

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022497Orig1s000**

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

## EXCLUSIVITY SUMMARY

NDA # 022497

SUPPL # N/A

HFD # 130

Trade Name FORFIVO XL

Generic Name bupropion hydrochloride 450mg extended-release tablets

Applicant Name IntelGenx Corp.

Approval Date, If Known 11/10/2011

### 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 used Wellbutrin XL as a RLD and submitted bioequivalence data to comparing their product (450mg) to the innovator (i.e., 3 x 150mg 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# 021515

WELLBUTRIN XL (bupropion hydrochloride 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: Kofi Ansah, Pharm.D.

Title: Senior Regulatory Project Manager

Date: 11/9/11

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

Title: Director, Division of Psychiatry Products

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KOFI B ANSAH  
11/10/2011

THOMAS P LAUGHREN  
11/10/2011

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 022497 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: FORFIVO XL Established/Proper Name: bupropion hydrochloride 450mg extended-release tablets Dosage Form: Tablets		Applicant: IntelGenx Corp. Agent for Applicant (if applicable): Bethany Hills, JD, MPH, Esq.; Hodgson Russ LLP, The Guaranty Buidling, 140 Pearl Street, Suite 100, Buffalo NY 14202 - 4040
RPM: Kofi Ansah, Pharm.D.		Division: Division of Psychiatry Products
<p><b>NDA:</b> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>WELLBUTRIN XL (bupropion hydrochloride extended-release tablets)</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>This product provides for only one higher strength; the bupropion hydrochloride 450mg extended-release tablets.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input checked="" type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check: 11/10/2011</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>November 13, 2011</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None    CR; 02/3/2010

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics<sup>2</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span>  Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR <span style="margin-left: 200px;">REMS: <input type="checkbox"/> MedGuide</span>  <input type="checkbox"/> Submitted in response to a PMC <span style="margin-left: 200px;"><input type="checkbox"/> Communication Plan</span>  <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 200px;"><input type="checkbox"/> ETASU</span>  <span style="margin-left: 200px;"><input checked="" type="checkbox"/> REMS not required</span></p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes     No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	Yes
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP Letter - November 10, 2011 CR Letter- February 3, 2010
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Identical to labeling agreed upon with sponsor and included with the AP Letter
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	11/9/11 agreed upon labeling (see AP Letter) 09/8/11 revised resubmission label 05/4/11 resubmission labeling 12/17/09 revised original label 03/31/09 original submission label
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	WELLBUTRIN XL; APLENZIN ER

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	see above
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	see above
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	see above
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	11/8/11
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	Acceptability: 09/6/11; 01/19/10 Reviews: 09/6/11; 01/13/10
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 08/23/11 <input checked="" type="checkbox"/> DMEPA 10/13/11 <input checked="" type="checkbox"/> DRISK 10/26/11 <input checked="" type="checkbox"/> DDMAC 10/14/11 <input checked="" type="checkbox"/> SEALD 11/9/11; 11/8/11 <input type="checkbox"/> CSS N/A <input checked="" type="checkbox"/> Other reviews OSE DUR 10/14/11
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	07/23/09
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> Not a (b)(2) 10/17/11 <input type="checkbox"/> Not a (b)(2) 11/10/11
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>September 21, 2011</u> (Peds Page/Record in DARRTS as <u>peds entry</u>) If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	see action package
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A or no mtg 06/10/10 Post-CR Action Meeting (Minutes dated 06/23/11)
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 07/14/08 - EOP2 Meeting (Minutes dated 07/28/11)
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	N/A
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	N/A
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 02/1/10 - DD's memo to CR
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11/9/11 -DDD's Memo
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	
• Clinical review(s) ( <i>indicate date for each review</i> )	10/24/11; 01/29/10
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	In clinical reviews see above
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input type="checkbox"/> None OSE/DRISK review 10/26/11; 03/3/10
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None N/A
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None N/A
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None N/A
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None N/A
Statistical Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None N/A
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/21/11; 01/29/10
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input type="checkbox"/> None 10/5/11; 10/3/11; 06/24/11; 06/17/11; 11/10/09
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11/8/11; 02/5/10 - Pharm/tox Memo
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested N/A

<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 01/29/10 (Summary Basis of Action for 1 <sup>st</sup> Cycle CR)
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None CMC- 09/29/11; 09/2/11; 01/28/10 Biopharmaceutics - 10/18/11; 04/20/10
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed N/A
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None OC Inspection Report - 10/31/11
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	01/28/10 in CMC review (see above dates)
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup>)</i>	Date completed: OC - 11/9/11 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>6</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ADRA.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KOFI B ANSAH  
11/10/2011

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 022497	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: FORFIVO XL Established/Proper Name: Bupropion Hydrochloride Extended-Release Tablets Dosage Form: Extended-Release Tablets Strengths: 450 mg		
Applicant: IntelGenx, Corp.		
Date of Receipt: May 13, 2011		
PDUFA Goal Date: November 13, 2011	Action Goal Date (if different): November 10, 2011	
Proposed Indication(s): Major Depressive Disorder		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Wellbutrin XL Tablets Prescribing Information, manufactured by GlaxoSmithKline (GSK) (now owned by Valeant)	Pharmacokinetic data, prescribing information (all sections)

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)  
Bioavailability and Bioequivalence studies comparing FORFIVO XL to WELLBUTRIN XL.

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO,” proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO



**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Wellbutrin XL (bupropion hydrochloride extended-release) tablets	NDA 021515	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support 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 capsule to solution").

This application provides for a higher strength extended-release (450 mg) tablet formulation.

*The purpose of the following two questions 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.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(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)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(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 listed drug(s) referenced by the application a pharmaceutical equivalent?  
YES  NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(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.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO   
If "NO", proceed to question #12.

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

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
YES  NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): generic bupropion hydrochloride tablets; Wellbutrin SR (NDA 020358); Zyban (NDA 020711) + generic XR tablets; Wellbutrin tablets (NDA 018644 + generic tablets.

**PATENT CERTIFICATION/STATEMENTS**

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 6096341; 10/30/2018

No patents listed  *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) 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.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 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):

Expiry date(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). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

*NDA holder/patent owner, proceed to question #15.*

- 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):  
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s): 6096341
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?  
YES  NO   
*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.  
YES  NO   
*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): 7/3/09 [Received by (b) (4)] and 7/6/09 [Received by GSK]

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

**Comments:** The patent infringement suit was dismissed in a United states District (Delaware) court on February 2, 2011.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KOFI B ANSAH  
11/10/2011

## Ansah, Kofi

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**From:** Ansah, Kofi  
**Sent:** Wednesday, November 09, 2011 4:56 PM  
**To:** 'Nadine Paiement'; 'Nancy Austin'  
**Cc:** 'Hills, Bethany'; 'Horst Zerbe'  
**Subject:** RE: 11-9-11 Agreed upon Labeling -- NDA 022497 /IntelGenX Corp/ FORFIVO XL/MDD

Hi Nadine,

Great -- Noted -- Thank you.

Best Regards,  
Kofi.

---

**From:** Nadine Paiement [mailto:nadine@intelgenx.com]  
**Sent:** Wednesday, November 09, 2011 4:57 PM  
**To:** Ansah, Kofi; 'Nancy Austin'  
**Cc:** 'Hills, Bethany'; 'Horst Zerbe'  
**Subject:** RE: 11-9-11 Agreed upon Labeling -- NDA 022497 /IntelGenX Corp/ FORFIVO XL/MDD

Dear Kofi,

My name is Nadine Paiement and I am the R&D director at Intelgenx and worked with Nancy Austin on the NDA submission. This email is to confirmed reception of your email regarding the agreed upon labelling.

Best regards,

Nadine

Nadine Paiement M.Sc.  
Intelgenx Corp.  
Director R&D  
6425 Abrams, Saint-Laurent  
(Quebec) H4S 1X9  
(514) 331-7440 ext. 205  
fax: 514-331-0436

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**From:** Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]  
**Sent:** Wednesday, November 09, 2011 4:41 PM  
**To:** 'Nancy Austin'  
**Cc:** 'Hills, Bethany'; 'Horst Zerbe'; 'Nadine Paiement'  
**Subject:** 11-9-11 Agreed upon Labeling -- NDA 022497 /IntelGenX Corp/ FORFIVO XL/MDD  
**Importance:** High

Hi Nancy,

We are in agreement on labeling -- Thank you for your prompt response. Attached is the agreed upon Labeling [PI, MG, & Bottle/Catton] in word and pdf. Please note that:

- (i) the reference at the bottom of page 20 of the PI (you mentioned in your email below) has been corrected to be consistent with all the other references in the PI.
- (ii) revision date at the bottom right corner of HL (i.e., page 1) has been inserted (and reads "Revised: 11/2011").

Please acknowledge/confirm receipt of this email ASAP. I will be in touch to give you an update as soon as we take an Action.

Best Regards,  
Kofi.

---

*Kofi Boadu Ansah, R.Ph., Pharm.D.*

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

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---

**From:** Nancy Austin [mailto:[nancy@intelgenx.com](mailto:nancy@intelgenx.com)]

**Sent:** Wednesday, November 09, 2011 11:48 AM

**To:** Ansah, Kofi

**Cc:** 'Hills, Bethany'; 'Horst Zerbe'; 'Nadine Paiement'

**Subject:** RE: 11-8-11 final Proposed Labeling for Agreement -- NDA 022497 /IntelGenX Corp/ FORFIVO XL/MDD

**Importance:** High

Dear Kofi,

As discussed, we have reviewed and Packaging Insert and Medication Guide and are in agreement with all changes. However, would like to draw your attention to the following:

Package Insert (PI):

At the bottom of page 20, the Sponsor has noticed that the cross-reference is capitalized. Please confirm this is a typo error on done on purpose.

The Sponsor would like to provide the PI and the MG as one document.

Medication Guide (MG):

The Sponsor is in agreement with all the changes made to the MG

Bottle/Carton Label:

As discussed, the Sponsor has provided the revised Bottle/Carton Label with the amended NDC number.

Attached to this email is a **cover letter**, an **agreement letter** (Attachment 1), summarizing the above agreement, and the **revised bottle/carton label** (Attachment 2). The attached documents along with a FDA Form 356h will be formally submitted to the central document room later today (11/9).

If you have any questions or need additional information please do not hesitate to contact me.

Best regards,  
Nancy

*Nancy Austin, M.Sc.*  
Regulatory Affairs and Compliance Manager  
IntelGenx Corp.  
6425 Abrams  
Saint-Laurent, Quebec  
H4S 1X9  
T: 514-331-7440 x206  
F: 514-331-0436  
nancy@intelgenx.com  
www.intelgenx.com

---

**From:** Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]  
**Sent:** Wednesday, November 09, 2011 7:48 AM  
**To:** Ansah, Kofi; 'Nancy Austin'  
**Cc:** 'Hills, Bethany'; 'Horst Zerbe'  
**Subject:** RE: 11-8-11 final Proposed Labeling for Agreement -- NDA 022497 /IntelGenX Corp/ FORFIVO XL/MDD

Hi Nancy,

We have decided to delete the highlighted sentence: "[REDACTED] (b) (4)  
[REDACTED]." on page 4 (referred to in my email below). Attached is the revised MG with this sentence deleted.

Please respond to provide confirmation that yes, we have agreement on labeling (PI, MG, & Container/Carton label with corrected NDC 14350-450-01). Please provide your response as soon as possible, preferably no later than noon today.

Thanks,  
Kofi.

---

*Kofi Boadu Ansah, R.Ph., Pharm.D.*  
CDR, US Public Health Service  
Regulatory Project Manager, Division of Psychiatry Products  
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109  
Silver Spring, MD 20993 - 0002  
Phone: (301) 796-4158  
Fax: (301) 796-9838

**Email:** [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

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ember 08, 2011 6:38 PM

: 'Horst Zerbe'  
1 final Proposed Labeling for Agreement -- NDA 022497 /IntelGenX Corp/ FORFIVO XL/MDD

Hello Nancy,

As per our telephone discussion today, please find attached our final proposed labeling for your review and agreement. We have corrected the NDC # in the PI to **14350-450-01** as per your request and note that:

- (i) you will be sending us revised container/carton label that reflects this change with your email response tomorrow (followed by a formal submission of the said label to your NDA).
- (ii) the PI and MG are going to be merged as one complete document.

<< File: 11-8-11 PI\_final\_FDA proposed\_CLEAN -- NDA 022497\_ FORFIVO XL.doc >> << File: 11-8-11 MG\_final\_FDA\_proposed\_CLEAN -- NDA 022497\_ FORFIVO XL.doc >>

Also, I draw your attention to the highlighted sentence on page 4 of the MG. We will be deleting/modifying this sentence after internal discussion tomorrow morning but rather than delay sending you these documents till tomorrow, I am sending them now to give you time to review them. I will update you tomorrow morning as to what changes, if any, we made to this sentence on page 4.

Please be plan to respond with your agreement by noon tomorrow.

Thanks,  
Kofi.

---

*Kofi Boadu Ansah, R.Ph., Pharm.D.*  
CDR, US Public Health Service  
Regulatory Project Manager, Division of Psychiatry Products  
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109  
Silver Spring, MD 20993 - 0002  
Phone: (301) 796-4158  
Fax: (301) 796-9838  
[Email: Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

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/s/  
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KOFI B ANSAH

11/09/2011

agreed upon labeling will be attached to our Action Letter

## Ansah, Kofi

---

**From:** Ansah, Kofi  
**Sent:** Friday, October 28, 2011 5:02 PM  
**To:** 'Hills, Bethany'; 'Nancy Austin'  
**Subject:** Proposed Labeling for Agreement -- NDA 022497 /IntelGenX Corp/ FORFIVO XL/MDD

**Importance:** High

**Attachments:** 10-28-11 PI\_FDA\_proposed\_based on\_09-8-11 \_Sponsor\_revised draft PI -- NDA 022497\_FORFIVO XL.doc; 10-28-11 MG FDA\_proposed\_based on\_Sponsor's\_09-8-11\_draft MG -- NDA 022497\_FORFIVO XL.doc; 09-8-11 Revised Bottle\_Catton LABEL -- NDA 022497\_FORFIVO XL.pdf

Dear Bethany & Nancy:

Attached are our proposed labeling (PI and MG and Bottle/Catton label) for your pending NDA. We have made extensive revisions to the PI and MG based on your 9/8/11 revised draft labeling. Please review the attached documents and make the requested changes noted below and then send them back to us with your revisions/comments in track changes (leaving our comments intact).



10-28-11  
FDA\_proposed\_base



10-28-11 MG  
A\_proposed\_based



09-8-11 Revised  
Bottle\_Catton...

We need you to make the following changes to the attached labeling:

### **A) Package Insert (PI):**

- (i) Revise TOC to ensure that the TOC matches the FPI (with regards to sections & subsections numbers and headings). Note: Medication Guide should not be assigned a subsection number in FPI and should not be listed in TOC.
- (ii) Correct the format of the cross references throughout the FPI as illustrated in the Boxed Warning. Cross references should be in italics, include the section heading (not the subsection heading) and the numerical identifier.
- (iii) Ensure that the toll free # (you've provided for ADR reporting under HL) is either a dedicated line or has a prompt that gives an option to speak to someone dedicated to dealing with ADR reporting.
- (iv) Align the columns in HL so that they are as close to the same length as possible.
- (iv) Provide/ insert the NDC number (as indicated in section 16).

### **B) Medication Guide (MG):**

- (i) Insert phonetic spelling of FORFIVO on the first page as indicated.
- (ii) You can add your web address for FORFIVO XL and a toll free # if you would like the information included in the MG. We recommend a toll free number that is solely dedicated to or have a prompt that is dedicated to patients seeking more information on FORFIVO XL.
- (iii) Add issued Month and Year to the last page of MG as indicated.

**C) Bottle/Catton Label:** Revise this to delete the word (b) (4) (above 450mg) out of the current label.

Please make the requested changes and submit your revised labeling (i.e., PI, MG, and Bottle/Catton labeling) back to us, as promptly as you can, with any comments or questions you may have by noon on Thursday; 11/3/11, and note in your response whether or not we have an agreement on this labeling.

Best Regards,  
Kofi.

---

*Kofi Boadu Ansah, R.Ph., Pharm.D.*

CDR, US Public Health Service  
Regulatory Project Manager, Division of Psychiatry Products  
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109  
Silver Spring, MD 20993 - 0002  
Phone: (301) 796-4158  
Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

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34 Page(s) of Draft Labeling have  
been Withheld in Full as b4 (CCI/TS)  
immediately following this page

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/s/  
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KOFI B ANSAH  
10/30/2011



NDA 22497

**INFORMATION REQUEST**

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

IntelGenx Corp  
Attention: Bethany Hills, JD, MPH, Esq.  
Hodgson Russ LLP  
The Guaranty Building  
140 Pearl Street, Suite 100  
Buffalo, NY 14202-4040

Dear Dr. Hills:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Forfivo XL (bupropion HCl) extended release tablets.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).<sup>1</sup> The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

---

<sup>1</sup> These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

**Please respond to this query within 30 days from the date of this letter.**

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Room 6300  
Silver Spring, MD 20993-0002

If you have any questions, email CAPT Steven D. Hardeman, R.Ph., Chief, Project Management Staff, at [Steven.Hardeman@FDA.HHS.GOV](mailto:Steven.Hardeman@FDA.HHS.GOV).

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/  
-----

STEVEN D HARDEMAN  
09/13/2011  
signed for Dr. Laughren

**Ansah, Kofi**

---

**From:** Ansah, Kofi  
**Sent:** Thursday, September 08, 2011 2:32 PM  
**To:** 'Nancy Austin'; 'Hills, Bethany'  
**Subject:** RE: Follow-up on Para. IV Cert -- NDA 022497/ Bupropion 450mg Extended Release [HODGSONRUSS-BUSINESS.FID2685661]

Dear Nancy,

Thank you for this update. Please formally submit this information to your NDA as a General Correspondence/ Information Amendment.

Best Regards,  
Kofi.

---

*Kofi Boadu Ansah, R.Ph., Pharm.D.*

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

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**From:** Nancy Austin [mailto:[nancy@intelgenx.com](mailto:nancy@intelgenx.com)]  
**Sent:** Thursday, September 08, 2011 9:55 AM  
**To:** 'Hills, Bethany'; Ansah, Kofi  
**Cc:** 'Horst Zerbe'; 'Nadine Paiement'  
**Subject:** RE: Follow-up on Para. IV Cert -- NDA 022497/ Bupropion 450mg Extended Release [HODGSONRUSS-BUSINESS.FID2685661]

Dear Kofi,

This letter is an informal response to the Agency's inquiry regarding the status of the Notice of Paragraph IV Certification for NDA 022497.

Along with this email you will find a letter stating the current status of the Paragraph IV Certification and a copy of the dismissal letter from the United States Court for the District of Delaware.

If these documents are not adequate or must be submitted formally, please advise on how to proceed.

Best regards,  
Nancy

*Nancy Austin, M.Sc.*  
Regulatory Affairs and Compliance Manager  
IntelGenx Corp.  
6425 Abrams  
Saint-Laurent, Quebec  
H4S 1X9  
T: 514-331-7440 x206  
F: 514-331-0436  
nancy@intelgenx.com  
www.intelgenx.com

---

**From:** Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]  
**Sent:** Thursday, September 01, 2011 4:30 PM  
**To:** Hills, Bethany  
**Cc:** 'Nancy Austin'  
**Subject:** Follow-up on Para. IV Cert -- NDA 022497/ Bupropion 450mg Extended Release

Hi Bethany,

Could you please give us an updated status on the infringement suit with regards to your Notice of Para. IV Certification ? If this update was provided in your resubmission, kindly point me to the location of that information in your submission.

Best Regards,  
Kofi.

---

*Kofi Boadu Ansah, R.Ph., Pharm.D.*  
CDR, US Public Health Service  
Regulatory Project Manager, Division of Psychiatry Products  
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109  
Silver Spring, MD 20993 - 0002  
Phone: (301) 796-4158  
Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

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# IntelGen<sub>x</sub> Corp.

September 8, 2011

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**RE: NDA 022497 –RE: Follow-up on Para. IV Cert -- NDA 022497/ Bupropion HCl 450mg  
Extended Release**

ATTN: CDR Kofi Ansah, Pharm. D., Senior Regulatory Project Manager

Dear Dr. Laughren,

Please refer to the email sent by CDR Kofi Ansah, Pharm. D., Senior Regulatory Project Manager, on September 1, 2011. The letter requested that the Sponsor provide an update on the status of the infringement suit with regards to the Sponsor's Notice of Paragraph IV Certification.

In response to this inquiry, please refer to the Amendment dated (August 19, 2009) to NDA 022497 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FORFIVO XL (bupropion hydrochloride 450 mg extended-release tablet). In this Amendment, the Sponsor had informed the Agency that in response to the Sponsor's Paragraph IV Certification, Valeant Pharmaceuticals International (the company formerly known as Biovail Laboratories International SLR) on August 13, 2009 launched a patent infringement suit against IntelGenx Corp. (the Sponsor) in the United States District Court for the District of Delaware (Case No. 09-605-LPS). Since then, a "Dismissal without Prejudice" was issued by the court on February 2, 2011. Enclosed with this letter you will find a copy of the Dismissal Letter from the United States District Court for the District of Delaware.

Please reach me at 514-331-7440 (ext. 206) if you have questions or need additional information. We look forward to working with you and thank you very much for your assistance.

Sincerely yours,



Manager, Regulatory Affairs and Compliance

cc: Bethany Hills Esq., Attorney at Senior Associate Hodgson Russ LLP and U.S. Agent

6425 Abrams • Saint-Laurent (Quebec) • H4S 1X9  
Tel.: (514)331-7440 • Facsimile: (514)331-0436  
[www.intelgenx.com](http://www.intelgenx.com)

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

BIOVAIL LABORATORIES	)	
INTERNATIONAL SLR,	)	
	)	
Plaintiff,	)	
	)	C.A. No. 09-605-LPS
v.	)	
	)	
INTELGENX CORP.,	)	
	)	
Defendant.	)	

**STIPULATION AND ORDER FOR DISMISSAL WITHOUT PREJUDICE**

Plaintiff Biovail Laboratories International SLR and Defendant IntelGenx Corp., through their respective counsel, respectfully stipulate to the dismissal without prejudice of this action and all claims therein, pursuant to Rule 41(a)(1)(A)(ii) of the Federal Rules of Civil Procedure, with each party bearing its own costs, expenses, and attorneys' fees.

POTTER ANDERSON & CORROON LLP                      RICHARDS, LAYTON & FINGER, P.A.

By: /s/ David E. Moore  
Richard L. Horwitz (#2246)  
David E. Moore (#3983)  
Hercules Plaza, 6th Floor  
1313 N. Market Street  
Wilmington, DE 19801  
Telephone: 302.984.6027  
[rhoorwitz@potteranderson.com](mailto:rhoorwitz@potteranderson.com)  
[dmoore@potteranderson.com](mailto:dmoore@potteranderson.com)

By: /s/ Frederick L. Cottrell, III  
Frederick L. Cottrell, III (#2555)  
Laura Hatcher (#5098)  
One Rodney Square  
920 N. King Street  
Wilmington, DE 19801  
Telephone: 302.651.7700  
[Cottrell@rlf.com](mailto:Cottrell@rlf.com)  
[hatcher@rlf.com](mailto:hatcher@rlf.com)

*Attorneys for Plaintiff Biovail Laboratories  
International SLR*

*Attorneys for Defendant IntelGenx Corp.*

IT IS SO ORDERED this 2nd day of February, 2011.

  
\_\_\_\_\_  
United States District Judge

997643/3496

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/s/  
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KOFI B ANSAH  
09/08/2011

## Ansah, Kofi

---

**From:** Ansah, Kofi  
**Sent:** Wednesday, September 07, 2011 3:42 PM  
**To:** 'Hills, Bethany'; 'Nancy Austin'  
**Subject:** Labeling related CMC IR -- NDA 022497/ Bupropion 450mg Extended Release/ MDD

Hello Bethany & Nancy,

We have the following CMC request pertaining to labeling. Include storage condition on the bottle/carton label. Include information on the number of tablets per bottle and the recommended storage condition in the package insert (section 16, how supplied/storage and handling). Correct the description of the tablet from (b) (4) tablets to the correct shape of the tablet in section 16.

Please include these changes in the labeling revision you are currently making per our 8/23/11 Advice Letter.

Best Regards,  
Kofi.

---

*Kofi Boadu Ansah, R.Ph., Pharm.D.*

CDR, US Public Health Service  
Regulatory Project Manager, Division of Psychiatry Products  
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109  
Silver Spring, MD 20993 - 0002  
Phone: (301) 796-4158  
Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

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/s/  
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KOFI B ANSAH  
09/07/2011

**Ansah, Kofi**

**From:** Ansah, Kofi  
**Sent:** Wednesday, September 07, 2011 4:21 PM  
**To:** 'Hills, Bethany'; 'Nancy Austin'  
**Cc:** Bouie, Teshara  
**Subject:** CMC Information Request 09-7-11 -- NDA 022497/ Bupropion 450mg Extended Release/ MDD

Dear Bethany & Nancy,

Regarding your NDA 022497 currently under review, we have the following CMC information request.

1. Correct the amount of (b) (4) present in Tables 2.3.P.1-1 and 3.2.P.3-4 (Bupropion Hydrochloride (b) (4) since you have (b) (4) in the reformulated product.
2. Provide updated stability protocol for the first three commercial stability batches to include both long-term (up to the proposed shelf-life) and accelerated (up to 6 months) conditions per ICHQ1A(R2) requirement.
3. The tablet sample you provided showed that the logo was not properly printed/centered on some tablets. Provide sample tablets made from the commercial printing equipment. Indicate if this problem has been resolved for the commercial manufacturing process.
4. Based on your dissolution data submitted in this cycle from 3 batches (**100012P3, 100015P3, 100016P3**), the Agency proposes the following dissolution specifications:

<b>Dissolution Acceptance Criteria</b>			
<b>Acid Stage</b>		<b>Buffer Stage</b>	
<b>Time (hrs)</b>	<b>% Dissolved</b>	<b>Time (hrs)</b>	<b>% Dissolved</b>
2	NMT (b) (4)	4	(b) (4)
		8	(b) (4)
		16	NLT (b) (4)

Concur or describe why you can not meet the Agency's proposed dissolution specifications.

Please provide the requested information as soon as possible, preferably by COB on 9/22/11.

Best Regards,  
Kofi.

-----  
*Kofi Boadu Ansah, R.Ph., Pharm.D.*  
CDR, US Public Health Service  
Regulatory Project Manager, Division of Psychiatry Products  
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109  
Silver Spring, MD 20993 - 0002  
Phone: (301) 796-4158  
Fax: (301) 796-9838  
Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)  
*Commissioned Corps of the United States Public Health Service- "Protecting, promoting, and advancing the health and safety of the Nation"*

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/s/  
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KOFI B ANSAH  
09/07/2011



NDA 022497

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

IntelGenX Corp.  
c/o Hodgson Russ LLP  
The Guaranty Building  
140 Pearl Street, Suite 100  
Buffalo, New York 14202-40

ATTENTION: Bethany J. Hills, Esq.

Dear Ms. Hills:

Please refer to your New Drug Application (NDA) dated March 31, 2009, received April 6, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, 450 mg.

We also refer to your June 8, 2011, correspondence, received June 9, 2011, requesting review of your proposed proprietary name, Forfivo XL. We have completed our review of the proposed proprietary name, Forfivo XL and have concluded that it is acceptable.

The proposed proprietary name, Forfivo XL, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your June 9, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kofi Ansah at (301) 796-4158.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
09/06/2011

**Ansah, Kofi**

---

**From:** Ansah, Kofi  
**Sent:** Thursday, September 01, 2011 4:23 PM  
**To:** 'Hills, Bethany'  
**Cc:** 'Nancy Austin'  
**Subject:** Response to Sponsor's Qs regarding 08-23-11 Advice Letter -- NDA 022497/ Bupropion 450mg Extended Release/ MDD

Dear Bethany,

Here is our response to the questions you posed below (in your 8/30/11 email) to our Advice Letter dated 8/23/11. With regards to:

Item 1: Provide the revised labeling in MS Word format. Be sure to submit both an annotated and a clean version and also send me an electronic copy via email.

Item 2: Yes, you may request a waiver of the HL length and BW length together, however, we strongly encourage you to try and shorten both the HL and BW.

Item 3: Contraindications: 1 (seizure disorder), 4 (abrupt discontinuation of alcohol or sedatives), 5 (concurrent use with an MAOI), and 6 (allergic response) need to describe the anticipated adverse reaction associated with the contraindicated use. For example, item 6 needs to describe the type and nature of the allergic reactions which have been seen.

Item 4: We encourage you to obtain a toll-free number for Adverse Reaction reporting, but it is not a "must."

Please provide your revised labeling as soon as possible as per our August 23, 2011 Advice Letter.

Best Regards,  
Kofi.

-----  
*Kofi Boadu Ansah, R.Ph., Pharm.D.*

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

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**From:** Nancy Austin [mailto:[nancy@intelgenx.com](mailto:nancy@intelgenx.com)]

**Sent:** Tuesday, August 30, 2011 2:23 PM  
**To:** Ansah, Kofi; 'Hills, Bethany'  
**Cc:** 'Nadine Paiement'; 'Horst Zerbe'  
**Subject:** RE: Advice Letter -- NDA 022497/ Bupropion 450mg Extended Release/ MDD  
**Importance:** High

Hi Kofi,

After going over the Advice Letter, we have a couple of items that need clarification:

- General: SPL format or word format: In which format should we provide the revised labeling in?
- Highlights - General comments (issue #1ii): We would like to request a waiver for the length of text in the "Highlights" section as well as the "Boxed Warning" section. Can one request letter be drafted instead of two?
- Highlights - Contraindications (issue #6): states that 'if the contraindication is not theoretical, describe the type and nature of the adverse reaction under FPI. – Describe the type and nature of the adverse reaction under FPI'. Please specify which adverse reaction you are referring to in the contraindications section.
- Highlights - Adverse Reactions (issue #7): states that 'only include toll-free numbers'. At the moment we do not have a toll free number available. Please advice on how this issue can be addressed.

Hope to hear from you soon,

Nancy  
*Nancy Austin, M.Sc.*  
Regulatory Affairs and Compliance Manager  
IntelGenx Corp.  
6425 Abrams  
Saint-Laurent, Quebec  
H4S 1X9  
T: 514-331-7440 x206  
F: 514-331-0436  
nancy@intelgenx.com  
www.intelgenx.com

---

**From:** Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]  
**Sent:** Tuesday, August 23, 2011 2:56 PM  
**To:** 'Hills, Bethany'  
**Cc:** 'Nancy Austin'  
**Subject:** Advice Letter -- NDA 022497/ Bupropion 450mg Extended Release/ MDD

Hi Bethany,

Find attached our Advice Letter with comments. You would receive a formal copy via postal mail. Please provide your response (i.e. revised labeling) as soon as possible.

Best Regards,  
Kofi.

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/s/  
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KOFI B ANSAH  
09/01/2011



NDA 022497

**GENERAL ADVICE**

IntelGenx Corp  
Attention: Bethany Hills, JD, MPH, Esq.  
Hodgson Russ LLP  
The Guaranty Building  
140 Pearl Street, Suite 100  
Buffalo, NY 14202-4040

Dear Ms. Hills:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FORFIVO XL (bupropion hydrochloride 450 mg extended-release tablet).

We also refer to your May 4, 2011, submission, containing your complete response to our February 3, 2010, action letter.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Highlights (HL)

1. General comments:

- i. HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font. – *The ½ page margins seem ok but HL should be corrected so that Contraindications immediately follow Dosage Forms & Strength (i.e. currently it's on the next page).*
- ii. HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission. – *Limit HL to ½ a page or request a waiver. If you have previously requested a waiver, please indicate which submission and where it's located in the submission.*
- iii. There is no redundancy of information. - *There is redundancy in HL (e.g. 5th bulleted item under Contraindications is redundant with 5th bulleted item under DI).*
- iv. If a Boxed Warning is present, it must be limited to 20 lines. [Boxed Warning (BW) lines do not count against the one-half page requirement.] - *Limit BW to 20 lines.*
- v. A horizontal line must separate the HL and Table of Contents (TOC). – *Insert this horizontal line.*

2. Product Title: Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol. – *This shouldn't be merged with HL limitation statement -- Must be on a separate line and should read; FORFIVO XL (bupropion hydrochloride extended-release tablets), for oral use.*
3. Boxed Warning: Summary of the warning must not exceed a length of 20 lines.
4. Recent Major Changes (RMC): Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions. - *Delete; not applicable in this case.*
5. Indications and Usage: If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at: <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>. - *[You may also refer to the Aplenzin labeling to see how it was done.]*
6. Contraindications: List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction under FPI. – *Describe the type and nature of the adverse reaction under FPI*
7. **Adverse Reactions:** For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers. - *The # provided was (b) (4) (i.e. must be a toll-free # if this is not such).*
8. Patient Counseling Information Statement: Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”. – *This product has a Medication Guide (i.e. must use the appropriate format as shown).*
9. Contents: Table of Contents (TOC)  
The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI. – (b) (4)

Full Prescribing Information (FPI)

10. General Format: A horizontal line must separate the TOC and FPI.

11. Boxed Warning: Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text. - *Missing the word "WARNING" and the text should be in bold.*

12. Adverse Reactions:

i. Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. – *(a) Both AE and AR are used in certain places -- Must use AR consistently (b) Subsection Headings (under 6) in TOC do not match those under FPI -- They should match.*

ii. For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.” – *This statement is missing (add it).*

iii. For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.” - *This statement is missing (add it).*

We request that you resubmit labeling that addresses these issues by 2-3 weeks from the date this letter was issued (preferably by September 8, 2011). The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov).

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 P LAUGHREN  
08/23/2011



NDA 022497

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

IntelGenx Corp  
Attention: Bethany Hills, JD, MPH, Esq.  
Hodgson Russ LLP  
The Guaranty Building  
140 Pearl Street, Suite 100  
Buffalo, NY 14202-4040

Dear Ms. Hills:

We acknowledge receipt on May 13, 2011, of your May 4, 2011, resubmission of your new drug application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for FORFIVO XL (bupropion hydrochloride 450 mg extended-release) tablet.

We consider this a complete, class 2 response to our February 3, 2010, action letter. Therefore, the user fee goal date is November 13, 2011.

If you have any questions please call me at (301)796-4158 or email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

CDR Kofi Ansah, Pharm.D.  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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KOFI B ANSAH  
06/09/2011

**From:** [Ansah, Kofi](#)  
**To:** ["Hills, Bethany"; "Nancy Austin";](#)  
**cc:** ["Horst Zerbe";](#)  
**Subject:** RE: MEETING MINUTES -- NDA 22-497 / INTELGENX CORP/ FORFIVO XL (BUPROPION HCL 450MG ER)/ MDD  
**Date:** Friday, October 22, 2010 10:45:23 PM

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Dear Ms. Hills:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Forfivo XL (bupropion hydrochloride) extended release 450 mg tablets.

We also refer to your August 2, 2010 submission, containing your post-meeting comments/ rebuttal to our meeting minutes dated June 23, 2010.

We have reviewed the referenced material and we do not have any additional response to any of your post-meeting comments except for 2 of the 3 points you made to our Additional Comments section of the official meeting minutes (from our ONDQA Biopharm group). Our two comments on those points are as follows:

1. It appears that your understanding was that the selection of the final dissolution acceptance criteria will not be based on the dissolution data currently available from the previous manufacturing site (b) (4) but these criteria will be based on the dissolution profile data generated from the new registration batches produced at the new manufacturing site (Pillar5Pharma).
2. Once enough data (complete dissolution profiles) have been generated at the new manufacturing site, the final dissolution acceptance criteria (specification times and ranges) will be proposed and submitted to FDA accordingly. The acceptance criteria should be within (b) (4) of the target values, unless an IVIVC is established to justify wider ranges. For the setting of the dissolution specifications without an IVIVC, please refer to the Guidance for Industry, entitled, "*Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations.*"

We remind you that our Meeting Minutes dated 6/23/10 remains the official Meeting Minutes. However we encourage you to submit your arguments or any information you deem necessary in your Complete Response to our February 3, 2010 Action Letter.

Best Regards,  
Kofi.

---

*Kofi Boadu Ansah, R.Ph., Pharm.D.*

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I

10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

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**From:** Nancy Austin [mailto:[nancy@intelgenx.com](mailto:nancy@intelgenx.com)]

**Sent:** Tuesday, August 03, 2010 10:02 AM

**To:** Ansah, Kofi; 'Hills, Bethany'

**Cc:** 'Horst Zerbe'; 'Patrick Noonan'; 'Nadine Paiement'

**Subject:** RE: MEETING MINUTES -- NDA 22-497 / INTELGENX CORP/ FORFIVO XL (BUPROPION HCL 450MG ER)/ MDD

**Importance:** High

Hi Kofi,

Internally we have all had a chance to review the Agency's Meeting Minutes for the meeting that took place on June 10, 2010 and have a few items we felt needed to be clarified or commented on. I have attached an electronic copy of this document.

I will formally submit 3 copies of the attached document by post to the following address:

**CDER Central Document Room:  
FDA/Center for Drug Evaluation and Research (CDER)  
Central Document Room (CDR)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266**

I would like to know if this is all right with you. If not, please let us know how to go about this.

Thanks,  
Nancy

*Nancy Austin, M.Sc.*  
Regulatory Affairs and Compliance Manager  
IntelGenx Corp.  
6425 Abrams  
Saint-Laurent, Quebec  
H4S 1X9  
T: 514-331-7440 x206  
F: 514-331-0436  
[nancy@intelgenx.com](mailto:nancy@intelgenx.com)  
[www.intelgenx.com](http://www.intelgenx.com)

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**From:** Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]  
**Sent:** Wednesday, June 23, 2010 2:39 PM  
**To:** Nancy Austin; Hills, Bethany  
**Cc:** Horst Zerbe  
**Subject:** MEETING MINUTES -- NDA 22-497 / INTELGENX CORP/ FORFIVO XL (BUPROPION HCL 450MG ER)/ MDD

Hi Bethany & Nancy,

Please find attached a courtesy copy of the Agency's Meeting Minutes for the meeting that took place on June 10, 2010. You would receive a formal copy by postal mail.

<<MEETING MINUTES -- NDA 022497 - IntelGenx\_Bupropion HCL 450mg ER (FORFIVO XL).pdf>>

Thanks,

Kofi.

---

***Kofi Boadu Ansah, R.Ph., Pharm.D.***

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I

10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

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August 2, 2010

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation-I  
Center for Drug Evaluation and Research  
Food and Drug Administration  
White Oak Campus, Bldg. 22, Rm. 4109  
Silver Spring, Maryland 20993-0002

Re: ***NDA 22-497 - Bupropion hydrochloride extended release tablets***

Attn: **LCDR Kofi Boadu Ansah, R.Ph., Pharm. D.**  
**Regulatory Project Manager, Division of Psychiatry Products**

Dear Dr. Laughren:

With reference to the official minutes of the meeting (“Memorandum of Meeting Minutes”) sent on June 23, 2010 for Forfivo XL (bupropion hydrochloride 450mg extended release tablets), the sponsor has enclosed comments on the official minutes of the meeting. The sponsor believes the meeting outcomes have been captured satisfactorily however would like to notify the Agency of a few items that should be considered.

The sponsor would appreciate if all of the significant differences in the meeting minutes enclosed be taken into consideration and clarified. All additional comments confirming your accord would be appreciated.

If there are any concerns or questions about the contents of the attached document, please contact us at your earliest convenience by phone (514-331-7440) or by e-mail ([nancy@intelgenx.com](mailto:nancy@intelgenx.com)).

Sincerely,



Nancy Austin, M.Sc.  
Manager, Regulatory Affairs & Compliance

CC: Bethany J. Hills, Esq., Hodgson Russ LLP

### Minutes of the Type C NDA Face-to-Face Meeting on June 10, 2010

**Meeting Date:** JUNE 10, 2010  
**Time:** 2:00 PM  
**Location:** FDA White Oak Campus, Building 22,  
Room #1419; 10903 New Hampshire Ave,  
Silver Spring, MD 20993  
**Application:** NDA 22-497  
**Drug Name:** FORFIVO XL (Bupropion HCl 450 mg  
Extended Release Tablets)  
**Type of Meeting:** Type C Meeting  
**Meeting Chair:** Thomas Laughren, M.D

On June 10, 2010, a Type C NDA Face-to-Face meeting was held with FDA. The purpose of this meeting was to confirm that the proposed plans for Forfivo XL. The sponsor requested this meeting to review and discuss:

1. The clinical plan,
2. Manufacturing site change, and
3. The CMC plan (number and size of registration batches and amount of stability data)

In preparation for this meeting, FDA requested that the company submit specific questions in writing to be addressed at the meeting. Below please find the question posed by Sponsor in advance of the meetings, the Agency's preliminary comments received prior to the meeting and the FDA's recounting of the discussion at the meeting (provided in the FDA's minutes). It is our understanding that we are permitted to request additional clarification and provide comments following the June 10, 2010 meeting. Below we identify specific areas where clarification is needed under the heading "Sponsor Post-Meeting Comments". Please include this as part of the NDA file so that these items will be considered in the review of our response to the FDA's Complete Response Letter and the amended NDA.

#### FDA ATTENDEES:

Thomas Laughren, M.D.	Division Director, Division of Psychiatry Products (DPP)
Mitchell Mathis, M.D.	Deputy Division Director, DPP
Jing Zhang, M.D.	Medical Team Leader
Jenn Sellers, M.D.	Medical Reviewer
Raman Baweja, Ph.D.	Clinical Pharmacology Team Leader
Bei Yu, Ph.D.	Clinical Pharmacology Reviewer
Linda Fossom, Ph.D.	Pharmacology/ Toxicology Team Leader
Shiny Mathew, Ph.D.	Pharmacology/Toxicology Reviewer
Ramesh Sood, Ph.D.	Branch chief, Division of New Drug Assessment I, ONDQA
Thomas Oliver, Ph.D.	CMC Lead, ONDQA

Pei-I Chu, Ph.D.	CMC Reviewer, ONDQA
Tapash Ghosh, Ph.D.	Biopharmaceutics Reviewer, DCP I, OCP
Teshara Bouie, MSA, OTR/L	Regulatory Project Manager, OPS/ ONDQA
William Bender, R.Ph.	Senior Regulatory Project Manager, DPP
Kofi Ansah, Pharm.D.	Senior Regulatory Project Manager, DPP

#### **CARY PHARMACEUTICALS, INC.'S ATTENDEES:**

Horst Zerbe, Ph.D. (b) (4)	President and CEO, IntelGenx Corp. (b) (4)
Nancy Austin	Manager, Regulatory Affairs & Compliance, IntelGenx Corp.

#### **Proceedings**

**Introductory comments:** The meeting commenced at 2:00 p.m. EST, June 10, 2010. The meeting was initiated by Dr. Thomas Laughren, M.D, the Division Director, Division of Psychiatry Products (DPP) where the FDA attendees introduced themselves. The Sponsor's attendees introduced themselves and then the meeting was turned over to Horst Zerbe, Ph.D., President and CEO of IntelGenx Corp.

**Specific Questions sent the prior to face-to-face meeting:** Since the meeting was limited to 1 hour, Dr. Kofi Ansah requested that specific questions be selected from the list of questions, which were submitted to FDA on May 10, 2010. From this list questions #1, 3, 4, 6, 7, 8, 9, 10, 11, 14, 15 and 18 were selected and sent, via email on Jun 9, 2010.

A general overview outlining the objective of this meeting was given by Horst Zerbe which consisted of 1) the clinical plan, 2) the manufacturing site change and 3) the CMC plan (number and size of registration batches and amount of stability data).

#### **Selected Questions From the Sponsor:**

##### ***Clinical Questions***

As described in the CMC section, the applicant plans to produce three (3) additional NDA registration stability batches consisting of (b) (4) tablets per batch that will be representative of the commercial formulation/process. These lots will be manufactured at the new manufacturing site (b) (4). This site will use the same/equivalent equipment, and the same SOPs, environmental conditions, and controls in the manufacturing process at the new site; no changes are anticipated to the executed batch records except for administrative information and location. In addition to the above mentioned plans, the applicant plans to introduce an (b) (4). This is discussed in more detail in the CMC section. One of these lots will be tested in the BE study described below.

The applicant plans to demonstrate the BE of Forfivo XL with 3 x 150 mg Wellbutrin XL under fasting conditions and the bioavailability of Forfivo XL in the fed state in a three-way cross over study comparing Forfivo XL fasting, Forfivo XL fed and 3 x 150 mg Wellbutrin XL fasting.

**Question 1:**

For this pivotal study, assuming that the fasting Wellbutrin XL and Forfivo XL treatment arms are bioequivalent and that AUC and  $C_{max}$  for the Forfivo XL fed arm are within  $\pm 20\%$  of Forfivo XL fasting, does **FDA agree that**

- a. **this study meets the FDA's requirements for a "single-dose, food-effect study",**
- b. **this study will address the food effect concerns outlined in the complete response letter (action letter), and that**
- c. **this study is sufficient to demonstrate that product manufactured at the new manufacturing site is bioequivalent to the RLD?**

***Preliminary Comments:** The study design for the proposed study (protocol No BPO-P0-520) is acceptable to evaluate BE between Forfivo XL (450 mg) and Wellbutrin XL (3 x150 mg) under fasted conditions, and to assess the effect of food on Forfivo XL (450 mg). The established criterion for BE, however, is not that the AUC and Cmax ratio for the Forfivo XL (450 mg) fed arm should be within + 20% of Forfivo XL fasting arm of the study. For evaluating both, BE between Forfivo XL 450 mg and 3 X 150 mg Wellbutrin XL, and, for assessing the effect of food on Forfivo XL 450 mg tablet (fed versus fasted states), the two one-sided 90 % confidence interval (CI) approach should be applied to the individual parameters of interest (e.g., AUC and CMAX) based on log transformed data. To declare equivalence the parameters of interest (AUC and Cmax) should fall within 80-125 %.*

**Discussion at Meeting:**

*The sponsor requested clarification of the Agency's concern in the CR letter on the increasing risk of incidence of seizures associated with the observed increase in Cmax with food for Forfivo XL without a concomitant increase in AUC. We clarified that the association is based on indirect evidence, e.g., clinical data has shown that a change in formulation from bupropion IR to XL has decreased the incidence of seizures. The Cmax for the XL formulation is lower than that for the IR formulation, while AUC is comparable for the two formulations. In NDA 22497, food increased the mean Cmax of bupropion for Forfivo XL by 25%. However, for Wellbutrin XL, food decreased the mean Cmax of bupropion (by 8%). Patients who will use Forfivo XL (450 mg) will necessarily have been titrated from lower doses using the available reference formulation which can be taken without regard to meals. Therefore, switching a patient from the reference formulation to Forfivo XL after using the former for titration has the potential for increasing the incidence of seizures.*

**Sponsor Post-Meeting Comments**

**Sponsor continues to disagree with the FDA's strong conclusion that switching a patient from the reference formulation to Forfivo XL has the potential for increasing the incidence of seizures. Sponsor plans to address this in the response to the Complete Response Letter.**

**Question 4:**

In the complete response letter (action letter) dated February 3, 2010, the “*Clinically Important Food Effect*” section, FDA pointed out that the clinical problem would require a very intensive educational effort and no such program has been provided. If the new pivotal study shows that Forfivo XL does not meet BE requirements when administered with food, the applicant plans to comply with this requirement and will work with FDA to provide an effective Risk Evaluation and Mitigation Strategy (REMS) in the NDA amendment submission. **Does FDA concur that this plan will address this clinical concern?**

***Preliminary Comments:*** *No. We do not believe that a REMS would address our clinical concerns regarding increased seizure risks of your product caused by significant food effects. Healthcare professionals have more than 20 years of experiences with bupropion, and are used to prescribing and/or dispensing bupropion without providing specific instructions to patients regarding food intake. We do not believe that the REMS with respect to significant food effects only on your product, a particular strength of bupropion, would be adequate or practical to ensure the communication of this important information to healthcare professionals and patients. The potential for confusion and medical errors remain a serious concern.*

***Discussion at Meeting:*** *The sponsor requested further clarification regarding why we think a REMS would not be adequate to address the food effect associated with their product. We again explained that, because their product is a 450 mg tablet, no patient would start treatment with their product, but rather, patients would be started with other bupropion products, including Wellbutrin XL, which has no significant food effect, and then might be switched to their product if clinically indicated. It would be very difficult for health care providers to change patient behavior with regard to food intake, given that they will have been used to taking bupropion without regard to food. Therefore, we do not believe that a REMS would adequately address the potential risk associated with the food effect.*

**Sponsor Post-Meeting Comments**

**Sponsor requests that the FDA reserve final decision on the need for a REMS program until additional data from the food effect study is available.**

***Chemistry Manufacturing and Control Questions (questions 6 and 18)***

As recommended, the applicant plans to produce three (3) additional NDA registration stability batches consisting of (b) (4) tablets per batch, that will be representative of the commercial formulation/process. These lots will be manufactured at the new manufacturing site (b) (4). This site will use the same equipment, SOPs, environmental conditions, and controls in the manufacturing process at the new site; no changes are anticipated to the executed batch records except for administrative information and location.

**Question 6:**

As per FDA's request for information, dated November 6, 2009, the applicant had proposed in an amendment, dated December 11, 2009, an upper limit (weight gain) for the (b) (4). The applicant plans on maintaining the specifications range of the (b) (4) and introducing (b) (4) in all future manufacturing instructions. This warning limit range is unlikely to have any detectable impact on the formulation quality and performance since the total weight of the dosage form and the (b) (4) are still within the original application range. **Does FDA concur that this proposed inclusion of (b) (4) would still be considered within the finished product specifications originally submitted on March 31, 2009?**

***Preliminary Comments:*** It is unclear how (b) (4) According to your batch records, the (b) (4) for batch 08039P-01 was (b) (4). At this point, we do not believe that you have provided adequate data to demonstrate that tablets produced in (b) (4) will meet the drug product specification. You will need to provide analytical data from batches manufactured at the (b) (4) to demonstrate that tablets produced at (b) (4) will meet the product specifications (e.g., assay, impurities, dissolution at release and on stability).

***Discussion at Meeting:*** The applicant stated that the (b) (4) is the target range and that batches with a (b) (4) would be released for commercial use. We stated that information will need to be submitted to support this (b) (4). The applicant stated they have manufactured five lots at the new manufacturing site (Pillar5 Pharma Inc.): 3 lots with (b) (4) 1 lot with (b) (4) and 1 lot with (b) (4). These five lots have been placed on stability. The applicant also stated that the observed food effect could be attributed to the (b) (4). We indicated that the sponsor will need to demonstrate that there is no observable food effect at the (b) (4). The acceptability of the (b) (4) will be based on the evaluation of the submitted data. Additionally, the stability behavior of the product (b) (4) will need to be demonstrated.

Since the (b) (4) is a critical quality attribute, we recommended the applicant provide the (b) (4) data in the NDA.

**Sponsor Post-Meeting Comments**

**The sponsor would like to clarify the following:**

- **As explained in the "discussion at meeting" section, 3 lots with (b) (4) were manufactured at the new manufacturing site (Pillar5 Pharma Inc.). This involves (b) (4)**

- Prior to (b) (4) a tablet sample of each of the above mentioned lots was retained and divided into two equal portions, thus resulting in 6 sub-batches. (b) (4)
- All 9 lots have been placed on stability at the same temperature and humidity conditions as well as stability protocol.

**Question 7:**

For these three (3) additional NDA registration stability batches, a side-by-side comparison of the manufacturing equipment is provided in **Error! Reference source not found.** of section 10 of this meeting package. **Does FDA have any other comments, recommendations, or requirements regarding the proposed plan to support the new manufacturing site for Forfivo XL, NDA 22-497?**

**Preliminary Comments:** *No additional comments.*

**Discussion at Meeting:** *We clarified that no additional manufacturing equipment information is needed at this time (however this information should be submitted in the sponsor's response to the CR letter). In addition, information should be provided in a response to any manufacturing process or packaging differences between the "old site" (b) (4) and the "new site" (Pillar5 Pharma Inc.).*

**Sponsor Post-Meeting Comments**

**The sponsor intends to address this in the Complete Response Letter as well as section 3.2.P.2.3 of the amended NDA.**

**Question 8:**

(b) (4)  
Following this observation a written investigation was not conducted however a visual inspection was performed by quality control personnel at (b) (4) on the finished product and the results conformed to the manufacturing specification. It was therefore concluded that this discrepancy would not have any adverse impact on the integrity of the finished product. In addition to the manufacturer's inspection, the release testing of the finished product was conducted as per the analytical testing specification and conformed. These results and the stability results collected indicate that all three batches (08016P-01, 08039P-01 and 08040P-01) behave similarly up to 12 months. See the dissolution profile of all three batches after the 12-month stability pull point.

*Figure 1 Dissolution profile comparison of all the previously manufactured batches (08016P-0, 08039P-01 and 08040P-01) after 12-months at 25°C*



Based on the stability data generated on the previously manufactured exhibit batches 08016P-01, 08039P-01 and 08040P-01, the applicant plans on relying on this stability data generated as pivotal data in determining the expiration date and will propose a 24-month expiry for the commercial drug product.  
**Does FDA concur with this plan?**

**Preliminary Comments:** *It should be noted that batch (# 08039P-01) was manufactured with the (b) (4) however, placebo tablets were (b) (4) and therefore, the process is not considered representative of the commercial process. In addition, the 18M dissolution data for batches 08039P-01 and 080106P-01 suggest that they fail the dissolution specification (refer to the Additional Comments section at end of the preliminary comments).*

*ICH Q1A (R2) recommends that a minimum of 12 months of long-term and 6 months of accelerated stability data be submitted at the time of submission. Based on the above concerns, we recommend that you submit 12 months of long term and 6 months of accelerated stability data (with appropriate amount of intermediate stability data, if required) for three batches of drug product representative of the commercial formulation/process manufactured at the new manufacturing site. The expiry date for your commercial product will be determined at the time of future NDA amendment review when stability data from the new manufacturing site is provided. SUPAC only applies to post approval changes. Since this product has not been*

*approved, SUPAC does not apply in this situation. The previous stability data may be considered as supportive data.*

**Discussion at Meeting:** *We stated that SUPAC does not apply to changes to a product that has not been approved. We recommended that the applicant submit 12 months of long term and 6 months of accelerated stability data (with appropriate amount of intermediate stability data, if required) for three batches of drug product representative of the commercial formulation/ process manufactured at the new manufacturing site. Clearly, we would like to assign a reasonable expiry. The applicant stated they would need more than 12 months to acquire the stability data and they were concerned of the consequences if they did not respond to the CR letter within 12 months as outlined in the letter.*

*Regarding the issue of responding to the CR letter within 12 months, the sponsor is encouraged to note that the Agency has the discretion to withdraw the application should the sponsor not respond within 1 year. However, since the sponsor is actively pursuing a response, we would not pursue this option. Alternatively, the sponsor could formally request an extension of time in which to resubmit the application. [Refer to **21CFR 314.110 Complete Response Letter to the applicant.**]*

**Sponsor Post-Meeting Comments**

- **The sponsor will resubmit application with the recommended amount of stability data.**
- **The sponsor will formally request an extension of time in which to resubmit the application.**

**Question 9:**

The applicant plans to apply the same manufacturing process as outlined in the original NDA 22-497 for previous exhibit batches 08016P-01, 08039P-01 and 08040P-01, for the three (3) above mentioned NDA registration stability batches. Because this is a (b) (4), and a “significant body of information” is not available, three months’ accelerated stability data will be provided for these three batches; long-term stability data of first three production batches will be reported in the annual report. Since the three (3) registration batches are identical with respect to manufacturing process and finished product specifications, the applicant plans to support the manufacturing site change with 3-month accelerated stability data. An NDA amendment providing the additional 6 -month of long-term stability data on all batches will be filed during the review period. **Does FDA concur with this plan?**

***Preliminary Comments:** Refer to the response to Question 8.*

***Discussion at Meeting:** Refer to the response to Question 8.*

**Sponsor Post-Meeting Comments**

**Refer to Question 8**

**Question 16:**

In the complete response letter, question #11a requested information on how (b) (4)

The applicant provided a literature reference in amendment dated December 11, 2009 which stated that bupropion hydrochloride demonstrates pH dependence and can be stabilized at low pH. It was determined that in order to maintain the integrity of the bupropion hydrochloride during (b) (4)

**If not, the applicant requests FDA’s guidance on how to address this matter.**

***Preliminary Comments:** The proposed in-process pH limit should include an acceptable pH range (b) (4). Any selected process parameters will need to be supported by experimental data.*

***Discussion at Meeting:** No further discussion.*

**Sponsor Post-Meeting Comments**

The sponsor would like to clarify the following:

- The pH test is an in-process test that will be removed prior to manufacturing of commercial product for the following reasons:
  - The pH tests performed on these registration batches were in place for research and developmental purposes only.
  - In the future, the amount and concentration of the diluted hydrochloric acid will be constant therefore the pH test will not be required.

**Question 17:**

Question #11d of the complete response letter stated that three drug product batches had a problem associated with the drug product (b) (4). To briefly summarize the manufacturing situation, a total of 6 stability lots were prepared in 2 manufacturing campaigns. All lots are identical with respect to their quantitative and qualitative composition and manufacturing procedure. During the stability testing of the first 3 lots (primary stability data), a slight drop of the dissolution rate after 1 month storage at accelerated storage conditions was observed. However, dissolution rates still were within specifications, and no further drop was observed at the subsequent pull points. This observation was attributed to (b) (4). During the manufacturing of the second 3 lots (supportive stability data), the processing parameters for (b) (4) (For all details regarding the optimization of (b) (4) of the stability lots refer to the report “Stability – BUP 450 Tablets” which is located in section 3.2.R.10 of the NDA 22-497.). The Agency further suggested that the dissolution profile of the drug product will be compromised if (b) (4) is not properly controlled. The applicant maintains that the current commercial process is optimized and that the inclusion of (b) (4) (used for batch no. 08016P-01, 08039-P01 and 08040P-01) resulted in meeting the product specifications (reference 3.2.P.8 of the CMC portion of the NDA 22-497). **Does the FDA agree that the analytical data provided confirm that the problem has been resolved?**

***Preliminary Comments:*** Refer to the response to Question 8. The adequacy of your manufacturing process will be determined as part of the review of your updated data package and any possible inspections.

***Discussion at Meeting:*** Refer to the discussion for Question 8.

**Sponsor Post-Meeting Comments**

Refer to Question 8.

**Question 18:**

Question 11f requested analytical data from batches manufactured at (b) (4) to demonstrate that the tablets (b) (4) will meet the product specifications (assay, dissolution and stability). Batch no. 08016P-01 was (b) (4) and batch no. 08039P-01 was (b) (4). All analytical data can be found in section 3.2.P.8 of the CMC portion of the NDA 22-497 and clearly demonstrate that these tablets, (b) (4) meet the product specifications. **Does FDA agree that the analytical data provided demonstrate that the tablets produced (b) (4) meet the product specifications?**

**Preliminary Comments:** *Refer to response to Question 6.*

**Discussion at Meeting:** *Refer to the discussion for Question 6.*

**Sponsor Post-Meeting Comments**

**Refer to Question 6.**

**Additional Comments section (at the end of the “Preliminary Comments – 06-07-10—NDA 22497- FORFIVO XL” letter)**

The following comments from the ONDQA Biopharm group were not included in the CR action letter dated February 3, 2010.

1. The proposed dissolution acceptance criteria for the 4 and 8 hours (buffer stage) sampling time points are not acceptable. The acceptance criteria should be within (b) (4) of the target values, unless an IVIVC is established to justify wider ranges. For the setting of the dissolution specifications without an IVIVC, please refer to the Guidance for Industry, entitled, “Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations”.
2. Based on the provided dissolution data, the following dissolution method and acceptance criteria are recommended for your product

Dissolution Method for Bupropion HCl Extended Release Tablets			
Acid Stage		Buffer Stage	
Apparatus	USP Apparatus 1 (Baskets)	Apparatus	USP Apparatus 1 (Baskets)
Medium	Simulated Gastric Fluid (HCl pH 1.2)	Medium	Tris Buffer pH 6.8
Volume	900 ml	Volume	900 ml
Temperature	37°C	Temperature	37°C
Rotation Speed	75 rpm	Rotation Speed	75 rpm
Sampling Time	2 hrs	Sampling Times	4, 8, and 16 hrs
Dissolution Acceptance Criteria			
Acid Stage		Buffer Stage	
Time	Percent Dissolved	Time	Percent Dissolved
2 hrs	NMT (b) (4)	4 hrs	(b) (4)
		8 hrs	(b) (4)
		16 hrs	NLT (b) (4)

Please revise the acceptance criteria sheet for your product

**Discussion:** The sponsor will check the available dissolution data. For the future batches, sufficient samples will be placed in the stability program to proceed if necessary up to Level 3 evaluation to comply with the Agency’s proposed dissolution specifications.

During the meeting, the sponsor was asked to clarify the proposed media to be used in the final dissolution methodology for Stage I (acid stage) and Stage II (buffer stage); (b) (4) have been used in different places of the application. The sponsor agreed to check this information and get back to us.

Sponsor Post-Meeting Comments

- The sponsor understood that the dissolution acceptance criteria will not be based on the available dissolution data from the previous manufacturing site (b) (4) but based on the dissolution data generated from the new registration batches produced at the new manufacturing site (Pillar5 Pharma).
- The sponsor will review the dissolution acceptance criteria once enough data has been generated at the new manufacturing site whereupon the sponsor will amend the acceptance criteria accordingly. The range of the dissolution specifications will depend on the variability of the dissolution data.
- The sponsor would like to clarify that the proposed media to be used in the final dissolution methodology for stage I (acid stage) to be 0.1N HCl and Stage II (buffer stage) to be Tris Buffer.

*We would appreciate it if you could confirm the above comments.*

The sponsor believes the meeting outcomes have been captured satisfactorily however would appreciate if all of the significant differences in the meeting minutes discussed above be taken into consideration and clarified. We would appreciate any additional comments confirming your accord in order to for us to properly manage and execute all recommendations (or requirements) from the Agency in a suitable manner.

If there are any concerns or questions about the contents of this document, please contact us at your earliest convenience by phone (514-331-7440) or by e-mail ([nancy@intelgenx.com](mailto:nancy@intelgenx.com)).

Best regards,



Nancy Austin  
Regulatory Affairs & Compliance Manager, IntelGenx Corp.

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

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/s/

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KOFI B ANSAH  
10/22/2010



NDA 022497

IntelGenx Corp  
Attention: Bethany Hills, JD, MPH, Esq.  
Hodgson Russ LLP  
The Guaranty Building  
140 Pearl Street, Suite 100  
Buffalo, NY 14202-4040

Dear Ms. Hills:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Forfivo XL (bupropion hydrochloride 450 mg extended release tablets).

We also refer to the meeting between representatives of your firm and the FDA on June 10, 2010. The purpose of the meeting was to discuss the issues raised in our Complete Response Letter dated February 3, 2010 and the current status/ future plans for the development of Forfivo XL for Major Depressive Disorder (MDD).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact CDR Kofi Ansah, Senior Regulatory Project Manager, at (301)796-4158.

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

Enclosure - Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** June 10, 2010  
**TIME:** 2:00pm  
**LOCATION:** White Oak CDER Bldg 22, Room 1419  
**APPLICATION:** NDA 022497  
**DRUG NAME:** FORFIVO XL (Bupropion HCL 450 mg Extended-Release)  
**TYPE OF MEETING:** Type C NDA Face-to-face Meeting

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

**FDA ATTENDEES:**

Thomas Laughren, M.D.	Division Director, Division of Psychiatry Products (DPP)
Mitchell Mathis, M.D.	Deputy Division Director, DPP
Jing Zhang, M.D.	Medical Team Leader
Jenn Sellers, M.D.	Medical Reviewer
Andre Jackson, Ph.D.	Clinical Pharmacology Reviewer
Bei Yu, Ph.D.	Clinical Pharmacology Reviewer
Barry Rosloff, Ph.D.	Pharmacology/ Toxicology Supervisor
Linda Fossom, Ph.D.	Pharmacology/ Toxicology Team Leader
Ramesh Sood, Ph.D.	Branch chief, Division of New Drug Assessment I, ONDQA
Thomas Oliver, Ph.D.	CMC Lead, ONDQA
Pei-I Chu, Ph.D.	CMC Reviewer, ONDQA
Tapash Ghosh, Ph.D.	Biopharmaceutics Reviewer, DCP I, OCP
Teshara Bouie, MSA, OTR/L	Regulatory Project Manager, OPS/ ONDQA
Kofi Ansah, Pharm.D.	Senior Regulatory Project Manager, DPP

**Cary Pharmaceuticals, Inc.'s Attendees:**

Horst Zerbe, M.D., Ph.D. (b) (4)	President and CEO, IntelGenx Corp. (b) (4)
Nancy Austin	Manager, Regulatory Affairs & Compliance IntelGenx Corp.

**Background:**

Cary Pharmaceuticals, Inc. (Cary) of Great Falls, Virginia and IntelGenx Corp., St-Laurent, Quebec, Canada, have developed an oral extended-release formulation of 450 mg bupropion hydrochloride (FORFIVO XL) for the treatment of major depressive disorder (MDD). Forfivo XL is a novel extended-release tablet that contains 450 mg of bupropion (b) (4) intended to be comparable to the reference listed drug

product Wellbutrin XL<sup>®</sup> (GlaxoSmithKline). The tablets are coated with an enteric coating layer. The release of the active substance is initially delayed and essentially completed 18 hours post-administration.

Cary's development program for this extended-release formulation containing 450 mg bupropion hydrochloride was under IND (b) (4). During the drug development phase, a PRE-IND meeting was held on January 30, 2007 and an end-of-phase II (EOP2) meeting was held on July 14, 2008. At the PRE-IND meeting, the Division required Cary Pharmaceuticals to do a food-effect study in addition to the bioequivalence study they proposed. The Division also advised Cary, at the EOP2 meeting, to do an alcohol dose dumping study to look at the *in vitro* effect of alcohol on dosing.

On March 31, 2009, Cary Pharmaceuticals submitted their new drug application (NDA 022497) under the provision of section 505(b)(2) of the Federal Food Drug, and Cosmetic Act to obtain marketing approval of Forfivo XL once daily for the indication of major depressive disorder (MDD). This submission included two clinical Phase I studies (bioequivalence and food effect studies) and one *in vitro* study (dose dumping with alcohol). Clinical efficacy studies were not conducted on this product. The reference listed drug (RLD) product is Wellbutrin XL<sup>®</sup> (bupropion hydrochloride) 150 mg Extended-Release Tablets, GlaxoSmithKline (GSK) approved by FDA on 08/28/2003 under NDA 021515. Wellbutrin XL<sup>®</sup> is indicated in the treatment of MDD and seasonal affective disorder in the dosage forms of 150 mg and 300 mg. Cary plans to only seek an indication for MDD, and not for seasonal affective disorder.

For the treatment of major depressive disorder, the currently available formulations of bupropion hydrochloride are: Wellbutrin immediate release (IR) tablet (75 mg and 100 mg) that is given three times daily; Wellbutrin sustained release (SR) tablet (50 mg, 100 mg, 150 mg, and 200 mg) that is given twice daily; and Wellbutrin XL<sup>®</sup> tablet (150 mg and 300 mg) that is given once daily after an up-titration. Bupropion hydrochloride 450 mg/day given as a single dose is an approved dose in the treatment of MDD in adults, but not an approved strength of Wellbutrin XL<sup>®</sup> (requiring administration of 150 and/or 300 mg tablets i.e., 3x150 mg, or 150 mg + 300 mg as a single dose). Forfivo XL would be a new higher strength formulation of the currently marketed bupropion hydrochloride extended-release drug product for which the highest strength is 300 mg.

Bupropion is extensively hepatically metabolized. It has three pharmacologically active metabolites, hydroxybupropion, threohydrobupropion (bupropion threoamino alcohol), and erythrohydrobupropion (bupropion erythroamino alcohol) that account for over 90% of the exposure following administration of bupropion. Based on an animal study, hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. Recently, an animal study showed that all three active metabolites caused seizures and were more potent convulsants than the parent drug. A summary of relative AUC at steady state, relative potency, and therapeutic contribution (AUC x Potency) for bupropion and its active metabolites is shown in the table below:

<b>Moiety</b>	<b>AUC</b>	<b>Potency</b>	<b>AUC x Potency</b>
<b>Bupropion</b>	1	1	1 (11%)
<b>Hydroxybupropion</b>	13	0.5	6.5 (71%)
<b>Erythrohydrobupropion</b>	1.4	0.2	0.28 (3%)
<b>Threohydrobupropion</b>	7	0.2	1.4 (15%)
<b>Total</b>	–	–	9.18 (100%)

*Ref: Wellbutrin XL Package Insert; Clinical Pharmacology.*

Cary argues that Forfivo XL would provide for the extended-release of bupropion and the blunting of C<sub>max</sub> compared to the instant release formulation, and like other extended-release formulations, should decrease the risk of seizures. Moreover, by allowing patients to take only one 450 mg tablet, rather than three 150 mg tablets, or a combination of 150 mg and 300 mg tablets, Cary predicts that this new formulation should decrease the risk of dosing errors and the consequent risk of inadvertent overdose. Cary also argues that Forfivo XL should also improve compliance and therefore efficacy, since it is easier for patients to take one tablet rather than a combination of two or three tablets. Forfivo XL, therefore, represents a “convenience reformulation” only and would not involve any changes to the dosage and administration section of the current labeling of the reference listed drug.

### **Questions from the sponsor:**

#### *CLINICAL QUESTIONS*

As described in the CMC section, the applicant plans to produce three (3) additional NDA registration stability batches consisting of (b) (4) tablets per batch that will be representative of the commercial formulation/process. These lots will be manufactured at the new manufacturing site (b) (4). This site will use the same/equivalent equipment, and the same SOPs, environmental conditions, and controls in the manufacturing process at the new site; no changes are anticipated to the executed batch records except for administrative information and location. In addition to the above mentioned plans, the applicant plans to (b) (4). This is discussed in more detail in the CMC section. One of these lots will be tested in the BE study described below.

The applicant plans to demonstrate the BE of Forfivo XL with 3 x 150 mg Wellbutrin XL under fasting conditions and the bioavailability of Forfivo XL in the fed state in a three-way cross over study comparing Forfivo XL fasting, Forfivo XL fed and 3 x 150 mg Wellbutrin XL fasting.

**Question 1:**

For this pivotal study, assuming that the fasting Wellbutrin XL and Forfivo XL treatment arms are bioequivalent and that AUC and  $C_{max}$  for the Forfivo XL fed arm are within  $\pm 20\%$  of Forfivo XL fasting. **Does FDA agree that**

- a. **this study meets the FDA’s requirements for a “single-dose, food-effect study”,**
- b. **this study will address the food effect concerns outlined in the complete response letter (action letter), and that**
- c. **this study is sufficient to demonstrate that product manufactured at the new manufacturing site is bioequivalent to the RLD?**

**Preliminary Comments:** *The study design for the proposed study (protocol No BPO-P0-520) is acceptable to evaluate BE between Forfivo XL (450 mg) and Wellbutrin XL (3 x 150 mg) under fasted conditions, and to assess the effect of food on Forfivo XL (450 mg).*

*The established criterion for BE, however, is not that the AUC and  $C_{max}$  ratio for the Forfivo XL (450 mg) fed arm should be within  $\pm 20\%$  of Forfivo XL fasting arm of the study. For evaluating both, BE between Forfivo XL 450 mg and 3 X 150 mg Wellbutrin XL, and, for assessing the effect of food on Forfivo XL 450 mg tablet (fed versus fasted states), the two one-sided 90 % confidence interval (CI) approach should be applied to the individual parameters of interest (e.g., AUC and  $C_{MAX}$ ) based on log transformed data. To declare equivalence the parameters of interest (AUC and  $C_{max}$ ) should fall within 80-125 %.*

**Discussion at Meeting:**

*The sponsor requested clarification of the Agency’s concern in the CR letter on the increasing risk of incidence of seizures associated with the observed increase in  $C_{max}$  with food for Forfivo XL without a concomitant increase in AUC. We clarified that the association is based on indirect evidence, e.g., clinical data has shown that a change in formulation from bupropion IR to XL has decreased the incidence of seizures. The  $C_{max}$  for the XL formulation is lower than that for the IR formulation, while AUC is comparable for the two formulations. In NDA 22497, food increased the mean  $C_{max}$  of bupropion for Forfivo XL by 25%. However, for Wellbutrin XL, food decreased the mean  $C_{max}$  of bupropion (by 8%). Patients who will use Forfivo XL (450 mg) will necessarily have been titrated from lower doses using the available reference formulation which can be taken without regard to meals. Therefore, switching a patient from the reference formulation to Forfivo XL after using the former for titration has the potential for increasing the incidence of seizures.*

**Question 2:**

For this pivotal study, the applicant plans to demonstrate the BE between Forfivo XL and Wellbutrin XL with respect to bupropion and hydroxybupropion, the primary active metabolite only. In addition the applicant plans to demonstrate the absence of an appreciable food effect by comparing Forfivo XL fasting and Forfivo XL fed with respect to bupropion and hydroxybupropion, the primary active metabolite only. **Does FDA concur with this plan?**

**Preliminary Comments:** *Based on the draft protocol (No BPO-P0-520), OCP has the following comments:*

1. *All four moieties, i.e., bupropion - the parent drug, and the three metabolites - hydroxybupropion, erythrohydrobupropion, and threohydrobupropion, should be analyzed in the study.*
2. *Additional PK blood sampling time points until 120-hour post dose should be added.*
3. *Smokers should not be included in the "Inclusion Criteria", i.e., only non-smokers should be enrolled in the study.*

*We look forward to receiving the final protocol.*

**Discussion at Meeting:** *No further discussion.*

**Question 3:**

In the complete response letter (action letter) dated February 3, 2010, the "*Clinically Important Food Effect*" section, FDA also pointed out that a number of subjects showed  $C_{max}$  values that were more than two-fold higher than the RLD. The applicant plans on demonstrating that inclusion of (b) (4)

(b) (4) will reduce or eliminate the apparent food effect, and reduce the excessive peak plasma concentrations that were observed after administration of (b) (4) tablets in the NDA study. **Does FDA concur that this plan will address this clinical concern?**

**Preliminary Comments:** *This will be a matter for review. You may include any number of processing changes including this one. The question above can only be answered after the data and the results obtained from the study, have been reviewed.*

**Discussion at Meeting:** *Please see CMC section for the discussion at meeting.*

**Question 4:**

In the complete response letter (action letter) dated February 3, 2010, the "*Clinically Important Food Effect*" section, FDA pointed out that the clinical problem would require a very intensive educational effort and no such program has been provided. If the new pivotal study shows that Forfivo XL does not meet BE requirements when administered with food, the applicant plans to comply with this requirement and will work with FDA to provide an effective Risk Evaluation and Mitigation Strategy (REMS) in the NDA amendment submission. **Does FDA concur that this plan will address this clinical concern?**

**Preliminary Comments:** *No. We do not believe that a REMS would address our clinical concerns regarding increased seizure risks of your product caused by significant food effects. Healthcare professionals have more than 20 years of experiences with bupropion, and are used to prescribing and/or dispensing bupropion without providing specific instructions to patients regarding food intake. We do not believe that the REMS with respect to significant food effects only on your product, a particular strength of bupropion, would be adequate or practical to ensure the communication of this important information to healthcare professionals and patients. The potential for confusion and medical errors remain a serious concern.*

**Discussion at Meeting:** *The sponsor requested further clarification regarding why we think a REMS would not be adequate to address the food effect associated with their product. We again explained that, because their product is a 450 mg tablet, no patient would start treatment with their product, but rather, patients would be started with other bupropion products, including Wellbutrin XL, which has no significant food effect, and then might be switched to their product if clinically indicated. It would be very difficult for health care providers to change patient behavior with regard to food intake, given that they will have been used to taking bupropion without regard to food. Therefore, we do not believe that a REMS would adequately address the potential risk associated with the food effect.*

**Question 5:**

Does FDA have any other comments, recommendations, or requirements regarding the BUP-450 clinical development plan to support the Forfivo XL 505(b) (2) NDA?

**Preliminary Comments:** *No additional comments.*

**Discussion at Meeting:** *No further discussion.*

**Chemistry Manufacturing and Controls Questions**

As recommended, the applicant plans to produce three (3) additional NDA registration stability batches consisting of (b)(4) tablets per batch, that will be representative of the commercial formulation/process. These lots will be manufactured at the new manufacturing site (b)(4). This site will use the same equipment, SOPs, environmental conditions, and controls in the manufacturing process at the new site; no changes are anticipated to the executed batch records except for administrative information and location.

**Question 6:**

As per FDA's request for information, dated November 6, 2009, the applicant had proposed in an amendment, dated December 11, 2009, an upper limit (weight gain) for the (b)(4). The applicant plans on maintaining the specifications range of the (b)(4) and introducing (b)(4) in all future manufacturing instructions. This warning limit range is unlikely to have any detectable impact on the formulation quality and performance since the total weight of the dosage form and the (b)(4)

(b) (4) are still within the original application range. **Does FDA concur that this proposed inclusion of (b) (4) would still be considered within the finished product specifications originally submitted on March 31, 2009?**

**Preliminary Comments:** *It is unclear how (b) (4) According to your batch records, the (b) (4) for batch 08039P-01 was (b) (4). At this point, we do not believe that you have provided adequate data to demonstrate that tablets produced in (b) (4) will meet the drug product specification. You will need to provide analytical data from batches manufactured at the (b) (4) to demonstrate that tablets produced at (b) (4) will meet the product specifications (e.g., assay, impurities, dissolution at release and on stability).*

**Discussion at Meeting:** *The applicant stated that the (b) (4) is the target range and that batches with a (b) (4) would be released for commercial use. We stated that information will need to be submitted to support this (b) (4). The applicant stated they have manufactured five lots at the new manufacturing site (Pillar5 Pharma Inc.): 3 lots with (b) (4), 1 lot with (b) (4) and 1 lot with (b) (4). These five lots have been placed on stability. The applicant also stated that the observed food effect could be attributed to the (b) (4). We indicated that the sponsor will need to demonstrate that there is no observable food effect at the (b) (4). The acceptability of the (b) (4) will be based on the evaluation of the submitted data. Additionally, the stability behavior of the product (b) (4) will need to be demonstrated.*

*Since the (b) (4) is a critical quality attribute, we recommended the applicant provide the (b) (4) data in the NDA.*

#### **Question 7:**

For these three (3) additional NDA registration stability batches, a side-by-side comparison of the manufacturing equipment is provided in **Error! Reference source not found.** of section 10 of this meeting package. **Does FDA have any other comments, recommendations, or requirements regarding the proposed plan to support the new manufacturing site for Forfivo XL, NDA 22-497?**

**Preliminary Comments:** *No additional comments.*

**Discussion at Meeting:** *We clarified that no additional manufacturing equipment information is needed at this time (however this information should be submitted in the sponsor's response to the CR letter). In addition, information should be provided in a response to any manufacturing process or packaging differences between the "old site" (b) (4) and the "new site" (Pillar5 Pharma Inc.).*

**Question 8:**

(b) (4)  
Following this observation a written investigation was not conducted however a visual inspection was performed by quality control personnel at (b) (4) on the finished product and the results conformed to the manufacturing specification. It was therefore concluded that this discrepancy would not have any adverse impact on the integrity of the finished product. In addition to the manufacturer's inspection, the release testing of the finished product was conducted as per the analytical testing specification and conformed. These results and the stability results collected indicate that all three batches (08016P-01, 08039P-01 and 08040P-01) behave similarly up to 12 months. See the dissolution profile of all three batches after the 12-month stability pull point.

*Figure 1 Dissolution profile comparison of all the previously manufactured batches (08016P-0, 08039P-01 and 08040P-01) after 12-months at 25°C*



Based on the stability data generated on the previously manufactured exhibit batches 08016P-01, 08039P-01 and 08040P-01, the applicant plans on relying on this stability data generated as pivotal data in determining the expiration date and will propose a 24-month expiry for the commercial drug product. **Does FDA concur with this plan?**

***Preliminary Comments:*** *It should be noted that batch (# 08039P-01) was manufactured with the (b) (4) however, placebo tablets were (b) (4) and therefore, the process is not considered representative of the*

*commercial process. In addition, the 18M dissolution data for batches 08039P-01 and 080106P-01 suggest that they fail the dissolution specification (refer to the Additional Comments section at end of the preliminary comments).*

*ICH Q1A (R2) recommends that a minimum of 12 months of long-term and 6 months of accelerated stability data be submitted at the time of submission. Based on the above concerns, we recommend that you submit 12 months of long term and 6 months of accelerated stability data (with appropriate amount of intermediate stability data, if required) for three batches of drug product representative of the commercial formulation/process manufactured at the new manufacturing site. The expiry date for your commercial product will be determined at the time of future NDA amendment review when stability data from the new manufacturing site is provided. SUPAC only applies to post approval changes. Since this product has not been approved, SUPAC does not apply in this situation. The previous stability data may be considered as supportive data.*

**Discussion at Meeting:** *We stated that SUPAC does not apply to changes to a product that has not been approved. We recommended that the applicant submit 12 months of long term and 6 months of accelerated stability data (with appropriate amount of intermediate stability data, if required) for three batches of drug product representative of the commercial formulation/process manufactured at the new manufacturing site. Clearly, we would like to assign a reasonable expiry. The applicant stated they would need more than 12 months to acquire the stability data and they were concerned of the consequences if they did not respond to the CR letter within 12 months as outlined in the letter.*

*Regarding the issue of responding to the CR letter within 12 months, the sponsor is encouraged to note that the Agency has the discretion to withdraw the application should the sponsor not respond within 1 year. However, since the sponsor is actively pursuing a response, we would not pursue this option. Alternatively, the sponsor could formally request an extension of time in which to resubmit the application. [Refer to 21CFR 314.110 Complete Response Letter to the applicant.]*

**Question 9:**

The applicant plans to apply the same manufacturing process as outlined in the original NDA 22-497 for previous exhibit batches 08016P-01, 08039P-01 and 08040P-01, for the three (3) above mentioned NDA registration stability batches. Because this is a (b) (4) change, and a “significant body of information” is not available, three months’ accelerated stability data will be provided for these three batches; long-term stability data of first three production batches will be reported in the annual report. Since the three (3) registration batches are identical with respect to manufacturing process and finished product specifications, the applicant plans to support the manufacturing site change with 3-month accelerated stability data. An NDA amendment providing the additional 6 -month of long-term stability data on all batches will be filed during the review period. **Does FDA concur with this plan?**

**Preliminary Comments:** *Refer to the response to Question 8.*

**Discussion at Meeting:** *Refer to the discussion for Question 8.*

**Question 10:**

The proposed drug product specification for the NDA-registration and eventual commercial drug product will be amended to include the black ink prior to commercialization. The applicant plans to submit 6-month long-term and 3-month accelerated stability data on the commercial drug product in the amended NDA. Are there additional tests that FDA would require be added to the specification for the drug product?

**Preliminary Comments:** *Refer to the response to Question 8. You are reminded that your product will need to have a unique identification for commercialization [refer to CFR 206.7(b)(1)(ii)].*

**Discussion at Meeting:** *We reminded the applicant that the drug product will need to have a unique identification. The drug product specification (i.e., appearance) will need to capture this unique identification. If the product is approved and then ultimately sold, the new owner may wish to change this identification code and they can do this with a prior approval supplement.*

**Question 11:**

The proposed NDA-registration stability protocol is provided in **Appendix 1** of this pre-meeting information package. Are there additional tests that FDA would recommend be added to the stability protocol for the drug product?

**Preliminary Comments:** *We recommend that you include water content and a microbial limits test.*

**Discussion at Meeting:** *We clarified that microbial limits will need to be evaluated. Testing should be performed at release and on stability (at 12 m, 24m, etc.). The applicant stated they were conducting an LOD test.*

**Question 12:**

In the complete response letter (action letter) dated February 3, 2010, question #4 requested that the analytical procedure used for acceptance testing be provided with validation data if the drug substances' analytical procedure is different from the USP methods. The applicant confirms that the drug substance has been tested as per the USP methods excluding the testing of *m*-chlorobenzoic acid, a related compound of bupropion HCl. The validation report for this method can be found in section 3.2.R. of the original NDA 22-497. The applicant plans on updating the CMC portion of the NDA to include this additional statement. **Does FDA agree that this statement will clarify the analytical procedures used for the testing of the drug substance? If not, please recommend what information would be considered sufficient to address this matter.**

**Preliminary Comments:** *Your approach seems reasonable.*

**Discussion at Meeting:** *No further discussion.*

**Question 13:**

In the complete response letter, question #8 requested open dish stability data of the commercial drug product (including appearance, assay, impurity and individual tablet dissolution data). The applicant has provided in amendment dated November 12, 2009 open dish stability data which demonstrated that the tablets meet the product specification for assay and impurity. The applicant plans to amend the analytical testing protocol to include drug product testing of the appearance, assay, impurity and individual tablet dissolution data is required. In addition the applicant plans to include a sampling time point after four (4) weeks at elevated temperature and humidity (40°C±2°C / 75% R.H.± 5% R.H.). **Does FDA agree with these proposed time points and conditions and the revised stability protocol? If not, what additional tests are required?**

**Preliminary Comments:** *Your approach seems reasonable.*

**Discussion at Meeting:** *Refer to the discussion for Question 14.*

**Question 14:**

In the complete response letter, question #9 requested in-use data to show that the product stability is not affected by opening and closing of the container during patient use. The applicant believes this concern is addressed in question #12 of this document. **Does FDA agree?**

**Preliminary Comments:** *The concerns in question #13 are not relevant to question #14. Your stability data showed that the product failed impurity specification under accelerated storage condition after 3 month at 40°C/75% RH. You have stated that this may be due to a potential seal problem. This suggests that the product stability may be affected by opening and closing of the container during patient use. An in-use stability study is needed to address this potential problem.*

**Discussion at Meeting:** *It was noted that the sponsor has observed drug product stability problems, which they attributed to an inadequate amount of torque being applied to the screw caps. Drug product will be stored for a certain period of time (warehouse) before being opened by a patient/caregiver. Individuals will use different torques to close the cap on the bottle after taking a tablet. We stated that the applicant will need to conduct an in-use-stability study (worst case scenario), which would simulate how the product would be used by a patient (e.g., 30 ct bottle where the minimum dose is 1 tablet a day would result in a 30 day study; which results in container closure being opened at least once a day over a 30 day period). All stability tests should be conducted and results reported at the end of this study.*

*It should be noted that the open dish stability studies did not generate the same level of problems, as discussed above, which may be due to different humidity conditions.*

**Question 15:**

Question #9 also requested information demonstrating that the amount of desiccant in the drug product container/closure is optimal. The applicant provided information in amendment dated December 11, 2009 which demonstrates that the amount of desiccants is satisfactory. This is further supported by the long term stability testing data which show that the drug product is stable for at least 18 months. Refer to section 3.2.P.8.3 of the CMC section of the NDA 22-497 for all stability details. Additional stability data is provided in *Appendix 2* and will be updated at the time that the NDA amendment is submitted. **Does FDA agree that these data are sufficient? If not, the applicant requests FDA's guidance on how to address this matter.**

**Preliminary Comments:** *As discussed in question #8, two batches failed dissolution at 18M. Additional data is needed to demonstrate that this is not due to insufficient desiccant in the bottle. This issue will be evaluated in part from the review of your 12 months of stability data from the new manufacturing site. In addition, we refer to Q14 (seal problem as it relates to stability problems) and the in-use stability study which will also evaluate whether an adequate amount of desiccant is being utilized.*

**Discussion at Meeting:** *Refer to the discussions for Questions 8 and 14.*

**Question 16:**

In the complete response letter, question #11a requested information on how (b) (4)

The applicant provided a literature reference in amendment dated December 11, 2009 which stated that bupropion hydrochloride demonstrates pH dependence and can be stabilized at low pH. It was determined that in order to maintain the integrity of the bupropion hydrochloride during (b) (4)

**If not, the applicant requests FDA's guidance on how to address this matter.**

**Preliminary Comments:** *The proposed in-process pH limit should include an acceptable pH range (b) (4) Any selected process parameters will need to be supported by experimental data.*

**Discussion at Meeting:** *No further discussion.*

**Question 17:**

Question #11d of the complete response letter stated that three drug product batches had a problem associated with the drug product (b) (4). To briefly summarize the manufacturing situation, a total of 6 stability lots were prepared in 2 manufacturing campaigns. All lots are identical with respect to their quantitative and qualitative composition and manufacturing procedure. During the stability testing of the first 3 lots (primary stability data), a slight drop of the dissolution rate after 1 month storage at accelerated storage conditions was observed. However, dissolution rates still were within specifications, and no further drop was observed at the subsequent pull points. This observation was attributed to (b) (4). During the manufacturing of the second 3 lots (supportive stability data), the processing parameters for (b) (4) (For all details regarding the optimization of (b) (4) of the stability lots refer to the report "Stability – BUP 450 Tablets" which is located in section 3.2.R.10 of the NDA 22-497.). The Agency further suggested that the dissolution profile of the drug product will be compromised if (b) (4) is not properly controlled. The applicant maintains that the current commercial process is optimized and that the inclusion of (b) (4) (used for batch no. 08016P-01, 08039-P01 and 08040P-01) resulted in meeting the product specifications (reference 3.2.P.8 of the CMC portion of the NDA 22-497). **Does the FDA agree that the analytical data provided confirm that the problem has been resolved?**

**Preliminary Comments:** Refer to the response to Question 8. The adequacy of your manufacturing process will be determined as part of the review of your updated data package and any possible inspections.

**Discussion at Meeting:** Refer to the discussion for Question 8.

### **Question 18:**

Question 11f requested analytical data from batches manufactured at (b) (4) to demonstrate that the tablets (b) (4) will meet the product specifications (assay, dissolution and stability). Batch no. 08016P-01 was (b) (4) and batch no. 08039P-01 was (b) (4). All analytical data can be found in section 3.2.P.8 of the CMC portion of the NDA 22-497 and clearly demonstrate that these tablets, (b) (4) meet the product specifications. **Does FDA agree that the analytical data provided demonstrate that the tablets produced (b) (4) meet the product specifications?**

**Preliminary Comments:** Refer to response to Question 6.

**Discussion at Meeting:** Refer to the discussion for Question 6.

### **Question 19:**

In the information request letter received November 6, 2010, question #3 requested information to support the use of this ink in tablet printing. The applicant plans on removing approximately (b) (4) tablets from each of the recommended registration batches (three batches in total), printing them with a black ink manufactured by (b) (4) and then placing them on stability. (b) (4) and the type of black ink applied used in this study will be identical to the process done on future commercial batches. The applicant plans on testing the printed tablet after 1 month under accelerated conditions only, 3 months at long term and accelerated stability conditions and 6 months long term and accelerated stability conditions as well. Although this printing trial will be conducted as a compatibility study, finished product and stability testing will be conducted as per the drug product analytical specifications. **Does FDA agree that this plan will provide information to support the use of this ink in the tablet printing?**

**Preliminary Comments:** Refer to response to Question 8. Clarify if this study will be conducted using tablets from the new drug product manufacturing site.

**Discussion at Meeting:** Sponsor's proposal seems reasonable.

**Question 20:**

Does FDA have any other comments, recommendations, or requirements regarding the BUP-450 CMC development plans?

**Preliminary Comments:** No further comments at this time.

**Discussion at Meeting:** No further discussion.

**Regulatory Question**

**Question 21:**

The applicant would like to know at which point during the review process of the amendment to the original NDA 22-497 will the pre-approval inspection at the manufacturing site (Pillar 5 Pharma) will occur?

**Preliminary Comments:** All sites will need to be ready for inspection at the time of your complete response to the CR letter.

**Discussion at Meeting:** No further discussion.

**Additional Comments**

The following comments from the ONDQA Biopharm group were not included in the CR action letter dated February 3, 2010.

1. The proposed dissolution acceptance criteria for the 4 and 8 hours (buffer stage) sampling time points are not acceptable. The acceptance criteria should be within (b) (4) of the target values, unless an IVIVC is established to justify wider ranges. For the setting of the dissolution specifications without an IVIVC, please refer to the Guidance for Industry, entitled, "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations".
2. Based on the provided dissolution data, the following dissolution method and acceptance criteria are recommended for your product.

<b>Dissolution Method for Bupropion HCl Extended Release Tablets</b>			
<b>Acid Stage</b>		<b>Buffer Stage</b>	
Apparatus	USP Apparatus 1 (Baskets)	Apparatus	USP Apparatus 1 (Baskets)
Medium	Simulated Gastric Fluid (HCl pH 1.2)	Medium	Tris Buffer pH 6.8
Volume	900 ml	Volume	900 ml
Temperature	37°C	Temperature	37°C
Rotation Speed	75 rpm	Rotation Speed	75 rpm
Sampling Time	2 hrs	Sampling Times	4, 8, and 16 hrs
<b>Dissolution Acceptance Criteria</b>			
<b>Acid Stage</b>		<b>Buffer Stage</b>	
Time	Percent Dissolved	Time	Percent Dissolved
2 hrs	NMT (b) (4)	4 hrs	(b) (4)
		8 hrs	(b) (4)
		16 hrs	NLT (b) (4)

Please revise the acceptance criteria sheets for your product.

**Discussion:** The sponsor will check the available dissolution data. For the future batches, sufficient samples will be placed in the stability program to proceed if necessary up to Level 3 evaluation to comply with the Agency’s proposed dissolution specifications.

During the meeting, the sponsor was asked to clarify the proposed media to be used in the final dissolution methodology for Stage I (acid stage) and Stage II (buffer stage); (b) (4)

 <sup>(b) (4)</sup> have been used in different places of the application. The sponsor agreed to check this information and get back to us.

**Post meeting comments regarding regulatory requirement pertaining to CR response time frames (also see discussion under Question 8):**

*The sponsor is again reminded that the Agency has the discretion to withdraw the application should the sponsor not respond within 1 year. Since the sponsor is actively pursuing a response, we would not pursue this option. Alternatively, the sponsor could formally request an extension of time in which to resubmit the application. [Refer to 21CFR 314.110 Complete Response Letter to the applicant.]*

These minutes are the official minutes of the meeting. IntelGenx Corp is responsible for notifying us of any significant differences in understanding the group has regarding the meeting outcomes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22497	GI-1	INTELGENX CORP	BUP-450 (BUPROPION HCL)450MG ER ORAL TAB

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

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/s/

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THOMAS P LAUGHREN  
06/23/2010

## FDA Preliminary Responses

NDA 22497 – FORFIVO XL (Bupropion HCL 450 mg Extended Release)  
Cary Pharmaceuticals, Inc.  
Type C Meeting  
Face-to-Face  
NDA

Cary Pharmaceuticals, Inc. (Cary) requested this meeting in a submission dated April 2, 2010 which was received April 6, 2010. This is a Type C NDA Face-to-Face meeting to discuss the current status and future plans for their developmental program for Forfivo XL (bupropion hydrochloride 450mg extended release tablets) for Major Depressive Disorder (MDD). The meeting package dated May 10, 2010 was received on May 10, 2010.

### FDA ATTENDEES:

Thomas Laughren, M.D.	Division Director, Division of Psychiatry Products (DPP)
Mitchell Mathis, M.D.	Deputy Division Director, DPP
Jing Zhang, M.D.	Medical Team Leader
Jenn Sellers, M.D.	Medical Reviewer
Raman Baweja, Ph.D.	Clinical Pharmacology Team Leader
Bei Yu, Ph.D.	Clinical Pharmacology Reviewer
Linda Fossom, Ph.D.	Pharmacology/ Toxicology Team Leader
Shiny Mathew, Ph.D.	Pharmacology/Toxicology Reviewer
Ramesh Sood, Ph.D.	Branch chief, Division of New Drug Assessment I, ONDQA
Thomas Oliver, Ph.D.	CMC Lead, ONDQA
Pei-I Chu, Ph.D.	CMC Reviewer, ONDQA
Tapash Ghosh, Ph.D.	Biopharmaceutics Reviewer, DCP I, OCP
Teshara Bouie, MSA, OTR/L	Regulatory Project Manager, OPS/ ONDQA
William Bender, R.Ph.	Senior Regulatory Project Manager, DPP
Kofi Ansah, Pharm.D.	Senior Regulatory Project Manager, DPP

### Cary Pharmaceuticals, Inc.'s Attendees:

Horst Zerbe, M.D., Ph.D. (b) (4)	President and CEO, IntelGenx Corp. (b) (4)
Nancy Austin	Manager, Regulatory Affairs & Compliance IntelGenx Corp.

### Background:

Cary Pharmaceuticals, Inc. (Cary) of Great Falls, Virginia and IntelGenx Corp., St-Laurent, Quebec, Canada, have developed an oral extended-release formulation of 450

mg bupropion hydrochloride (FORFIVO XL) for the treatment of major depressive disorder (MDD). Forfivo XL is a novel extended-release tablet that contains 450 mg of bupropion (b) (4) intended to be comparable to the reference listed drug product Wellbutrin XL (GlaxoSmithKline). The tablets are (b) (4). The release of the active substance is initially delayed and essentially completed 18 hours post-administration.

Cary's development program for this extended-release formulation containing 450 mg bupropion hydrochloride was under IND (b) (4). During the drug development phase, a PRE-IND meeting was held on January 30, 2007 and an end-of-phase II (EOP2) meeting was held on July 14, 2008. At the PRE-IND meeting, the Division required Cary Pharmaceuticals to do a food-effect study in addition to the bioequivalence study they proposed. The Division also advised Cary, at the EOP2 meeting, to do an alcohol dose dumping study to look at the *in vitro* effect of alcohol on dosing.

On March 31, 2009, Cary Pharmaceuticals submitted their new drug application (NDA 022497) under the provision of section 505(b)(2) of the Federal Food Drug, and Cosmetic Act to obtain marketing approval of Forfivo XL once daily for the indication of major depressive disorder (MDD). This submission included two clinical Phase I studies (bioequivalence and food effect studies) and one *in vitro* study (dose dumping with alcohol). Clinical efficacy studies were not conducted on this product. The reference listed drug (RLD) product is Wellbutrin XL<sup>®</sup> (bupropion hydrochloride) 150 mg Extended-Release Tablets, GlaxoSmithKline (GSK) approved by FDA on 08/28/2003 under NDA 021515. Wellbutrin XL<sup>®</sup> is indicated in the treatment of MDD and seasonal affective disorder in the dosage forms of 150 mg and 300 mg. Cary plans to only seek an indication for MDD, and not for seasonal affective disorder.

For the treatment of major depressive disorder, the currently available formulations of bupropion hydrochloride are: Wellbutrin immediate release (IR) tablet (75 mg and 100 mg) that is given three times daily; Wellbutrin sustained release (SR) tablet (50 mg, 100 mg, 150 mg, and 200 mg) that is given twice daily; and Wellbutrin XL<sup>®</sup> tablet (150 mg and 300 mg) that is given once daily after an up-titration. Bupropion hydrochloride 450 mg/day given as a single dose is an approved dose in the treatment of MDD in adults, but not an approved strength of Wellbutrin XL<sup>®</sup> (requiring administration of 150 and/or 300 mg tablets i.e., 3x150 mg, or 150 mg + 300 mg as a single dose). Forfivo XL would be a new higher strength formulation of the currently marketed bupropion hydrochloride extended-release drug product for which the highest strength is 300 mg.

Bupropion is extensively hepatically metabolized. It has three pharmacologically active metabolites, hydroxybupropion, threohydrobupropion (bupropion threoamino alcohol), and erythrohydrobupropion (bupropion erythroamino alcohol) that account for over 90% of the exposure following administration of bupropion. Based on an animal study, hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. Recently, an animal study showed that all three active metabolites caused seizures and were more potent convulsants than the parent drug. A summary of relative AUC at steady state, relative potency, and

therapeutic contribution (AUC x Potency) for bupropion and its active metabolites is shown in the table below:

Moiety	AUC	Potency	AUC x Potency
<b>Bupropion</b>	1	1	1 (11%)
<b>Hydroxybupropion</b>	13	0.5	6.5 (71%)
<b>Erythrohydrobupropion</b>	1.4	0.2	0.28 (3%)
<b>Threo hydrobupropion</b>	7	0.2	1.4 (15%)
<b>Total</b>	–	–	9.18 (100%)

*Ref: Wellbutrin XL Package Insert; Clinical Pharmacology.*

Cary argues that Forfivo XL would provide for the extended-release of bupropion and the blunting of  $C_{max}$  compared to the instant release formulation, and like other extended-release formulations, should decrease the risk of seizures. Moreover, by allowing patients to take only one 450 mg tablet, rather than three 150 mg tablets, or a combination of 150 mg and 300 mg tablets, Cary predicts that this new formulation should decrease the risk of dosing errors and the consequent risk of inadvertent overdose. Cary also argues that Forfivo XL should also improve compliance and therefore efficacy, since it is easier for patients to take one tablet rather than a combination of two or three tablets. Forfivo XL, therefore, represents a “convenience reformulation” only and would not involve any changes to the dosage and administration section of the current labeling of the reference listed drug.

### Questions from the sponsor:

#### *Clinical Questions*

As described in the CMC section, the applicant plans to produce three (3) additional NDA registration stability batches consisting of (b) (4) tablets per batch that will be representative of the commercial formulation/process. These lots will be manufactured at the new manufacturing site (b) (4). This site will use the same/equivalent equipment, and the same SOPs, environmental conditions, and controls in the manufacturing process at the new site; no changes are anticipated to the executed batch records except for administrative information and location. In addition to the above mentioned plans, the applicant plans to (b) (4). This is discussed in more detail in the CMC section. One of these lots will be tested in the BE study described below.

The applicant plans to demonstrate the BE of Forfivo XL with 3 x 150 mg Wellbutrin XL under fasting conditions and the bioavailability of Forfivo XL in the fed state in a three-way cross over study comparing Forfivo XL fasting, Forfivo XL fed and 3 x 150 mg Wellbutrin XL fasting.

### **Question 1:**

For this pivotal study, assuming that the fasting Wellbutrin XL and Forfivo XL treatment arms are bioequivalent and that AUC and  $C_{max}$  for the Forfivo XL fed arm are within  $\pm 20\%$  of Forfivo XL fasting. **Does FDA agree that**

- a. **this study meets the FDA’s requirements for a “single-dose, food-effect study”,**
- b. **this study will address the food effect concerns outlined in the complete response letter (action letter), and that**
- c. **this study is sufficient to demonstrate that product manufactured at the new manufacturing site is bioequivalent to the RLD?**

**Preliminary Comments:** *The study design for the proposed study (protocol No BPO-P0-520) is acceptable to evaluate BE between Forfivo XL (450 mg) and Wellbutrin XL (3 x 150 mg) under fasted conditions, and to assess the effect of food on Forfivo XL (450 mg). The established criterion for BE, however, is not that the AUC and  $C_{max}$  ratio for the Forfivo XL (450 mg) fed arm should be within  $\pm 20\%$  of Forfivo XL fasting arm of the study. For evaluating both, BE between Forfivo XL 450 mg and 3 X 150 mg Wellbutrin XL, and, for assessing the effect of food on Forfivo XL 450 mg tablet (fed versus fasted states), the two one-sided 90 % confidence interval (CI) approach should be applied to the individual parameters of interest (e.g., AUC and  $C_{MAX}$ ) based on log transformed data. To declare equivalence the parameters of interest (AUC and  $C_{max}$ ) should fall within 80-125 %.*

### **Discussion at Meeting:**

### **Question 2:**

For this pivotal study, the applicant plans to demonstrate the BE between Forfivo XL and Wellbutrin XL with respect to bupropion and hydroxybupropion, the primary active metabolite only. In addition the applicant plans to demonstrate the absence of an appreciable food effect by comparing Forfivo XL fasting and Forfivo XL fed with respect to bupropion and hydroxybupropion, the primary active metabolite only. **Does FDA concur with this plan?**

**Preliminary Comments:** *Based on the draft protocol (No BPO-P0-520), OCP has the following comments:*

1. *All four moieties, i.e., bupropion - the parent drug, and the three metabolites - hydroxybupropion, erythrohydrobupropion, and threohydrobupropion, should be analyzed in the study.*
2. *Additional PK blood sampling time points until 120-hour post dose should be added.*

3. *Smokers should not be included in the “Inclusion Criteria”, i.e., only non-smokers should be enrolled in the study.*

*We look forward to receiving the final protocol.*

**Discussion at Meeting:**

**Question 3:**

In the complete response letter (action letter) dated February 3, 2010, the “*Clinically Important Food Effect*” section, FDA also pointed out that a number of subjects showed  $C_{max}$  values that were more than two-fold higher than the RLD. The applicant plans on demonstrating that inclusion of (b) (4)

(b) (4) will reduce or eliminate the apparent food effect, and reduce the excessive peak plasma concentrations that were observed after administration of (b) (4) tablets in the NDA study.

**Does FDA concur that this plan will address this clinical concern?**

**Preliminary Comments:** *This will be a matter for review. You may include any number of processing changes including this one. The question above can only be answered after the data and the results obtained from the study, have been reviewed.*

**Discussion at Meeting:**

**Question 4:**

In the complete response letter (action letter) dated February 3, 2010, the “*Clinically Important Food Effect*” section, FDA pointed out that the clinical problem would require a very intensive educational effort and no such program has been provided. If the new pivotal study shows that Forfivo XL does not meet BE requirements when administered with food, the applicant plans to comply with this requirement and will work with FDA to provide an effective Risk Evaluation and Mitigation Strategy (REMS) in the NDA amendment submission. **Does FDA concur that this plan will address this clinical concern?**

**Preliminary Comments:** *No. We do not believe that a REMS would address our clinical concerns regarding increased seizure risks of your product caused by significant food effects. Healthcare professionals have more than 20 years of experiences with bupropion, and are used to prescribing and/or dispensing bupropion without providing specific instructions to patients regarding food intake. We do not believe that the REMS with respect to significant food effects only on your product, a particular strength of bupropion, would be adequate or practical to ensure the communication of this important information to healthcare professionals and patients. The potential for confusion and medical errors remain a serious concern.*

**Discussion at Meeting:**

**Question 5:**

Does FDA have any other comments, recommendations, or requirements regarding the BUP-450 clinical development plan to support the Forfivo XL 505(b) (2) NDA?

**Preliminary Comments:** *No additional comments.*

**Discussion at Meeting:**

***Chemistry Manufacturing and Control Questions***

As recommended, the applicant plans to produce three (3) additional NDA registration stability batches consisting of (b) (4) tablets per batch, that will be representative of the commercial formulation/process. These lots will be manufactured at the new manufacturing site (b) (4). This site will use the same equipment, SOPs, environmental conditions, and controls in the manufacturing process at the new site; no changes are anticipated to the executed batch records except for administrative information and location.

**Question 6:**

As per FDA's request for information, dated November 6, 2009, the applicant had proposed in an amendment, dated December 11, 2009, an upper limit (weight gain) for the (b) (4). The applicant plans on maintaining the specifications range of the (b) (4) and introducing (b) (4) in all future manufacturing instructions. This warning limit range is unlikely to have any detectable impact on the formulation quality and performance since the total weight of the dosage form and the (b) (4) are still within the original application range. **Does FDA concur that this proposed inclusion of (b) (4) would still be considered within the finished product specifications originally submitted on March 31, 2009?**

**Preliminary Comments:** *It is unclear how (b) (4) According to your batch records, the (b) (4) for batch 08039P-01 was (b) (4). At this point, we do not believe that you have provided adequate data to demonstrate that tablets produced in the proposed (b) (4) will meet the drug product specification. You will need to provide analytical data from batches manufactured at the (b) (4) to demonstrate that tablets produced at (b) (4) will meet the product specifications (e.g., assay, impurities, dissolution at release and on stability).*

**Discussion at Meeting:**

**Question 7:**

For these three (3) additional NDA registration stability batches, a side-by-side comparison of the manufacturing equipment is provided in **Error! Reference source not found.** of section 10 of this meeting package. **Does FDA have any other comments, recommendations, or requirements regarding the proposed plan to support the new manufacturing site for Forfivo XL, NDA 22-497?**

**Preliminary Comments:** *No additional comments.*

**Discussion at Meeting:**

**Question 8:**

(b) (4)  
Following this observation a written investigation was not conducted however a visual inspection was performed by quality control personnel at (b) (4) on the finished product and the results conformed to the manufacturing specification. It was therefore concluded that this discrepancy would not have any adverse impact on the integrity of the finished product. In addition to the manufacturer's inspection, the release testing of the finished product was conducted as per the analytical testing specification and conformed. These results and the stability results collected indicate that all three batches (08016P-01, 08039P-01 and 08040P-01) behave similarly up to 12 months. See the dissolution profile of all three batches after the 12-month stability pull point.

*Figure 1 Dissolution profile comparison of all the previously manufactured batches (08016P-0, 08039P-01 and 08040P-01) after 12-months at 25°C*



Based on the stability data generated on the previously manufactured exhibit batches 08016P-01, 08039P-01 and 08040P-01, the applicant plans on relying on this stability data generated as pivotal data in determining the expiration date and will propose a 24-month expiry for the commercial drug product. **Does FDA concur with this plan?**

**Preliminary Comments:** *It should be noted that batch (# 08039P-01) was manufactured with the (b) (4) however, placebo tablets were (b) (4) and therefore, the process is not considered representative of the commercial process. In addition, the 18M dissolution data for batches 08039P-01 and 080106P-01 suggest that they fail the dissolution specification (refer to the Additional Comments section at end of the preliminary comments).*

*ICH Q1A (R2) recommends that a minimum of 12 months of long-term and 6 months of accelerated stability data be submitted at the time of submission. Based on the above concerns, we recommend that you submit 12 months of long term and 6 months of accelerated stability data (with appropriate amount of intermediate stability data, if required) for three batches of drug product representative of the commercial formulation/process manufactured at the new manufacturing site. The expiry date for your commercial product will be determined at the time of future NDA amendment review when stability data from the new manufacturing site is provided. SUPAC only applies to post approval changes. Since this product has not been approved, SUPAC*

*does not apply in this situation. The previous stability data may be considered as supportive data.*

**Discussion at Meeting:**

**Question 9:**

The applicant plans to apply the same manufacturing process as outlined in the original NDA 22-497 for previous exhibit batches 08016P-01, 08039P-01 and 08040P-01, for the three (3) above mentioned NDA registration stability batches. Because this is a (b) (4) change, and a “significant body of information” is not available, three months’ accelerated stability data will be provided for these three batches; long-term stability data of first three production batches will be reported in the annual report. Since the three (3) registration batches are identical with respect to manufacturing process and finished product specifications, the applicant plans to support the manufacturing site change with 3-month accelerated stability data. An NDA amendment providing the additional 6 -month of long-term stability data on all batches will be filed during the review period. **Does FDA concur with this plan?**

**Preliminary Comments:** *Refer to the response to Question 8.*

**Discussion at Meeting:**

**Question 10:**

The proposed drug product specification for the NDA-registration and eventual commercial drug product will be amended to include the black ink prior to commercialization. The applicant plans to submit 6-month long-term and 3-month accelerated stability data on the commercial drug product in the amended NDA. Are there additional tests that FDA would require be added to the specification for the drug product?

**Preliminary Comments:** *Refer to the response to Question 8. You are reminded that your product will need to have a unique identification for commercialization [refer to CFR 206.7(b)(1)(ii)].*

**Discussion at Meeting:**

**Question 11:**

The proposed NDA-registration stability protocol is provided in **Appendix 1** of this pre-meeting information package. Are there additional tests that FDA would recommend be added to the stability protocol for the drug product?

**Preliminary Comments:** *We recommend that you include water content and a microbial limits test.*

**Discussion at Meeting:**

**Question 12:**

In the complete response letter (action letter) dated February 3, 2010, question #4 requested that the analytical procedure used for acceptance testing be provided with validation data if the drug substances' analytical procedure is different from the USP methods. The applicant confirms that the drug substance has been tested as per the USP methods excluding the testing of *m*-chlorobenzoic acid, a related compound of bupropion HCl. The validation report for this method can be found in section 3.2.R. of the original NDA 22-497. The applicant plans on updating the CMC portion of the NDA to include this additional statement. **Does FDA agree that this statement will clarify the analytical procedures used for the testing of the drug substance? If not, please recommend what information would be considered sufficient to address this matter.**

**Preliminary Comments:** *Your approach seems reasonable.*

**Discussion at Meeting:**

**Question 13:**

In the complete response letter, question #8 requested open dish stability data of the commercial drug product (including appearance, assay, impurity and individual tablet dissolution data). The applicant has provided in amendment dated November 12, 2009 open dish stability data which demonstrated that the tablets meet the product specification for assay and impurity. The applicant plans to amend the analytical testing protocol to include drug product testing of the appearance, assay, impurity and individual tablet dissolution data is required. In addition the applicant plans to include a sampling time point after four (4) weeks at elevated temperature and humidity (40°C±2°C / 75% R.H.± 5% R.H.). **Does FDA agree with these proposed time points and conditions and the revised stability protocol? If not, what additional tests are required?**

**Preliminary Comments:** *Your approach seems reasonable.*

**Discussion at Meeting:**

**Question 14:**

In the complete response letter, question #9 requested in-use data to show that the product stability is not affected by opening and closing of the container during patient use. The applicant believes this concern is addressed in question #12 of this document. **Does FDA agree?**

**Preliminary Comments:** *The concerns in question #13 are not relevant to question #14. Your stability data showed that the product failed impurity specification under accelerated storage condition after 3 month at 40°C/75% RH. You have stated that this may be due to a potential seal problem. This suggests that the product stability may be affected by opening and closing of the container during patient use. An in-use stability study is needed to address this potential problem.*

**Discussion at Meeting:**

**Question 15:**

Question #9 also requested information demonstrating that the amount of desiccant in the drug product container/closure is optimal. The applicant provided information in amendment dated December 11, 2009 which demonstrates that the amount of desiccants is satisfactory. This is further supported by the long term stability testing data which show that the drug product is stable for at least 18 months. Refer to section 3.2.P.8.3 of the CMC section of the NDA 22-497 for all stability details. Additional stability data is provided in *Appendix 2* and will be updated at the time that the NDA amendment is submitted. **Does FDA agree that these data are sufficient? If not, the applicant requests FDA's guidance on how to address this matter.**

**Preliminary Comments:** *As discussed in question #8, two batches failed dissolution at 18M. Additional data is needed to demonstrate that this is not due to insufficient desiccant in the bottle. This issue will be evaluated in part from the review of your 12 months of stability data from the new manufacturing site. In addition, we refer to Q14 (seal problem as it relates to stability problems) and the in-use stability study which will also evaluate whether an adequate amount of desiccant is being utilized.*

**Discussion at Meeting:**

**Question 16:**

In the complete response letter, question #11a requested information on how (b) (4)

The applicant provided a literature reference in amendment dated December 11, 2009 which stated that bupropion hydrochloride demonstrates pH dependence and can be stabilized at low pH. It was determined that in order to maintain the integrity of the bupropion hydrochloride during the (b) (4)

**If not, the applicant requests FDA's guidance on how to address this matter.**

**Preliminary Comments:** *The proposed in-process pH limit should include an acceptable pH range (b) (4). Any selected process parameters will need to be supported by experimental data.*

**Discussion at Meeting:**

**Question 17:**

Question #11d of the complete response letter stated that three drug product batches had a problem associated with the drug product (b) (4). To briefly summarize the manufacturing situation, a total of 6 stability lots were prepared in 2 manufacturing campaigns. All lots are identical with respect to their quantitative and qualitative composition and manufacturing procedure. During the stability testing of the first 3 lots (primary stability data), a slight drop of the dissolution rate after 1 month storage at accelerated storage conditions was observed. However, dissolution rates still were within specifications, and no further drop was observed at the subsequent pull points. This observation was attributed to (b) (4). During the manufacturing of the second 3 lots (supportive stability data), the processing parameters for (b) (4) (For all details regarding the optimization of (b) (4) of the stability lots refer to the report “Stability – BUP 450 Tablets” which is located in section 3.2.R.10 of the NDA 22-497.). The Agency further suggested that the dissolution profile of the drug product will be compromised if (b) (4) is not properly controlled. The applicant maintains that the current commercial process is optimized and that the inclusion of (b) (4) (used for batch no. 08016P-01, 08039-P01 and 08040P-01) resulted in meeting the product specifications (reference 3.2.P.8 of the CMC portion of the NDA 22-497). **Does the FDA agree that the analytical data provided confirm that the problem has been resolved?**

**Preliminary Comments:** *Refer to the response to Question 8. The adequacy of your manufacturing process will be determined as part of the review of your updated data package and any possible inspections.*

**Discussion at Meeting:**

**Question 18:**

Question 11f requested analytical data from batches manufactured at (b) (4) (b) (4) to demonstrate that the tablets (b) (4) will meet the product specifications (assay, dissolution and stability). Batch no. 08016P-01 was (b) (4) and batch no. 08039P-01 was (b) (4). All analytical data can be found in section 3.2.P.8 of the CMC portion of the NDA 22-497 and clearly demonstrate that these tablets, (b) (4) meet the product specifications. **Does FDA agree that the**

analytical data provided demonstrate that the tablets produced meet the product specifications?

(b) (4)

**Preliminary Comments:** Refer to response to Question 6.

**Discussion at Meeting:**

**Question 19:**

In the information request letter received November 6, 2010, question #3 requested information to support the use of this ink in tablet printing. The applicant plans on removing approximately 2000 tablets from each of the recommended registration batches (three batches in total), printing them with a black ink manufactured by (b) (4) and then placing them on stability. (b) (4) and the type of black ink applied used in this study will be identical to the process done on future commercial batches. The applicant plans on testing the printed tablet after 1 month under accelerated conditions only, 3 months at long term and accelerated stability conditions and 6 months long term and accelerated stability conditions as well. Although this printing trial will be conducted as a compatibility study, finished product and stability testing will be conducted as per the drug product analytical specifications. **Does FDA agree that this plan will provide information to support the use of this ink in the tablet printing?**

**Preliminary Comments:** Refer to response to Question 8. Clarify if this study will be conducted using tablets from the new drug product manufacturing site.

**Discussion at Meeting:**

**Question 20:**

Does FDA have any other comments, recommendations, or requirements regarding the BUP-450 CMC development plans?

**Preliminary Comments:** No further comments at this time.

**Discussion at Meeting:**

**Regulatory Question**

**Question 21:**

The applicant would like to know at which point during the review process of the amendment to the original NDA 22-497 will the pre-approval inspection at the manufacturing site (Pillar 5 Pharma) will occur?

**Preliminary Comments:** All sites will need to be ready for inspection at the time of your complete response to the CR letter.

**Discussion at Meeting:**

**Additional Comments**

The following comments from the ONDQA Biopharm group were not included in the CR action letter dated February 3, 2010.

1. The proposed dissolution acceptance criteria for the 4 and 8 hours (buffer stage) sampling time points are not acceptable. The acceptance criteria should be within (b)(4) of the target values, unless an IVIVC is established to justify wider ranges. For the setting of the dissolution specifications without an IVIVC, please refer to the Guidance for Industry, entitled, "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations".
2. Based on the provided dissolution data, the following dissolution method and acceptance criteria are recommended for your product.

<b>Dissolution Method for Bupropion HCl Extended Release Tablets</b>			
<b>Acid Stage</b>		<b>Buffer Stage</b>	
Apparatus	USP Apparatus 1 (Baskets)	Apparatus	USP Apparatus 1 (Baskets)
Medium	Simulated Gastric Fluid (HCl pH 1.2)	Medium	Tris Buffer pH 6.8
Volume	900 ml	Volume	900 ml
Temperature	37°C	Temperature	37°C
Rotation Speed	75 rpm	Rotation Speed	75 rpm
Sampling Time	2 hrs	Sampling Times	4, 8, and 16 hrs
<b>Dissolution Acceptance Criteria</b>			
<b>Acid Stage</b>		<b>Buffer Stage</b>	
Time	Percent Dissolved	Time	Percent Dissolved
2 hrs	NMT (b)(4)	4 hrs	(b)(4)
		8 hrs	(b)(4)
		16 hrs	NLT (b)(4)

Please revise the acceptance criteria sheets for your product.

*General Comments: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion during the face-to-face meeting scheduled for June 10, 2010 between Cary Pharmaceuticals, Inc and the Division of Psychiatry Products. This material is shared to promote a collaborative and successful discussion during the meeting. 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 CDR Kofi Ansah). 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 CDR Kofi Ansah to discuss the possibility of including these for discussion at the meeting.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22497	GI-1	INTELGENX CORP	BUP-450 (BUPROPION HCL)450MG ER ORAL TAB

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/s/

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KOFI B ANSAH  
06/07/2010



NDA 022497

**ACKNOWLEDGE TRANSFER NDA OWNERSHIP**

IntelGenx Corp  
Attention: Bethany Hills, JD, MPH, Esq.  
Hodgson Russ LLP  
The Guaranty Building  
140 Pearl Street, Suite 100  
Buffalo, NY 14202-4040

Dear Ms. Hills:

We acknowledge receipt on May 18, 2010, of your May 10, 2010, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product: Bupropion hydrochloride 450mg extended-release tablets

NDA Number: 022497

Name of New Applicant: IntelGenx Corp

Name of Previous Applicant: Cary Pharmaceuticals, Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate IntelGenx, Corp as the applicant of record 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:

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, contact CDR Kofi Ansah, Senior Regulatory Project Manager, at (301)796-4158.

Sincerely,

*{See appended electronic signature page}*

CAPT Paul David, R.Ph.  
Chief, Project Management Staff  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc: Cary Pharmaceuticals, Inc.  
Attention: Douglas D. Cary  
President and CEO  
9903 Windy Hollow Road  
Great Falls, VA 22066 - 3550

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22497	GI-1	CARY PHARMACEUTICA LS INC	BUP-450 (BUPROPION HCL)450MG ER ORAL TAB

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/s/

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PAUL A DAVID  
05/21/2010

**From:** [Ansah, Kofi](#)  
**To:** ["Doug Cary";](#)  
**Subject:** MEETING REQUEST GRANTED -- NDA 22-497 /  
CARY PHARMS/ FORFIVO XL (BUPROPION HCL 450MG ER)/ MDD  
**Date:** Thursday, April 08, 2010 7:29:56 PM  
**Attachments:** [FOREIGN VISITOR DATA REQUEST FORM.doc](#)

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Dear Mr. Cary,

Your meeting requested on April 2, 2010 has been granted. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type C meeting as described in our guidance for industry titled Formal Meetings with Sponsors and Applicants for PDUFA Products (February 2000). The meeting is scheduled:

**A. FOR A FACE-TO-FACE MEETING**

**Date: JUNE 10, 2010**

**Time: 2:00 PM**

**Location: FDA White Oak Campus, Building 22, Room #1419  
10903 New Hampshire Ave, Silver Spring, MD 20993**

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov) so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards the following numbers to request an escort to the conference room: CDR Kofi Ansah, x 6-4158 or Dave Berman, x 6-1044.

Provide the **background information** for this meeting (three copies to the NDA and 15 desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by **11 May 2010**, we may cancel or reschedule the meeting.

Please mail the **desk copies** to the following address:

ATTN: CDR Kofi B. Ansah  
FDA/ CDER/ OND/ ODE-I/ DPP  
White Oak Bldg 22, Room 4109

10903 New Hampshire Avenue,  
Silver Spring, MD 20993 - 0002

Additionally, please e-mail me ([Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)) an electronic/ or word file containing your proposed questions at the same time at which you send in the meeting package.

Finally, please find attached a Foreign Visitor Data Request Form that needs to be completed and submitted for each international attendee. If applicable in your case, this form must be completed and submitted to me via secured email no later than 12 days before the meeting [i.e. by May 28, 2010].

Thanks,  
Kofi.

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***Kofi Boadu Ansah, R.Ph., Pharm.D.***

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I

10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22497

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GI-1

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CARY  
PHARMACEUTICA  
LS INC

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BUP-450 (BUPROPION  
HCL)450MG ER ORAL TAB

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/s/  
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KOFI B ANSAH  
04/08/2010

**From:** [Ansah, Kofi](#)  
**To:** ["Doug Cary";](#)  
**cc:** [Henry, Don;](#)  
**Subject:** MEETING REQUEST DENIED -- NDA 22-497 /  
CARY PHARMS/ FORFIVO XL (BUPROPION HCL 450MG ER)/ MDD  
**Date:** Friday, January 22, 2010 3:22:56 PM

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Dear Mr. Cary,

Regarding your NDA 22497 currently under review, we are unable to grant your Meeting Request submitted on January 19, 2010 and received January 20, 2010.

Given that your pending application is before us at the moment, with an Action Date of February 6, 2010, we feel that it would not be appropriate to offer you a meeting to discuss issues when we are actively reviewing these issues. Once we have acted on your application, and you have received our Action Letter [ identifying the issues of concern], then you may request a meeting to discuss the issues.

Thanks,  
Kofi.

-----  
*Kofi Boadu Ansah, R.Ph., Pharm.D.*

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I

10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22497

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GI-1

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CARY  
PHARMACEUTICA  
LS INC

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BUP-450 (BUPROPION  
HCL)450MG ER ORAL TAB

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/s/  
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KOFI B ANSAH

01/28/2010



NDA 022497

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Cary Pharmaceuticals Inc.  
9903 Windy Hollow Road  
Great Falls, Virginia 22066-3550

ATTENTION: Douglas D. Cary, R.Ph, MBA  
President & CEO

Dear Mr. Cary:

Please refer to your New Drug Application (NDA) dated March 31, 2009, received April 6, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, 450 mg.

We also refer to your October 23, 2009, correspondence, received October 26, 2009, requesting review of your proposed proprietary name, Forfivo XL. We have completed our review of the proposed proprietary name, Forfivo XL and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your October 23, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kofi Ansah at (301) 796-4158.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22497

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ORIG-1

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CARY  
PHARMACEUTICA  
LS INC

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BUP-450 (BUPROPION  
HCL)450MG ER ORAL TAB

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/s/  
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CAROL A HOLQUIST  
01/19/2010

**From:** [Ansah, Kofi](#)  
**To:** ["Doug Cary";](#)  
**cc:** [Bender, William;](#)  
**Subject:** RE: TCON with FDA (2) -- NDA 22-497 /  
CARY PHARMS/ FORFIVO XL (BUPROPION HCL 450MG ER)/ MDD  
**Date:** Thursday, December 31, 2009 12:19:50 PM

---

Dear Mr. Cary,

This is to confirm the upcoming teleconference between Cary Pharmaceuticals and FDA on January 7, 2010 from 1:00 - 2:00 pm. Please use the following information to dial for this meeting:

**TELECONFERENCE INFORMATION: Call-in #:** [REDACTED] <sup>(b) (4)</sup> **and**  
**Passcode:** [REDACTED] <sup>(b) (4)</sup>

We will activate the line by 1:05 pm and you may call in at that time or earlier.

Thanks,  
Kofi.

---

**From:** Ansah, Kofi  
**Sent:** Wednesday, December 23, 2009 2:39 PM  
**To:** 'Doug Cary'  
**Cc:** Bender, William  
**Subject:** TCON with FDA (2) -- NDA 22-497 /CARY PHARMS/ FORFIVO XL (BUPROPION HCL 450MG ER)/ MDD  
**Importance:** High

Dear Mr. Cary,

Regarding your NDA 022497 currently under review, the Division would like to have another teleconference with you on January 7, 2010 from 1:00 - 2:00 pm. Please let me know, as soon as possible, if you can't make this meeting. Once I have received your confirmation, I will provide you with the teleconference information.

Thanks,

Kofi.

[Note: Please copy CDR William Bender on all correspondence you send to me regarding this NDA from 1/3 - 1/17/2010 as I will be away from the office.]

---

*Kofi Boadu Ansah, R.Ph., Pharm.D.*

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I

10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

*Commissioned Corps of the United States Public Health Service- "Protecting, promoting, and advancing the health and safety of the Nation"*

IMPORTANT NOTICE: This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution, disclosure, copying, or use of the information contained herein is strictly prohibited. If you think you have received this e-mail message in error, please notify the sender immediately.

Application  
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Submission  
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Submitter Name

Product Name

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NDA-22497

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ORIG-1

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CARY  
PHARMACEUTICA  
LS INC

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BUP-450 (BUPROPION  
HCL)450MG ER ORAL TAB

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/s/  
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KOFI B ANSAH

01/05/2010

**From:** [Ansah, Kofi](#)  
**To:** ["Doug Cary";](#)  
**cc:** [Bender, William; Griffith, Sandra J;](#)  
**Subject:** RE: PROPOSED LABELING -- RE: NDA 022497/ BUP-450 XL  
**Date:** Monday, December 14, 2009 4:53:32 PM

---

Dear Mr. Cary,

This is a follow up to my previous email below. Please submit revised labels and labeling to include the proposed name "Forfivo XL". The original labels/labeling state (b) (4) In addition, email me a Clean-Word and an Annotated-pdf copy [that shows the changes you made to the template you used].

Thanks,  
Kofi.

---

***Kofi Boadu Ansah, R.Ph., Pharm.D.***

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

***Commissioned Corps of the United States Public Health Service- "Protecting, promoting, and advancing the health and safety of the Nation"***

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**From:** Ansah, Kofi  
**Sent:** Monday, December 07, 2009 2:27 PM  
**To:** 'Doug Cary'  
**Cc:** Bender, William  
**Subject:** PROPOSED LABELING -- RE: NDA 022497/ BUP-450 XL

Dear Mr. Cary,

Regarding you NDA 022497 currently under review, please email me a word copy and an

annotated copy of your proposed labeling if there has been any changes/ updates since you submitted your application in April 2009.

Thanks,  
Kofi.

Application  
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Type/Number

Submitter Name

Product Name

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NDA-22497

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CARY  
PHARMACEUTICA  
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BUP-450 (BUPROPION  
HCL)450MG ER ORAL TAB

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KOFI B ANSAH  
12/17/2009



NDA 22-497

**INFORMATION REQUEST**

Cary Pharmaceuticals, Inc.  
Attention: Douglas D. Cary  
President & C.E.O.  
9903 Windy Hollow Road  
Great Falls, VA 22066 - 3550

Dear Mr. Cary:

Please refer to your March 31, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BUP-450 XL (bupropion hydrochloride) 450mg 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 prompt written response in order to continue our evaluation of your NDA.

1. Describe the importance of drug substance particle size distribution in terms of drug product manufacturing, and processing. Provide the test method used in determining particle size. Provide information including graphical data on particle size distribution of different drug substance lots.
2. Provide information on the analytical procedures used to accept a drug substance batch for drug product manufacturing.
3. In the drug labeling section, you state that the tablet is printed with the product logo using a black ink. Provide information to support the use of this ink in tablet printing. Provide a description of the process used in applying the black ink.
4. Provide data to show how the (b) (4) was selected.
5. Provide an (b) (4) or provide data to justify that an (b) (4) is not needed.
6. You have set a limit for the (b) (4). Provide information on how (b) (4) was determined and demonstrate that the physical and chemical properties (b) (4) are not affected when (b) (4).

8. Provide information to support the use of (b) (4) coil and the desiccant bag, or a Letter of Authorization (LOA) to allow cross reference to this information.
9. Provide data to show that the amount of desiccant used is sufficient to provide adequate protection.
10. Provide rationale for the claim that this is a (b) (4) (refer to 3.2.P.2.5, page 1)
11. Provide a representative COA for each excipient used in the drug product.
12. It is noted that the assay values fluctuate during stability studies. For example, batch 07039P-01 assay value ranges (b) (4) Explain this observation.
13. Provide an updated stability protocol for the post approval stability batches to include both long-term and accelerated (up to 6 months) conditions.
14. Provide information to demonstrate that the seal problem observed during the accelerated stability study has been resolved. Summarize corrective actions implemented to justify using this type of seal for commercial use.
15. Correct the equation used in the EIC calculations (b) (4)

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22497

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ORIG-1

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CARY  
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BUP-450 (BUPROPION  
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/s/  
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THOMAS F OLIVER  
11/06/2009

**From:** [Ansah, Kofi](#)  
**To:** ["Doug Cary";](#)  
**cc:** [Bender, William;](#)  
**Subject:** RE: Cary Pharmaceuticals NDA 22-497 -- REMS Template  
**Date:** Friday, October 16, 2009 2:32:05 PM

---

Dear Mr. Cary:

Thank you for your email. You can not reference another sponsor's REMS. However, you are more than welcome to justify your proposed REMS by the Agency's previous actions. Please address the issues contained within the template we sent to you. Once you feel that you have a REMS plan together that addresses all the potential safety issues, then you should submit it to us for review by our REMS team.

Thanks,  
Kofi.

---

**From:** Doug Cary [mailto:doug.cary@carypharma.com]  
**Sent:** Thursday, October 15, 2009 3:26 PM  
**To:** Ansah, Kofi  
**Cc:** Bender, William  
**Subject:** Re: Cary Pharmaceuticals NDA 22-497 -- REMS Template

Dr. Ansah,

I am requesting your guidance on how we should proceed to satisfy your October 01, 2009 request for a "Medguide only REMS." We are preparing to develop a Proposed REMS to support approval of 505(b)(2) NDA 22-497 for BUP 450 XL. Before we proceed on creating a new REMS for BUP 450 XL, is it possible to reference, under Freedom of Information, the FDA approved REMS for Aplenzin, bupropion hydrobromide 522 mg extended- release tablet, approved under NDA 022108 on April 23, 2008? The Aplenzin Package Insert (p 4) 2.4 Switching Patients from Wellbutrin, Wellburin SR or Wellbutrin XL, includes the statement that bupropion hydrobromide 522 mg is equivalent to bupropion hydrochloride 450 mg.

The Package Insert and 17.2 FDA-Approved Patient Labeling (Medication Guide) for BUP 450 XL used the FDA approved Aplenzin, Biovail International, Package Insert and 17.2 FDA-Approved Patient Labeling (Medication Guide) as a template.

Thank you very much for your assistance in this matter.

Best regards,  
Douglas D. Cary

703-759-7460

----- Original Message -----

**From:** [Ansah, Kofi](#)

**To:** [Doug Cary](#)

**Cc:** [Bender, William](#)

**Sent:** Thursday, October 01, 2009 4:55 PM

**Subject:** Cary Pharmaceuticals NDA 22-497 -- REMS Template

Mr. Cary,

Please find attached a REMS template for a " Medguide only REMS." Submit your plan, as soon as possible, if you have not already submitted it. Please code your submission as R-O (REMS-Other), not as an SLR or Supplement as stated in the template (that is for post-approval). Please contact me with any questions.

<<REMS template OCC final.doc>>

Thanks,  
Kofi.

---

***Kofi Boadu Ansah, R.Ph., Pharm.D.***

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

Application  
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Submitter Name

Product Name

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NDA-22497

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CARY  
PHARMACEUTICA  
LS INC

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BUP-450 (BUPROPION  
HCL)450MG ER ORAL TAB

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/s/  
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KOFI B ANSAH

11/02/2009

**From:** [Ansah, Kofi](#)  
**To:** ["Doug Cary";](#)  
**Subject:** RE: Cary Pharmaceuticals NDA 22-497  
**Date:** Wednesday, September 30, 2009 10:08:50 AM

---

Mr. Cary,

Our OSE group would prefer the Trade name Request submission to be done electronically. Please refer to FDA guidance on electronic submission of Trade name Request and let me know if you are able to submit your request electronically.

Thanks,  
Kofi.

---

**From:** Doug Cary [mailto:doug.cary@carypharma.com]  
**Sent:** Tuesday, September 29, 2009 11:57 AM  
**To:** Ansah, Kofi  
**Subject:** Re: Cary Pharmaceuticals NDA 22-497

Kofi,

Thank you very much for the information.

Best regards,  
Doug

----- Original Message -----

**From:** [Ansah, Kofi](#)  
**To:** [Doug Cary](#)  
**Sent:** Tuesday, September 29, 2009 8:30 AM  
**Subject:** Cary Pharmaceuticals NDA 22-497

Dear Mr. Cary,

When you do submit your Trade Name Request regarding this NDA 22-497 [in triplicate, identified by the above NDA number, clearly marked as a Trade name Request], please submit it to OSE/DMEPA [Attention: Sarah Simon] at the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology/ DMEPA  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You may send 2 desk copies to my attention at my office address below [and I will ensure Sarah gets 1].

Thanks,  
Kofi.

---

*Kofi Boadu Ansah, R.Ph., Pharm.D.*

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

Application  
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Submission  
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Product Name

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NDA-22497

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KOFI B ANSAH

11/02/2009



NDA 22-497

**INFORMATION REQUEST**

Cary Pharmaceuticals, Inc.  
Attention: Douglas D. Cary  
President & C.E.O.  
9903 Windy Hollow Road  
Great Falls, VA 22066 - 3550

Dear Mr. Cary:

Please refer to your March 31, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BUP-450 XL (bupropion hydrochloride) 450mg 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 prompt written response in order to continue our evaluation of your NDA.

1. Provide samples of your drug product.
2. Provide CoAs for all drug product lots manufactured to date.
3. Provide individual tablet dissolution data generated from the six stability batches.
4. Provide open dish stability data of the drug product

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22497

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/s/  
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RAMESH K SOOD

10/20/2009

**From:** [Ansah, Kofi](#)  
**To:** ["Doug Cary";](#)  
**cc:** [Bender, William;](#)  
**Subject:** Cary Pharmaceuticals NDA 22-497 -- REMS Template  
**Date:** Thursday, October 01, 2009 4:55:00 PM  
**Attachments:** [REMS template\\_OCC final.doc](#)

---

Mr. Cary,

Please find attached a REMS template for a " Medguide only REMS." Submit your plan, as soon as possible, if you have not already submitted it. Please code your submission as R-O (REMS-Other), not as an SLR or Supplement as stated in the template (that is for post-approval). Please contact me with any questions.

Thanks,  
Kofi.

---

***Kofi Boadu Ansah, R.Ph., Pharm.D.***

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

**RESPONSE TO REQUEST FOR INFORMATION ABOUT  
SUBMISSION OF PROPOSED REMS**

We are providing this information in response to your request for information about how to submit a proposed REMS. We suggest that your proposed REMS submission include two parts: a “Proposed REMS” and a “REMS Supporting Document.”

Attached is a suggested template for the Proposed REMS that you should complete with concise, specific information, as applicable. Additionally, all relevant REMS materials, such as enrollment forms, informed consents, and educational and communication materials should be appended to the Proposed REMS. We recommend that the Timetable for Assessments section specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval. Once FDA reviews the Proposed REMS and finds the content acceptable, we will include this document as an attachment to the approval letter for the REMS. The REMS, once approved, will create enforceable obligations

The second part of the submission should be a REMS Supporting Document that includes a thorough explanation of the rationale for, and supporting information about, the content of the Proposed REMS. This REMS Supporting Document should include the following sections 1. through 5., as well as a table of contents. For section 3., only those elements we have determined are necessary and are required should be included in the Proposed REMS :

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
  - a. Medication Guide
  - b. Patient Package Insert
  - b. Communication Plan
  - c. Elements to Assure Safe Use
  - d. Implementation System
  - e. Timetable for Assessment of the REMS
  - f. Information Needed for Assessments
4. Other Relevant Information

The two parts should be submitted as a new supplemental application. The submission should be prominently identified with the following wording in bold capital letters at the top of the first page of the submission:

**NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]  
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**SUPPLEMENT [assigned #]  
PROPOSED REMS – AMENDMENT**

Please contact [insert OND RPM name and contact info] if you have any questions.

**REMS TEMPLATE**

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name

Address

Contact Information

**PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL(S):**

List the goals and objectives of the REMS.

**II. REMS ELEMENTS:**

**A. Medication Guide or PPI**

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

**B. Communication Plan**

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Append the printed material and web shots to the REMS Document

**C. Elements To Assure Safe Use**

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

7/31/08 OCC

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

#### **D. Implementation System**

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

#### **E. Timetable for Submission of Assessments**

Specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks.

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Submission  
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Submitter Name

Product Name

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NDA-22497

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BUP-450 (BUPROPION  
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/s/  
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KOFI B ANSAH

10/07/2009



NDA 22-497

**INFORMATION REQUEST**

Cary Pharmaceuticals, Inc.  
Attention: Douglas D. Cary  
President & C.E.O.  
9903 Windy Hollow Road  
Great Falls, VA 22066 - 3550

Dear Mr. Cary:

Please refer to your March 31, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BUP-450 XL (bupropion hydrochloride) 450mg extended release tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission (refer to Table 3.2.P.8-1) and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- Provide the raw dissolution data for each batch.
- Provide the dissolution profiles for each batch.
- Confirm that all 6 batches mentioned in the table are compositionally identical to clinical/bio batches.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22497	ORIG-1	CARY PHARMACEUTICA LS INC	BUP-450 (BUPROPION HCL)450MG ER ORAL TAB

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/s/

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DON L HENRY  
09/09/2009

RAMESH K SOOD  
09/09/2009

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

<b>Application Information</b>		
NDA # 22-497 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Bupropion Hydrochloride Extended-Release Tablets Dosage Form: Extended-Release Tablet Strengths: 450 mg		
Applicant: Cary Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: March 31, 2009 Date of Receipt: April 6, 2009 Date clock started after UN:		
PDUFA Goal Date: February 6, 2010	Action Goal Date (if different):	
Filing Date: May 26, 2009 Date of Filing Meeting: May 26, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed Indication(s): Major Depressive Disorder		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>Refer to Appendix A for further information.</i>		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):	
List referenced IND Number(s): (b) (4)	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a>  If yes, explain:  If yes, has OC/DMPQ been notified of the submission?  Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  Comments:	<input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES # years requested: 3 <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. 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 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<b>Format and Content</b>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>		<p>Datasets, Annotated Labeling</p>	
<p><b>If electronic submission:</b>  <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p><b>If electronic submission</b>, does it follow the eCTD guidance? (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p>If not, explain (e.g., waiver granted):</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b> We are obtaining the FEI# for a testing site in Canada.</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input type="checkbox"/> legible  <input type="checkbox"/> English (or translated into English)  <input type="checkbox"/> pagination  <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><i>If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.</i></b></p> <p><i>Note: Debarment Certification should use wording in FD&amp;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...”</i></p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<b><u>PREA</u></b>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<b>Comments:</b>	
<b>BPCA (NDAs/NDA efficacy supplements only):</b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b>	
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Package insert (PI) submitted in PLR format?  <b>If no</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If before</b> , what is the status of the request?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b> Not at the time of filing.	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b> Not at the time of filing.	
REMS consulted to OSE/DRISK?	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b> Not at the time of filing.	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b> Not at the time of filing.	

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b> July 14, 2008</p>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** May 26, 2009

**NDA/BLA #:** 22-497

**PROPRIETARY/ESTABLISHED NAMES:** BUP 450 XL (Bupropion Hydrochloride 450 mg Extended-Release Tablets)

**APPLICANT:** Cary Pharmaceuticals, Inc.

**BACKGROUND:** This NDA is for an extended-release formulation.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kofi Ansah, Pharm.D.	Y
	CPMS/TL:	Paul David, R.Ph.	N
Cross-Discipline Team Leader (CDTL)	Gwen Zornberg		Y
Clinical	Reviewer:	Jenn Sellers, M.D.	Y
	TL:	Gwen Zornberg, M.D.	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OSE	Reviewer:		N
	TL:		N
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Bei Yu, Ph.D.	Y
	TL:	Raman Baweja, Ph.D.	Y
Biostatistics	Reviewer:		N
	TL:		N
Nonclinical (Pharmacology/Toxicology)	Reviewer:		Y
	TL:	Linda Fossom, Ph.D.	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Pei-I Chu, Ph.D.	N
	TL:	Thomas Oliver, Ph.D.	Y
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

**OTHER ATTENDEES:** Ginneh Stowe and Rosemary Addy (PMHS)

505(b)(2) filing issues? <b>If yes,</b> list issues: Filing issues to be communicated by Day 74.	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? <b>If no,</b> explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Electronic Submission comments</b></p> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>BIOSTATISTICS</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>PRODUCT QUALITY (CMC)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <ul style="list-style-type: none"> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Sterile product?</li> </ul> <p><b>If yes</b>, was Microbiology Team consulted for</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES

validation of sterilization? (NDAs/NDA supplements only)	<input type="checkbox"/> NO
<b>FACILITY (BLAs only)</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Thomas Laughren, MD, Director of Psychiatry Products	
<b>GRMP Timeline Milestones:</b> Meetings have been scheduled.	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

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 OND ADRA or OND IO.

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

/s/

-----  
Kofi B Ansah  
7/23/2009 02:58:46 PM  
CSO

**From:** [Ansah, Kofi](#)  
**To:** ["Doug Cary";](#)  
**cc:** ["Matthew J. Solow";](#)  
**Subject:** RE: Request for Permission to FedEx Notice of Para.  
IV Certification for NDA 22-497  
**Date:** Tuesday, June 23, 2009 12:43:44 PM

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Dear Mr. Cary,

Regarding your NDA 22-497 for Bupropion ER 450mg tablets; Yes, Cary Pharmaceuticals Inc. may send it's Notice of Paragraph IV Certification to the NDA holder, patent owner(s), and representatives via FedEx.

Please, note that you are obligated to amend your application with a notice of receipt (i.e., all patent holders and RLD NDA holder are notified of the pending b2 application [see specific criteria under 314.52(c)].

Thanks,  
Kofi.

---

**From:** Matthew J. Solow [mailto:msolow@hgcpatent.com]  
**Sent:** Monday, June 22, 2009 3:48 PM  
**To:** Ansah, Kofi  
**Subject:** Request for Permission to FedEx Notice of Para.IV Certification for NDA 22-497

Dear Dr. Ansah,

We represent Cary Pharmaceuticals Inc. which is seeking permission to send its Notice of Paragraph IV certification via FedEx® to the NDA holder; the patent owner (s); and to their representatives. The Notice of Paragraph IV certification will be directed towards NDA No. (b) (4) for WELLBUTRIN XL®, bupropion hydrochloride tablets, 150 mg and 300 mg.

Cary's NDA has been given the No. 22-497, and it has received its Notice of Acceptance.

We had previously requested permission to use FedEx® from Mr. Martin Shimer, but he stated that his authority for permitting use of an alternate means of providing notice only pertains to ANDAs submitted under Section 505(j). Mr. Shimer then suggested that we contact the Project Manager.

If you need any other information, or have any questions, please contact me.

Best regards

Matthew J. Solow, Esq.  
HEDMAN & COSTIGAN, P.C.  
1185 Avenue of the Americas  
New York, New York 10036  
(V) 212-302-8989  
(F) 212-302-8998  
email: [MSolow@hgcpatent.com](mailto:MSolow@hgcpatent.com)

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/s/

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Kofi B Ansah  
6/23/2009 02:39:25 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-497

Cary Pharmaceuticals, Inc.  
Attention: Douglas D. Cary  
President & C.E.O.  
9903 Windy Hollow Road  
Great Falls, VA 22066 - 3550

Dear Mr. Cary:

We acknowledge receipt of your new drug application (NDA) dated March 31, 2009, received April 6, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for BUP-450 XL (bupropion hydrochloride) 450mg extended release tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is February 6, 2010.

During our filing review of your application, we identified the following potential review issues:

1. You should conduct studies to investigate dose dumping in the presence of alcohol. To fulfill this request, you should perform in vitro dissolution studies for the 450 mg strength of your Bupropion ER tablet using the dissolution conditions with the addition of the following alcohol concentrations for the in vitro dissolution studies (using 12 units each): 0%, 5%, 10%, 20%, and 40%.

You are requested to submit this information to the Agency within 30 days of receipt of this letter.

We are providing the above comments to give you preliminary notice of potential 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. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Submit proposed Trade Name and Prescribing Labeling.

2. Provide certified receipt with respect to your notification of each owner of the patent.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. However, because this application does not trigger PREA, no waiver is necessary.

If you have any questions, contact LCDR Kofi Ansah, Senior Regulatory Project Manager, at (301)796-4158.

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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this page is the manifestation of the electronic signature.**  
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/s/

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Thomas Laughren  
6/17/2009 11:40:22 AM