

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202133Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202133

SUPPL #

HFD # 130

Trade Name

Generic Name Fluoxetine hydrochloride

Applicant Name Edgemont Pharmaceuticals, LLC.

Approval Date, If Known October 6, 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.

Study 101 was a comparative bioequivalence study of 1 x 60mg fluoxetine scored tablet (Edgemont, manufactured by Orion Pharma) vs. 3 x 20mg fluoxetine tablets (generic) under fasted conditions. The primary measure of bioequivalence was based on fluoxetine PK.

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?

No

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# 18936

Prozac Capsules

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

YES
Explain:

! NO
! Explain:

Investigation #2

!
!

YES
Explain:

! NO
! Explain:

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

YES NO

If yes, explain:

=====

Name of person completing form: Hiren Patel, Pharm.D.
Title: Regulatory Project Manager
Date: 10/3/11

Name of Office/Division Director signing form: Thomas Laughren, MD
Title: Division Director

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

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

/s/

HIREN PATEL
10/06/2011

THOMAS P LAUGHREN
10/06/2011

Patel, Hiren

From: Patel, Hiren
Sent: Friday, October 07, 2011 9:41 AM
To: 'Oglesby, Scott A'
Subject: RE: NDA 202133 - Approval
Importance: High

Dear Scott,

We do not agree with your requested shelf life of (b) (4). An expiry of 24 months has been granted for the drug product.

Regards,
Hiren

*Hiren D. Patel, Pharm.D., M.S.
LCDR USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov*

From: Oglesby, Scott A [mailto:SOglesby@beckloff.com]
Sent: Thursday, October 06, 2011 4:44 PM
To: Patel, Hiren
Subject: RE: NDA 202133 - Approval

Dear Hiren, on behalf of Edgemont, I acknowledge receipt of your e-mail below. Thanks to the DPDP for their efforts in the earlier approval. The Edgemont team did have one question:

Does the Agency accept the Sponsor's requested shelf life of (b) (4) with the additional commitment (SN 0006) of accelerated stability, up to six months, on the first three commercial batches?

We will submit (subject to a response to the above question) the final immediate container label in the time frame requested. We will also submit the labeling in SPL format to the eLIST system in the time frame specified.

Scott A. Oglesby, Ph.D.
Director, Executive Consulting
Beckloff Associates
(a Cardinal Health Company)
Phone: 919-933-2620
e-mail: soglesby@beckloff.com

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From: Patel, Hiren [mailto:Hiren.Patel@fda.hhs.gov]

Sent: Thursday, October 06, 2011 2:31 PM
To: Oglesby, Scott A
Cc: Patel, Hiren
Subject: RE: NDA 202133 - Approval

Scott,

The attached Approval Letter includes labeling.

-Hiren

October 06, 2011 2:17 PM
A'
202133 - Approval

Dear Scott,

Attached is an electronic copy of the Approval Letter for NDA 202133. Please acknowledge receipt of this email.

<< File: NDA 202133 - Approval Letter.pdf >>
Regards,
Hiren

*Hiren D. Patel, Pharm.D., M.S.
LCDR USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov*

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Svenska: www.cardinalhealth.com/legal/email

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

/s/

HIREN PATEL
10/07/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202133 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: Fluoxetine USP Dosage Form: Immediate-release scored tablets		Applicant: Edgemont Pharmaceuticals, LLC Agent for Applicant (if applicable):
RPM: Hiren Patel		Division: Division of Psychiatry Products
<p>NDA: 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>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 18936 - Prozac Capsules</p> <p>Provide a brief explanation of how this product is different from the listed drug. This fluoxetine product is a 60 mg scored tablet.</p> <p>If no listed drug, explain. <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><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></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 10/5/11</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>October 9, 2011</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input checked="" type="checkbox"/> None
❖ 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain		<input type="checkbox"/> Received

¹ 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.

❖ Application Characteristics ²	
<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 BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input checked="" type="checkbox"/> REMS not required</p> <p>Comments:</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)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<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

² 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"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> 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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> 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> 	<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"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input checked="" type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III 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). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV 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> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input 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>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Yes
Officer/Employee List	
❖ 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
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 10/6/11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	October 3, 2011
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	December 9, 2010
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ 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>) 	<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"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	October 3, 2011
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	December 9, 2010
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	September 30, 2011
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • 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. 	N/A
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA August 19, 2011 <input checked="" type="checkbox"/> DRISK August 24, 2011 <input checked="" type="checkbox"/> DDMAC August 29, 2011 <input checked="" type="checkbox"/> SEALD October 3, 2011, October 5, 2011 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	RPM Filing Review date: February 28, 2011 RPM PLR Labeling Review date: February 17, 2011 505(b)(2) clearance date: September 22, 2011 505(b)(2) Assessment date: October 3, 2011 <input type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>This application does not trigger PREA</u> Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
❖ 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>)	10/4/11, 9/13/11, 8/18/11, 5/4/11, 3/10/11, 2/17/11, 2/7/11, 12/23/10
❖ Internal memoranda, telecons, etc.	October 4, 2011
❖ 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 checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg March 5, 2010
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	N/A
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ 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 checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None October 3, 2011
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	7/21/11
• Clinical review(s) (<i>indicate date for each review</i>)	
• 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>)	See Clinical Team Leader Review 7/21/11
❖ 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

⁵ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) 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>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology <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 type="checkbox"/> None 08/29/11
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input type="checkbox"/> None 08/12/11
Nonclinical <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 09/06/11, 1/31/11
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ 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

Product Quality <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 9/27/11, 9/2/11, 12/20/10
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/2/11, 4/7/11, 1/24/11
❖ Microbiology Reviews <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 (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ 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>	see ONDQA review dated 9/2/11
<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 sites⁶)</i>	Date completed: September 22, 2011 <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)

⁶ 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.

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

/s/

HIREN PATEL
10/05/2011

Patel, Hiren

From: Abdus-Samad, Jibril
Sent: Tuesday, October 04, 2011 10:02 AM
To: Patel, Hiren
Cc: Griffith, Sandra J
Subject: RE: NDA 202133 - Labeling

Acceptable.

Thank you

Jibril Abdus-Samad, PharmD
Safety Evaluator
Division of Medication Error Prevention and Analysis
Office 301-796-2196

From: Patel, Hiren
Sent: Tuesday, October 04, 2011 9:54 AM
To: Abdus-Samad, Jibril
Subject: FW: NDA 202133 - Labeling
Importance: High

Hi Jibril,

Please see the sponsor's response below and let me know if you are okay with their response.

Thanks,
Hiren

From: Oglesby, Scott A [mailto:SOglesby@beckloff.com]
Sent: Tuesday, October 04, 2011 6:36 AM
To: Patel, Hiren
Subject: RE: NDA 202133 - Labeling

Dear Hiren, the Sponsor agrees with the Agency changes reflected in the attachment to your e-mail below.

In response to your question on the shipping carton, there is no label on the shipping carton, it is merely a conveyance, outer corrugated shipper.

Scott A. Oglesby, Ph.D.
Director, Executive Consulting
Beckloff Associates
(a Cardinal Health Company)
Phone: 919-933-2620
e-mail: soglesby@beckloff.com

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From: Patel, Hiren [mailto:Hiren.Patel@fda.hhs.gov]
Sent: Monday, October 03, 2011 4:59 PM
To: Oglesby, Scott A
Subject: NDA 202133 - Labeling
Importance: High

Dear Scott,

The attached fluoxetine labeling includes the Agency's revisions. Please let me know if you agree with the changes by 12:00PM tomorrow.

Also, please verify whether there is carton labeling for this product. We note that in your submission dated September 30, 2011, there is a statement that reads, "The shipping carton will contain 24 bottles."

Regards,
Hiren

*Hiren D. Patel, Pharm.D., M.S.
LCDR USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov*

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/s/

HIREN PATEL
10/04/2011



NDA 202133

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

EDGEMONT PHARMACEUTICALS LLC
C/O BECKLOFF ASSOC INC
Attention: Scott Oglesby, PhD
7400 WEST 110TH ST STE 300
OVERLAND PARK, KS 66210

Dear Dr. Oglesby:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fluoxetine 60 mg 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 [REDACTED] (b)(4)¹. The pervasiveness and egregious nature of the violative practices by [REDACTED] (b)(4) has led FDA to have significant concerns that the bioanalytical data generated at [REDACTED] (b)(4) 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 [REDACTED] (b)(4) 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 [REDACTED] (b)(4) 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.

¹ These violations include studies conducted by [REDACTED] (b)(4) specific to the [REDACTED] (b)(4) facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by [REDACTED] ^{(b) (4)} 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.

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

Patel, Hiren

From: Patel, Hiren
Sent: Thursday, August 18, 2011 1:41 PM
To: 'Oglesby, Scott A'
Subject: NDA 202133 - Labeling

Attachments: NDA 202133_Labeling Edits_Fluoxetine 60 mg_FDA Edits 08172011.doc

Dear Scott,

Please refer to your December 9, 2010 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fluoxetine 60 mg tablets. We also refer to our February 17, 2011, letter in which we notified you of our target date of September 11, 2011 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES - FISCAL YEARS 2008 through 2012."

On March 31, 2011, we received your March 31, 2011 proposed labeling submission to this application, and have proposed revisions that are included as an attachment.



NDA
33_Labeling Edits_F

Regards,

Hiren

*Hiren D. Patel, Pharm.D., M.S.
LCDR USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov*

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/s/

HIREN PATEL
08/18/2011

Patel, Hiren

From: Patel, Hiren
Sent: Wednesday, May 04, 2011 1:33 PM
To: 'Oglesby, Scott A'
Subject: NDA 202133

Dear Scott,

We have the following CMC information request:

[Redacted content] (b) (4)

2. Provide all the updated primary stability data for the drug product.

Regards,

*Hiren D. Patel, Pharm.D., M.S.
LT USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov*

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/s/

HIREN PATEL
05/04/2011

Patel, Hiren

From: Oglesby, Scott A [SOglesby@beckloff.com]
Sent: Thursday, March 10, 2011 12:52 PM
To: Patel, Hiren
Subject: RE: NDA 202133 - Filing Letter

Thanks Hiren. This clarifies things. Should have the revisions filed to the NDA in the next couple of weeks.

Warm Regards,
Scott A. Oglesby, Ph.D.
 Director, Executive Consulting
 Beckloff Associates
 (a Cardinal Health Company)
 Phone: 919-933-2620
 e-mail: soglesby@beckloff.com

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From: Patel, Hiren [mailto:Hiren.Patel@fda.hhs.gov]
Sent: Thursday, March 10, 2011 11:37 AM
To: Oglesby, Scott A
Subject: RE: NDA 202133 - Filing Letter

Dear Scott,

Please see my responses in blue below.

Regards,

Hiren

*Hiren D. Patel, Pharm.D., M.S., LT USPHS
 Regulatory Health Project Manager
 Division of Psychiatry Products
 Center For Drug Evaluation and Research, FDA
 Office of Drug Evaluation I
 Ph: (301) 796-2087
 Email: hiren.patel@fda.hhs.gov*

From: Oglesby, Scott A [mailto:SOglesby@beckloff.com]
Sent: Thursday, March 10, 2011 8:54 AM
To: Patel, Hiren
Subject: RE: NDA 202133 - Filing Letter

Dear Hiren, thank you for the feedback. We are a bit confused at this point. Perhaps we can chat briefly to clarify? Below are our questions in response to your latest e-mail.

1. Edgemont will add Prozac to the 356h **in addition** to the Mylan product. Is this acceptable or is the Agency requesting that **only** Prozac be included in the 356h form?

We request that you only include Prozac in the 356h form as you are relying on our finding of safety and efficacy

Reference ID: 2916488

3/10/2011

for Prozac and not any other product.

2. Edgemont used the Mylan (Par) PI in the side-by-side comparison (based on Teva's PLR format). Is this acceptable or is the Agency requesting that Prozac capsules be used as the comparator instead?

We request that you used the Prozac PI in the side-by-side comparison as you are relying on our finding of safety and efficacy for Prozac and not any other product.

3. Edgemont cross-referenced a statement from the Teva PI and ANDA regarding fluoxetine-olanzapine drug interactions in their annotated PI. Is this acceptable or should the innovator product (Symbyax, NDA 21-250) be the referenced application?

The drug interactions statement also appears in the Prozac PI. Therefore, it is sufficient to only reference Prozac (NDA 18-936).

Please give me a call at your earliest convenience or we can set up a brief teleconference if the above approach and questions do not meet the intent of your communications.

Warm Regards,

Scott A. Oglesby, Ph.D.

Director, Executive Consulting
Beckloff Associates

(a Cardinal Health Company)

Phone: 919-933-2620

e-mail: soglesby@beckloff.com

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From: Patel, Hiren [mailto:Hiren.Patel@fda.hhs.gov]

Sent: Wednesday, March 09, 2011 9:51 AM

To: Oglesby, Scott A

Subject: RE: NDA 202133 - Filing Letter

Dear Scott,

Please revise the 356h to reflect that you are relying on NDA 18-936 (Prozac) and state clearly in your cover letter that you are bridging to Prozac using Mylan's ANDA 75755 product. Additionally, please resubmit annotated labeling that references NDA 18-936 (Prozac) as you are relying on our finding of safety and efficacy for Prozac and not any other product.

Sincerely,

Hiren

*Hiren D. Patel, Pharm.D., M.S., LT USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov*

From: Oglesby, Scott A [mailto:SOglesby@beckloff.com]

Sent: Thursday, March 03, 2011 6:14 PM

To: Patel, Hiren

Reference ID: 2916488

3/10/2011

Subject: RE: NDA 202133 - Filing Letter

Dear Hiren,

Thank you for clarifying the Agency's position regarding reliance on a generic vs. an innovator product for Edgemont's 505(b)(2) application. Edgemont will provide an updated patent certification that will include NDA 18-936 for Prozac. In addition, Edgemont will add this drug to the Form FDA 356h as a RLD that is the basis for submission, along with the Mylan product (ANDA 075755) used as the RLD comparator in their clinical bioequivalence trial. Both applications are already listed in Module 1, Section 1.4.4 (Cross-Reference to Other Applications).

Please confirm that the aforementioned updates will meet the Agency's requirement for establishment of Prozac (NDA 18-936) as an additional RLD for NDA 202133 (along with the Mylan product, ANDA 075755).

Scott A. Oglesby, Ph.D.
 Director, Executive Consulting
 Beckloff Associates
 (a Cardinal Health Company)
 Phone: 919-933-2620
 e-mail: soglesby@beckloff.com

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From: Patel, Hiren [mailto:Hiren.Patel@fda.hhs.gov]
Sent: Tuesday, March 01, 2011 5:09 PM
To: Oglesby, Scott A
Subject: RE: NDA 202133 - Filing Letter

Dear Scott,

Reliance on a generic for this 505(b)(2) application is not acceptable to support approval of your product. You must rely on the innovator product because you are relying on the Agency's previous findings of safety and efficacy for fluoxetine hydrochloride and only NDAs have previous findings of safety and effectiveness. We also note that you will be using the generic product to bridge back to the innovator product. Therefore, you must submit an appropriate patent certification or statement and address any unexpired exclusivity for NDA 18-936 for Prozac (fluoxetine hydrochloride) capsules.

With regards to the requested labeling change, you may include the change during labeling negotiations.

Sincerely,

Hiren

Hiren D. Patel, Pharm.D., M.S., LT USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov

From: Oglesby, Scott A [mailto:SOglesby@beckloff.com]
Sent: Monday, February 28, 2011 1:30 PM
To: Patel, Hiren
Subject: NDA 202133 - Filing Letter

Reference ID: 2916488

3/10/2011

Dear Hiren, Thank you.

In response to the potential review issue identified in your letter regarding patent certification, Edgemont affirms that the RLD for this NDA is fluoxetine hydrochloride tablets, EQ 20 mg base (Mylan), for oral administration, ANDA 075755, Product Number 002. Identification of the RLD was made in Module 1, Section 1.12.11 (Basis for Submission), and is based upon the Orange Book wherein the Mylan product is included as a RLD for the tablet dosage form. In addition, Edgemont performed a clinical study demonstrating bioequivalence to this drug. For these reasons, the patent certification included in Module 1, Section 1.3.5.2, refers only to the Mylan product. Any references to Prozac within NDA 202133 were provided for historical context only and Edgemont regrets any confusion this may have caused. Edgemont intends that only one RLD (the Mylan 20 mg tablet) be considered for this Section 505(b)(2) application and hopes this explanation provides necessary clarification on the issue. **Does FDA require any additional follow-up with regard to patent certification?**

Also, in response to the labeling format issue identified in your letter, Edgemont agrees to make the requested change and will insert the words "patient-labeling" to their existing statement in the Patient Counseling section of their proposed prescribing information (currently, "See FDA-approved Medication Guide"). Edgemont believes the statement as currently worded is within compliance of 21 CFR 201.57(c)(18) and notes that the statement was copied verbatim from FDA-approved prescribing information for generic fluoxetine tablets, USP. An amendment to the pending NDA (as requested by March 4, 2011), to make the requested change would require modification of annotated labeling and as such, all hyperlinks in the current annotated labeling document would become non-functional unless they are completely rebuilt for the amended document. **In consideration of these points, is it acceptable to FDA if Edgemont includes this minor, but important, change to the text with the final content of labeling documentation rather than amending the pending NDA at this time?**

We look forward to FDA's response on the above two issues.

Scott A. Oglesby, Ph.D.
Director, Executive Consulting
Beckloff Associates
(a Cardinal Health Company)
Phone: 919-933-2620
e-mail: soglesby@beckloff.com

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/s/

HIREN PATEL
03/10/2011



NDA 202133

FILING COMMUNICATION

Edgemont Pharmaceuticals, LLC
Attention: Scott A. Oglesby, Ph.D.
Director, Executive Consulting
Beckloff Associates, Inc.
7400 West 110th Street, Suite 300
Overland Park, KS 66210

Dear Dr. Oglesby:

Please refer to your New Drug Application (NDA) dated December 9, 2010, received December 9, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for fluoxetine 60 mg scored 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 October 9, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 11, 2011.

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

Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any listed patents that claim the listed drug on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed drug. Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 18936 for Prozac (fluoxetine hydrochloride) capsules but does not contain a patent certification or statement with respect to any patent(s) listed in FDA's "Approved Drug Products with

Therapeutic Equivalence Evaluations” (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)). In accordance with section 505(b)(2) of the FDCA and 21 CFR 314.50(i), you must submit an appropriate patent certification or statement and address any unexpired exclusivity for the listed drug on which you rely.

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.

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

- Patient Counseling Information - Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling)” should appear at the beginning of Section 17 for prominence. For example, “See FDA-approved patient labeling (Medication Guide).”

We request that you resubmit labeling that addresses these issues by March 4, 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.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Hiren Patel, Pharm.D., Regulatory Project Manager, at (301) 796-2087.

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/

THOMAS P LAUGHREN
02/17/2011

Patel, Hiren

From: Patel, Hiren
Sent: Monday, February 07, 2011 4:31 PM
To: 'SOglesby@beckloff.com'
Subject: NDA 202133

Dear Scott,

Reference is made to NDA 202133 submitted and received on December 9, 2010 and your email dated February 3, 2011. We acknowledge that there are no active studies or new studies completed and Fluoxetine 60 mg scored tablets are not currently marketed. Therefore, we agree with your request for a waiver from the 120-day safety update requirement.

Sincerely,
Hiren

*Hiren D. Patel, Pharm.D., M.S., LT USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov*

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/s/

HIREN PATEL
02/07/2011



NDA 202133

NDA ACKNOWLEDGMENT

Edgemont Pharmaceuticals, LLC
Attention: Scott A. Oglesby, Ph.D.
Director, Executive Consulting
Beckloff Associates, Inc.
7400 West 110th Street, Suite 300
Overland Park, KS 66210

Dear Dr. Oglesby:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Fluoxetine 60 mg scored tablets

Date of Application: December 9, 2010

Date of Receipt: December 9, 2010

Our Reference Number: NDA 202133

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 7, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Hiren Patel, Pharm.D., Regulatory Project Manager, at (301) 796-2087.

Sincerely,

{See appended electronic signature page}

LT Hiren D. Patel, Pharm.D.
Regulatory Health Project Manager
Office of Drug Evaluation I
Division of Psychiatry Products
Center for Drug Evaluation and Research

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/s/

HIREN PATEL
12/23/2010



PIND 107525

Beckloff Associates, Inc
Attention: Scott A. Oglesby, Ph.D.
Director, Executive Consulting
7400 West 110th Street, Suite 300
Overland Park, Kansas 66210

Dear Dr. Oglesby:

Please refer to your PreInvestigational New Drug Application (PIND) file for FXT 60 mg.

We also refer to the meeting between representatives of your firm and the FDA on March 5, 2010. The purpose of the meeting was to discuss the development of FXT 60 mg (fluoxetine HCl) scored tablets for the same patient populations and indications as the innovator product Prozac.

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 Hiren D. Patel, Pharm.D., Regulatory Project Manager, at (301) 796-2087.

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: March 5, 2010
TIME: 3:00PM – 4:00PM
LOCATION: White Oak CDER Bldg 22, Room 1311
APPLICATION: PIND 107525
DRUG NAME: FXT 60 mg
TYPE OF MEETING: Pre-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
Ni Aye Khin, M.D.	Medical Team Leader, DPP
Silvana Borges, M.D.	Medical Reviewer, DPP
Linda Fossom, Ph.D.	Pharmacology/Toxicology Team Leader, DPP
Antonia Dow, Ph.D.	Pharmacology/Toxicology Reviewer, DPP
Thomas Oliver, Ph.D.	Pharmaceutical Assessment Lead, ONDQA
Chhagan Tele, Ph.D.	Pharmaceutical Assessment Reviewer, ONDQA
John Duan, Ph.D.	Biopharmaceutics Reviewer, ONDQA
Raman Baweja, Ph.D.	Clinical Pharmacology Team Leader
Huixia Zhang, Ph.D.	Clinical Pharmacology Reviewer
Kim Updegraff, M.S.	Senior Regulatory Project Manager, DPP

Edgemont Pharmaceuticals, LLC Attendees:

Doug Saltel	President CEO, Edgemont Pharmaceuticals
Scott Oglesby, Ph.D.	Consultant, Clinical and Regulatory Affairs Beckloff Associates, Inc.
William Trey Putnam, Ph.D., RAC	Consultant, CMC, Beckloff Associates, Inc.
Christine Blumhardt, Pharm.D.	Edgemont Regulatory Affairs Advisor
Michael Vachon, M.Sc.Pharm, Ph.D.	Edgemont Formulation Development and CMC Advisor

Background:

Prozac (fluoxetine HCl) was first approved by the FDA in 1987, and Prozac 60 mg capsules was later approved in 1999 (NDA 18-936/S-054). However, the original sponsor, Eli Lilly, discontinued the 60 mg strength Prozac, and today there remains no 60 mg fluoxetine dosage strength available in the U.S. market. Edgemont Pharmaceuticals believes there is a clinical need for a 60 mg dosage strength of fluoxetine, and plans to submit an NDA under section 505(b)(2) seeking approval for FXT 60 mg (fluoxetine HCl) scored tablets for the same patient populations and indications as the innovator product Prozac.

For this purpose, Edgemont has acquired a license from Orion Pharma to market their Seronil 60 mg (fluoxetine HCl) scored tablets in the United States. Orion has manufactured and marketed this dosage strength in Finland since 1997. Seronil 60 mg scored tablets was originally approved in Finland on the basis of bioequivalence (BE) to their own Seronil 20 mg capsules (3 x 20 mg caps vs. 1 x 60 mg tab). Seronil 20 mg capsules was approved in Finland (1992) based on demonstrated BE to Eli Lilly's Fontex (fluoxetine HCl) 20 mg capsules (Seronil 2 x 20 mg vs. Fontex 2 x 20 mg).

As part of this license agreement, Orion will be the sole manufacturer of drug product for Edgemont. Edgemont will import (b) (4); from Orion and then have the tablets bottled by Patheon Inc. at their facility in Puerto Rico. There are two fluoxetine HCl drug substance manufacturers qualified at Orion for use in the manufacture of FXT 60 mg: Orion Corporation's Fermion Oy (Fermion) in Hanko, Finland; (b) (4)

Edgemont plans to initially use only Fermion as a supplier, (b) (4)

Edgemont believes it has sufficient CMC development data, PK data, and bridging dissolution data to support an approvable NDA 505(b)(2) application for FXT 60 mg, and is planning to seek a biowaiver that eliminates the need for Edgemont to conduct additional *in-vivo* BE studies. In this meeting, they plan to discuss the development of FXT 60 mg (fluoxetine HCl) scored tablets for the same patient populations and indications as the innovator product Prozac.

Questions from the sponsor:

GENERAL QUESTIONS

Question 1: In their Section 505(b)(2) NDA filing, Edgemont will reference FDA's prior finding of an adequate risk-benefit for oral fluoxetine HCl with regards to major depressive disorder, OCD, bulimia nervosa, and panic disorder in NDAs 18-936, 18-936/S054, 20-974, and 21-235 (Prozac capsules, tablets, and delayed release capsules), and the applicable postmarketing safety database.

Does FDA agree with this approach?

Preliminary Comments: *Yes, this approach appears acceptable.*

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

Question 2: The approved fluoxetine dosage range for these indications already includes specific references to 30 and 60 mg/day doses and the approved patient populations. Given this, Edgemont plans to adopt the current labeling and prescribing information for the approved immediate release (IR) fluoxetine HCl products (NDAs: 18-936 and 20-974) and will implement the same boxed warning and Patient Medication Guide in its proposed PI for FXT 60 mg.

Does FDA agree with this approach?

Preliminary Comments: Yes, if granted approval status, FXT 60 mg would have the same labeling as the approved fluoxetine innovator products.

Discussion at Meeting: The sponsor asked if they need to submit REMS for approval. We clarified that they will need medguide-only REMS for their product.

CMC QUESTIONS

Question 3: Edgemont intends to present Orion's collected body of knowledge detailing the pharmaceutical development, validation, and commercial production of FXT 60 mg as comprehensive verification of product quality, product performance, and manufacturing processes. Edgemont is proposing specifications for drug substance, excipients, container/closure, and drug product under relevant USP and European Pharmacopoeia (Ph. Eur.) monographs and believes that these are consistent with FDA expectations and ICH guidelines.

Does FDA agree with these proposed specifications?

Preliminary Comments: Your proposed testing appears reasonable at this time. Ultimate acceptability of your specifications (test methods and specification limits) will be determined as part of the NDA review. The dissolution specification should be justified in a dissolution method development report.

It should be noted that new excipients and/or impurities/degradants may need to be qualified.

Discussion at Meeting: No further discussion.

Question 4: There are two fluoxetine HCl drug substance manufacturers qualified at Orion for use in the manufacture of FXT 60 mg drug product. Namely, these two vendors are Orion Corporation's Fermion Oy (Fermion) in Hanko, Finland (b)(4). (b)(4). Edgemont plans to initially use only Fermion as a supplier of fluoxetine HCl due to business reasons. Edgemont may seek to qualify (b)(4); as an alternate supplier for the production of FXT 60 mg postapproval. (b)(4)

Both Fermion and (b)(4); produce drug substance that meets the USP requirements for fluoxetine HCl and meet general U.S. regulatory and scientific requirements for drug substances. Both drug substance vendors have active Type II U.S. DMFs for their respective drug substances.

Does FDA agree with this approach?

Preliminary Comments: Your proposal to add (b) (4) st-approval is fine, but you are reminded that you will need to submit a supplement. It is unclear what supportive drug substance data from (b) (4); will be submitted in the NDA as Orion Corporation's Fermion Oy (Fermion) will be the only drug substance manufacturer. Orion will need to have adequate information in their DMF to support the manufacture of fluoxetine.

Discussion at Meeting: No further discussion.

Question 5: In an effort to support the FDA "2004 unit of use" initiative for all antidepressant products, Edgemont plans to market only a 30 tablet count in an HDPE bottle with a child-resistant cap (CRC). Edgemont is proposing for the original NDA submission to submit 3 month room temperature (long-term) and 3 month accelerated ICH stability data of an ongoing stability program for one batch of the drug product manufactured at Orion at the intended commercial scale (b) (4) to support drug product in this preferred U.S. packaging format. This batch will be packaged at Patheon, the proposed U.S. commercial packager, into the proposed U.S. container closure system (b) (4). The HDPE container and closure for the U.S. market is similar to those used by Orion Pharma in materials of construction and size. The stability data will be directly compared to stability data collected on the product currently marketed in Finland. The drug product has been manufactured and marketed for 12 years in Finland in various HDPE bottle sizes and tablet counts. Comparative evaluation between the proposed U.S. package presentation and the currently marketed container closure systems in Finland, including the headspace volume, will also be provided in the NDA filing.

Does FDA agree with this approach?

Preliminary Comments: We recommend that you submit 12 months of stability data from three batches of the drug product manufactured at Orion using the to be marketed formulation and packaging and a manufacturing process that simulates the commercial process. Two of the three batches should be at least pilot scale batches and the third one can be smaller, if justified. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance. Refer to ICH Q1A(R2): Stability Testing of New Drug Substances and Products.

Discussion at Meeting: Edgemont clarified that the NDA would contain stability data from the Orion drug product which has been manufactured and marketed for 12 years in Finland. The sponsor indicated that this data was collected under ICH conditions and that there are only minor container closure differences between the currently marketed Finnish product Seronil 60 mg and the proposed US product. Information to demonstrate that the US container closure is equivalent or superior to the container closure used for the Finnish product will be included in the NDA. The sponsor will be submitting 3 months of long-term and 3 months of accelerated ICH stability data for one drug product batch manufactured by Orion at the intended commercial scale (b) (4) tablets) to support the preferred U.S. packaging format. A comparative analysis of this

data to historical data will be included in the NDA. The sponsor has committed to submitting stability updates as they become available during the NDA review. The current specification for dosage form shape (capsule tablet) is ambiguous. We recommend using: capsule shaped tablet.

Question 6: Based on the well-established tablet manufacturing process and the results of the half tablet uniformity of mass test results and the half tablet versus full tablet comparative dissolution data results, Edgemont believes there is sufficient evidence to support the continued bisectonal scoring of tablets.

Does the FDA agree that the proposed information to be provided will be sufficient to support a marketing application that will include the scored tablet format?

Preliminary Comments: *Your approach seems reasonable. You should continue to evaluate half tablets from future drug product batches and submit this information in your original NDA submission. You will need to provide adequate stability testing data (e.g., appearance, assay, degradants, dissolution, content uniformity, and friability data) for the half tablets. The adequacy of this data will be determined as part of the NDA review.*

Discussion at Meeting: *Edgemont agreed to evaluate half tablets from future drug product batches and provide adequate stability testing data in the original NDA submission.*

Question 7: For comparative dissolution studies, multimedia dissolution studies, and demonstration of rapid dissolution, Edgemont has utilized FDA and USP recommended dissolution conditions for fluoxetine tablets with appropriate pH adjustment for the multimedia studies: USP Apparatus I (baskets) at 100 rpm, 1000 mL of 0.1N HCl as the medium (or buffers for multimedia studies) with sampling times of 5, 10, 15, 20, and 30 min. The August 2000, FDA *Guidance for Industry, "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System"*, recommends a dissolution medium of not more than 900 mL for demonstration of rapid dissolution. Based on FDA and USP recommendations for dissolution of fluoxetine tablets, the determined dissolution of FXT 60 mg, and the use of FDA and USP recommended conditions with other fluoxetine tablets, Edgemont believes that the conditions employed including 1000 mL of dissolution medium are the most appropriate dissolution medium for comparative and multimedia dissolution studies.

Does the FDA agree with the approach taken? Does the FDA agree that no further in-vitro dissolution work is required to support the FXT 60 mg 505(b)(2) application?

Preliminary Comments: *Yes, we agree with the overall dissolution approach. However, the testing details including individual dissolution data should be provided. In addition, the dissolution method development report should be provided (see Q3).*

Discussion at Meeting: *No further discussion.*

CLINICAL QUESTIONS

Question 8: Literature and direct experimental data (in-vivo and in-vitro) are presented in this meeting information package for FXT 60 mg to support the position that no additional in-vivo bioavailability (BA) studies (biowaiver) should be required to support the approval of FXT 60 mg. This position is supported by the solubility and permeability profile of fluoxetine HCl, the history of demonstrated BE across all oral fluoxetine formulations, and the fact that the rapidly dissolving FXT 60 mg tablets have a very similar release profile to the other approved fluoxetine IR formulations. In addition, Edgemont believes that when the above information is combined with the PK clinical trial data produced by Orion and the bridging dissolution data produced by Edgemont, there is sufficient in-vitro and in-vivo data to support an approvable NDA 505(b)(2) application.

Does the FDA agree that no additional FXT™ 60 mg pharmacokinetic clinical trial data will be required to support an NDA 505(b)(2) approval? If not, what additional information would the FDA require?

Preliminary Comments: *Currently fluoxetine is not classified as a Class I and therefore an in vivo bioavailability waiver based on BCS classification is not possible.*

If the sponsor wants to claim that the product is a class 1, supportive information as described in the BCS guidance should be provided and approved by the BCS Committee.

Alternatively,

OCP Comment:

A single-dose biostudy under fasted conditions will be needed to compare FXT™ 60 mg to an approved US product, both dosed at 60mg.

Sponsor's response to preliminary comments: *The sponsor submitted a synopsis of a BE study protocol (Study 101) entitled "A randomized open-label, two-period, two-sequence, single-dose crossover study comparing the pharmacokinetic profiles following oral dosing of 1 x 60 mg fluoxetine HCl tablets to 3 x 20 mg fluoxetine HCl tablets in the fasted state in Healthy Subjects."*

Discussion at Meeting: *The sponsor asked for clarification about the responses for the biowaiver request based BCS classification. The Agency stated that a BCS-based biowaiver is useful only when the products to be linked are pharmaceutical equivalents (under the definition at 21 CFR 320.1 (c)). The pharmaceutical equivalence between the proposed product and US marketed product has not been shown.*

The procedure for making a BCS Class I claim was clarified. The sponsor would need to submit a package with detailed information. After the initial screening, the primary

reviewer will submit the package to BCS Committee for approval. The committee meets once a month usually, however, it was noted that the entire process could take up to 6 months..

Based on discussion at the meeting, the sponsor indicated that they will proceed with their plan to conduct a biostudy. They were told that they can submit a detailed protocol for Comments from OCP (see below also).

Based on the synopsis submitted, they were asked about the test formulation, fluoxetine 60 mg tablet, that they plan to use in the biostudy. They indicated that they plan to study the product made by Orion in Finland and that this is also the product they they would plan to market in the United States. Further, they understand that the reference product should be an approved U.S. product.

The study will assay for both fluoxetine and norfluoxetine. At the meeting the sponsor was told that PK parameters and statistics need to be calculated and performed for both moieties. We agreed that data for norfluoxetine will not be considered as the primary data to support bioequivalence of the two dosage forms.

Post-meeting comments: *Please be advised that this proposed study protocol (study 101) should be submitted under the PIND if the sponsor requests comments from the Division.*

SUBMISSION-SPECIFIC QUESTIONS

Question 9: Edgemont proposes that in CTD Module 2.4, Edgemont will cross-reference CTD Module 1.12.11 (Basis for Submission) to clarify the absence of nonclinical data in this 505(b)(2) NDA submission.

Does FDA agree with this approach?

Preliminary Comments: *Your proposal is acceptable.*

Discussion at Meeting: *No further discussion.*

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

ND-107525

GI-1

Edgemont
Pharmaceuticals,
LLC (Edgemont)

FXT 60mg (fluoxetine HCl 60mg
scored tablets)

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/s/

THOMAS P LAUGHREN

03/11/2010