell me what the status of the application is?

Lidia

---

The information contained in this e-mail message may be privileged and confidential information and is intended only for the use of the individual and/or entity identified in the address of this message. If the reader of this message is not the intended recipient, or an employee or agent responsible to deliver it to the intended recipient, you are hereby requested not to distribute or copy this communication. If you have received this communication in error, please notify us immediately by return e-mail. In this circumstance, we request that you delete the original message from your system.

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/s/

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Renmeet Grewal  
11/27/2006 01:19:30 PM  
CSO

**From:** Grewal, Renmeet  
**To:** Viswanathan, CT; Himaya, Amalia; Yau, Martin K;  
**CC:** Bender, William; Grewal, Renmeet;  
**Subject:** FW: New NDA 22108, Bupropion Hydrobromide, Biovail - Request for Inspection of a Biostudy  
**Date:** Wednesday, November 15, 2006 12:20:33 PM  
**Attachments:**

---

Hello DSI team,

OCP requests the inspection of a Biostudy for this NDA. Please forward this request from the clinical division to DSI. The details of the study are as follows:

Study Number 3230 (B06-756PK-10121)

Title: A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Comparative Bioavailability Study of Bupropion HBr XL 348 mg Tablets versus Wellbutrin XL 300 mg Tablets in Normal, Healthy, Non-Smoking Male and Female Subjects

The NDA is in the Electronic Document Room, here is the link: \\CDSESUB1\N22108\N\_000\2006-09-27

DSI report deadline: 5/9/07

Sincerely,  
Rimmy

-----  
*Renmeet Grewal, Pharm.D., LCDR USPHS  
 Regulatory Project Manager  
 Division of Psychiatry Products  
 Center For Drug Evaluation and Research, FDA  
 Office of Drug Evaluation I  
 Ph: (301) 796-1080  
 Email: renmeet.grewal@fda.hhs.gov  
 Fax: (301) 796-9838*

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/s/

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Renmeet Grewal  
11/15/2006 12:36:06 PM  
CSO



NDA 22-108

INFORMATION REQUEST LETTER

Biovail Technologies, Ltd.  
Attention: Lidia D. Mostovy Director,  
Regulatory Liaison  
CNS and Pain  
Biovail Technologies, Ltd.  
700 Route 202/206 North  
Bridgewater, NJ 08807

Dear Ms. Mostovy:

Please refer to your September 27, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bupropion hydrobromide extended-release tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by November 22, 2006 in order to timely evaluate your NDA within the PDUFA review time frame.

Please provide confirmation that the following manufacturing facilities are the only facilities involved in the manufacturing, release and analytical testing, packaging and labeling of the drug substance (bupropion hydrobromide) and drug product (bupropion hydrobromide extended-release tablets):

Manufacturer of the Drug Substance:

Manufacturer of the Drug Product:

Biovail Corporation,  
Manufacturing Division,  
100 LifeSciences Parkway,  
Steinbach, Manitoba,  
CANADA

b(4)

You should also provide the CFN numbers for these facilities.

Provide information (address, CFN number and contact information) for any additional facility involved in the operations mentioned above related to the production of the drug substance and drug product.

NDA 22-108  
CMC IR Letter 1  
Page 2

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at 301-796-2055.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

cc:  
Keller and Heckman LLP  
Attention: John B. Dubeck, US Agent for  
Biovail Laboratories International SRL  
1001 G Street NW Suite 500W  
Washington, DC 20001

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/s/

-----  
Ramesh Sood  
11/8/2006 01:33:53 PM



NDA 22-108

**NDA ACKNOWLEDGMENT**

Biovail Laboratories International SRL  
Attention: John Dubeck, U.S. Agent  
Keller and Heckman LLP  
1001 G Street, N.W, Suite 500 West  
Washington, DC 20001

Dear Mr. Dubeck:

We have received your new drug application (NDA) submitted under section 505(b)2 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Bupropion Hydrobromide Extended-Release Tablets,  
174 mg and 348 mg

Review Priority Classification: Standard (S)

Date of Application: September 27, 2006

Date of Receipt: September 28, 2006

Our Reference Number: NDA 22-108

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 27, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 28, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

NDA 22-108

Page 2

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Psychiatry Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call Renmeet Grewal, Regulatory Project Manager, at (301) 796-1080.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, MD.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Thomas Laughren  
10/11/2006 01:56:30 PM

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-108 Supplement # Efficacy Supplement Type SE-

Proprietary Name:  
Established Name: Bupropion Hydrobromide Extended Release Tablets  
Strengths: 174mg & 348mg

Applicant: Biovail  
Agent for Applicant (if applicable):

Date of Application: 9/27/06  
Date of Receipt: 9/28/06  
Date clock started after UN:  
Date of Filing Meeting: 11/14/06  
Filing Date: 11/27/06  
Action Goal Date (optional): User Fee Goal Date: 7/28/07

Indication(s) requested: MDD

Type of Original NDA: (b)(1)  (b)(2) X  
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S X P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 2N  
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO

User Fee Status: Paid Exempt (orphan, government)  505b2  
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as a partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, \_\_\_\_\_ Years NO X  
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**  
*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X Full Waiver NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO X  
If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES X NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO
- PDUFA and Action Goal dates correct in tracking system? YES X NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 73,781
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO   
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ NO X  
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) \_\_\_\_\_ NO X  
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) \_\_\_\_\_ NO X  
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES X NO   
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO X
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES  NO
- Risk Management Plan consulted to OSE/IO? N/A X YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES X NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team? YES  NO

ATTACHMENT  
**MEMO OF FILING MEETING**

DATE: 11/14/06

NDA #: 22-108

DRUG NAMES: Bupropion HBr

APPLICANT: Biovail

**BACKGROUND:**

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

**ATTENDEES:**

**ASSIGNED REVIEWERS (including those not present at filing meeting) :**

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Bob Levin
Secondary Medical:	
Statistical:	
Pharmacology:	
Statistical Pharmacology:	
Chemistry:	Lyudmila Soldatova, Tom Oliver
Environmental Assessment (if needed):	
Biopharmaceutical:	Kofi Kumi, Ray Baweja
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	C.T. Viswanathan, Amalia Himaya
OPS:	
Regulatory Project Management:	Renmeet Grewal
Other Consults:	

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE

- Clinical site audit(s) needed? YES  NO   
If no, explain: depended on biopharmaceutical studies therefore Biopharm site audited
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS	N/A	X	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
BIOPHARMACEUTICS			FILE	X	REFUSE TO FILE	<input type="checkbox"/>
					X	NO <input type="checkbox"/>
• Biopharm. study site audits(s) needed? YES						
PHARMACOLOGY/TOX	N/A	X	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
					YES	<input type="checkbox"/>
• GLP audit needed? NO <input type="checkbox"/>						
CHEMISTRY			FILE	X	REFUSE TO FILE	<input type="checkbox"/>
					YES	<input type="checkbox"/>
• Establishment(s) ready for inspection? NO <input type="checkbox"/>						
					YES	<input type="checkbox"/>
• Sterile product? NO <input type="checkbox"/>						
					YES	<input type="checkbox"/>
If yes, was microbiology consulted for validation of sterilization? NO <input type="checkbox"/>						

ELECTRONIC SUBMISSION:  
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:  
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5.  Convey document filing issues/no filing issues to applicant by Day 74.

Renmeet Grewal, Pharm.D.  
Regulatory Project Manager  
Version 6/14/2006

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES X NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 21-515;  
Wellbutrin XL

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES  NO X

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES  NO X

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES  NO X

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES X NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES X NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES X NO

*If "Yes," to (c), proceed to question 7.*

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES  NO X

*If "No," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application has a new salt (hydrobromide)

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES  NO X

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES  NO X

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES  NO
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES  NO
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

Not applicable (e.g., solely based on published literature. See question # 7

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s): 6096341, 6143327

**NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must *subsequently* submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES  NO

*If "Yes," what is the listed drug product(s) Wellbutrin XL and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug Clinical Pharmacology*

*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES  NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A  YES  NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration
21-515	002	1-497	6-12-2009

**Exclusivity is for the new indication of seasonal affective disorder, and the sponsor is not pursuing this claim.**

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/s/

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Renmeet Grewal  
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CSO