

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**204516Orig1s000**

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

**PATENT INFORMATION SUBMITTED UPON AND  
AFTER APPROVAL OF AN NDA OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation or  
Composition) and/or Method of Use*

NDA NUMBER

204-516

NAME OF APPLICANT/NDA HOLDER

Noven Therapeutics, LLC

**The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.**

TRADE NAME

BRISDELLE

ACTIVE INGREDIENT(S)

Paroxetine Mesylate

STRENGTH(S)

7.5 mg

DOSAGE FORM

Capsule; Oral

APPROVAL DATE OF NDA OR SUPPLEMENT

June 28, 2013

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

**For hand-written or typewriter versions of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

7,598,271

b. Issue Date of Patent

10/06/2009

c. Expiration Date of Patent

02/12/2023

d. Name of Patent Owner

Noven Therapeutics, LLC

Address (of Patent Owner)

11960 SW 144th Street

City/State

Miami, Florida

ZIP Code

33186

FAX Number (if available)

305-251-1887

Telephone Number

305-253-5099

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**FDA will not list the patent in the Orange Book as claiming the drug substance if:**

- the answers to 2.1 and 2.2 are "No," or,
- the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,
- the answer to 2.3 is "Yes" and there is no response to 2.4, or,
- the answer to 2.5 or 2.6 is "Yes."
- the answer to 2.7 is "No."

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**FDA will not list the patent in the Orange Book as claiming the drug product if:**

- the answer to question 3.1 is "No," or,
- the answer to question 3.2 is "Yes," or,
- the answer to question 3.3 is "No."

**4. Method of Use**

**Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more approved methods of using the approved drug product?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim an approved method of use of the approved drug product?	<input type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
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**4.2b** If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.

Use: (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)

FDA will not list the patent in the Orange Book as claiming the method of use if:

- the answer to question 4.1 or 4.2 is "No," or
- if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.

**5. No Relevant Patents**

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1** The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2** Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) Date Signed

*Joel S. Lippman, MD* 7/8/2013

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input checked="" type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Joel S. Lippman, M.D.	
Address 11960 S.W. 144th Street	City/State Miami, Florida
ZIP Code 33186	Telephone Number 305-254-5099
FAX Number (if available)	E-Mail Address (if available) jlippman@noven.com

The public reporting burden for this collection of information has been estimated to average 5 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, Room 400  
Rockville, MD 20850

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

## INFORMATION AND INSTRUCTIONS FOR FORM 3542

### PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

#### General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use. Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

#### First Section

Complete all items in this section.

##### 1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.
- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

#### 2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the approved NDA or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be listed. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be listed as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

#### 3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the approved NDA or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

#### 4. Method of Use

Complete all items in this section if the patent claims one or more methods of use of the drug product that is the subject of the approved NDA or supplement.

- 4.2) For each approved use of the drug claimed by the patent, identify by number the claim(s) in the patent that claim the approved use of the drug. An applicant may list together multiple patent claim numbers and information for each approved method of use, if applicable. However, each approved method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the approved drug labeling that is claimed by the patent.
- 4.2b) The answer to this question will be what FDA uses to create a "use-code" for Orange Book publication. The use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. Use a maximum of 240 characters for each "use code."

#### 5. No Relevant Patents

Complete this section only if applicable.

#### 6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

## EXCLUSIVITY SUMMARY

NDA # 204516

SUPPL #

HFD #

Trade Name Brisdelle

Generic Name paroxetine

Applicant Name Noven Therapeutics, Inc.

Approval Date, If Known 6-28-2013

### **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.

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?

3

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# 021299 Pexeva

NDA# 020031 Paxil

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 N30-003 and N30-004

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 similar investigation was relied on:

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

Studies N30-003 and N30-004

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1  
IND # 076636      YES       ! NO   
! Explain:

Investigation #2  
IND # 076636      YES       ! NO   
! Explain:

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

Investigation #1  
!

YES   
Explain:

! NO   
! Explain:

Investigation #2

!

!

YES   
Explain:

! NO   
! Explain:

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

YES  NO

If yes, explain:

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Name of person completing form: Kim Shiley  
Title: Regulatory Health Project Manager  
Date: 6-27-2013

Name of Office/Division Director signing form:  
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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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KIMBERLY A SHILEY  
06/27/2013

HYLTON V JOFFE  
06/28/2013

### 1.3.3 DEBARMENT CERTIFICATION

Noven Therapeutics, LLC 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.

Joel S. Lippman, M.D.

Joel S. Lippman, M.D.  
Authorized Representative

8/9/2012

Date

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 204516 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: BRISDELLE™ Established/Proper Name: paroxetine Dosage Form: capsules		Applicant: Noven Pharmaceuticals LLC Agent for Applicant (if applicable):
RPM: Kim Shiley		Division: DBRUP

<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>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><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):          Paxil NDA #020031</p> <p>Provide a brief explanation of how this product is different from the listed drug.          New indication and new dosage form</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> 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: 6-28-13</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>
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<b>❖ Actions</b>	
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>6-28-13</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 checked="" type="checkbox"/> None

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

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<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>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 10</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></p> <p>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: 100px;"><input type="checkbox"/> Communication Plan</span>  <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 100px;"><input type="checkbox"/> ETASU</span>  <span style="margin-left: 400px;"><input type="checkbox"/> MedGuide w/o REMS</span>  <span style="margin-left: 400px;"><input 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>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Press Office notified of action (by OEP)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<p><input type="checkbox"/> None  <input checked="" type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other</p>

<sup>3</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 BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? 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.</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? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</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? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</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? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</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)? (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.)</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 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 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). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</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>	<p><input type="checkbox"/> Yes    <input checked="" type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

<p>❖ Copy of this Action Package Checklist<sup>4</sup></p>	
<p align="center"><b>Officer/Employee List</b></p>	
<p>❖ 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>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p align="center"><b>Action Letters</b></p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) 6-28-13</p>
<p align="center"><b>Labeling</b></p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<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>	<p>6-27-13</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>8-8-12</p>
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	<p>n/a</p>

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

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"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	6-27-13
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	8-8-12
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	n/a
❖ 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> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	6-27-13
❖ 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>	3-15-2013 3-14-2013
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM 11-8-12 <input checked="" type="checkbox"/> DMEPA 5-21-13 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 6-26-13 <input checked="" type="checkbox"/> OPDP (DDMAC) 6-24-13 <input checked="" type="checkbox"/> SEALD 6-27-13 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	11-8-12
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2) 5-2-13
❖ NDAs (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input type="checkbox"/> Not a (b)(2) 6-27-13
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ 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>	
<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
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC 5-22-13 If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" 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

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	
❖ 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 checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 5-29-12
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 9-20-10
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	SPA 2-14-11
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	3-4-13
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	3-26-13
<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 checked="" type="checkbox"/> None 6-28-13
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None 6-28-13
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	6-28-13
• Clinical review(s) ( <i>indicate date for each review</i> )	5-21-13
• 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 Review dated May 21, 2013, page 13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None Pediatric & Maternal Health Staff 6-17-13 OHOP/DOP1 3-18-13 DPP 2-5-13
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• 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
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 5-28-13 5-14-13; 5-24-13; 6-28-13

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 5-22-13
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 5-22-13
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 5-17-13
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 5-17-13
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 2-4-14 & 5-14-13
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 2-1-13
Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 6-27-13, 5-1-13
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 6-27-13, 5-1-13
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None Biopharmaceutics 5-24-13, 4-26-13

Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See Product Quality Discipline Review, dated 5-1-13, page 64
<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 type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )	Date completed: 6-27-13 <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</i> ) ( <i>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 checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</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.

Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See Product Quality Discipline Review, dated 5-1-13, page 64
<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 type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )	Date completed: see Product Quality Memorandum/Addendum dated 6-27-13 <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</i> ) ( <i>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 checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</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.



NDA 204516

**INFORMATION REQUEST**

**From:** Shah, Snehal N. [mailto:SShah@noven.com]  
**Sent:** Wednesday, June 12, 2013 1:36 PM  
**To:** Shiley, Kimberly  
**Subject:** RE: NDA 204516: Response to Agency's Labeling Comments Revised Section 6.2

Thanks!

Kind Regards,

**Snehal Shah, Pharm.D.**  
Regulatory Affairs  
Noven Pharmaceuticals, Inc.  
Phone: (212) 287-0971  
[REDACTED] (b) (6)  
[sshah@noven.com](mailto:sshah@noven.com)

**From:** Shiley, Kimberly [mailto:Kimberly.Shiley@fda.hhs.gov]  
**Sent:** Wednesday, June 12, 2013 1:16 PM  
**To:** Shah, Snehal N.  
**Subject:** RE: NDA 204516: Response to Agency's Labeling Comments Revised Section 6.2

Hi Snehal,

I received the following to answer your questions:

1. We are definitely NOT accepting [REDACTED] (b) (4)
2. In general, your methodology for 6.2 appears appropriate, but we are still reviewing specifics of the ARs.

Also, we will request you return by noon Monday, June 17<sup>th</sup>.

Kim Shiley, RN, BSN  
Regulatory Health Project Manager  
Division of Bone, Reproductive, and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Bldg 22, Room 5377  
office: 301-796-2117

fax: 301-796-9897  
[kimberly.shiley@fda.hhs.gov](mailto:kimberly.shiley@fda.hhs.gov)

**From:** Shah, Snehal N. [mailto:SShah@noven.com]  
**Sent:** Wednesday, June 12, 2013 12:38 PM  
**To:** Shiley, Kimberly  
**Subject:** RE: NDA 204516: Response to Agency's Labeling Comments Revised Section 6.2

**Thanks Kim!**

**We will make the change on the physician sample pack and I will email you a revised label.**

**Understanding the label will be available late tomorrow, we will do everything we can to provide a 24 hour turnaround. To help facilitate a quick turnaround and so I can prepare my Noven Team can you provide the following information:**

- 1. Did the Agency accept Noven's proposed wording or something similar in section 6.1 regarding [REDACTED] (b) (4)?**
- 2. Was the Agency ok with Noven's methodology for the postmarketing adverse reactions section 6.2 or is further information/ evaluation needed by Noven?**

**Any high-level information you can provide me on these two topics today would be greatly helpful and allow Noven to prepare for the Agency's comments tomorrow.  
Thanks!**

**Kind Regards,**

**Snehal Shah, Pharm.D.**  
Regulatory Affairs  
Noven Pharmaceuticals, Inc.  
Phone: (212) 287-0971  
[REDACTED] (b) (6)  
[sshah@noven.com](mailto:sshah@noven.com)

**From:** Shiley, Kimberly [mailto:Kimberly.Shiley@fda.hhs.gov]  
**Sent:** Wednesday, June 12, 2013 12:24 PM  
**To:** Shah, Snehal N.  
**Subject:** RE: NDA 204516: Response to Agency's Labeling Comments Revised Section 6.2

**Hi Snehal,**

**I have the following comment regarding carton & container:**

**On the principal display panel for the physician sample, delete or revise the statement "TAKE ONCE DAILY AT BEDTIME" to appear in title case as follows- "Take Once Daily at Bedtime". Currently the statement competes with the established name, dosage form, and strength.**

**I was hoping to also send back the PI but it will not be ready until very late tomorrow. I will forward when it is ready and am hoping you can turn around quickly; 24 hours if possible. I have another meeting scheduled on the 18<sup>th</sup>.**

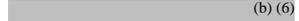
*Kim Shiley, RN, BSN*

Regulatory Health Project Manager  
Division of Bone, Reproductive, and Urologic Products  
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office: 301-796-2117  
fax: 301-796-9897  
[kimberly.shiley@fda.hhs.gov](mailto:kimberly.shiley@fda.hhs.gov)

**From:** Shah, Snehal N. [mailto:SShah@noven.com]  
**Sent:** Wednesday, June 12, 2013 12:12 PM  
**To:** Shiley, Kimberly  
**Subject:** RE: NDA 204516: Response to Agency's Labeling Comments Revised Section 6.2

Hello Kim I hope you are doing well.  
I wanted to touch-base with you if we should be expecting today any further labeling comments or other information requests based on the Agency's internal meeting.  
Thanks for all your help!

Kind Regards,

**Snehal Shah, Pharm.D.**  
Regulatory Affairs  
Noven Pharmaceuticals, Inc.  
Phone: (212) 287-0971  
 (b) (6)  
[sshah@noven.com](mailto:sshah@noven.com)

**From:** Shiley, Kimberly [mailto:Kimberly.Shiley@fda.hhs.gov]  
**Sent:** Friday, June 07, 2013 3:35 PM  
**To:** Shah, Snehal N.  
**Subject:** RE: NDA 204516: Response to Agency's Labeling Comments Revised Section 6.2

Thank you Snehal,

Have a nice weekend. I'll be back in touch either Tuesday or Wednesday; after our meeting.

*Kim Shiley, RN, BSN*  
Regulatory Health Project Manager  
Division of Bone, Reproductive, and Urologic Products  
Office of Drug Evaluation III  
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10903 New Hampshire Avenue  
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office: 301-796-2117  
fax: 301-796-9897  
[kimberly.shiley@fda.hhs.gov](mailto:kimberly.shiley@fda.hhs.gov)

**From:** Shah, Snehal N. [mailto:SShah@noven.com]  
**Sent:** Friday, June 07, 2013 1:30 PM

To: Shiley, Kimberly  
Subject: RE: NDA 204516: Response to Agency's Labeling Comments Revised Section 6.2

Dear Kim,

Attached for your review please find a revised Section 6.2 that complies with the instructions the Agency provided to us. We include in the attachment above, a Methodology discussion that outlines our approach to the revised proposal for Section 6.2. As you will see, we omitted any adverse reactions that are duplicated in other sections of the Brisdelle label and identified the basis for our decisions on which reactions to list for both non-serious and serious cases. Naturally, we are concerned about any inconsistencies with the list of AEs that is included in the approved Pexeva label, however, we have now deleted those events in response to the Agency's guidance to focus on medical appropriateness. We believe that our methodology complies with both the AR Guidance and the Agency's requests. Also attached is summary information/data sources utilized for the analysis so the Agency can verify the Adverse Reactions (Appendix 1, Appendix 2, Pexeva and Paxil USPI).

We greatly appreciate the Agency's consideration of these revisions. Please let us know if the Agency accepts our methodology and the requested changes we made to Section 6.2. We would be glad to discuss any of these issues further in a teleconference. Thanks again for all your help and please let us know if you have any questions or concerns.

Kind Regards,

**Snehal Shah, Pharm.D.**  
Regulatory Affairs  
Noven Pharmaceuticals, Inc.  
Phone: (212) 287-0971

(b) (6)

[sshah@noven.com](mailto:sshah@noven.com)

From: Shiley, Kimberly [mailto:Kimberly.Shiley@fda.hhs.gov]  
Sent: Thursday, June 06, 2013 4:31 PM  
To: Shah, Snehal N.  
Subject: RE: NDA 204516: Response to Agency's Labeling Comments (Brisdelle USPI and MedGuide)

Hi Snehal,

We are reviewing Noven's responses to our labeling comments and will be doing so over several more days. However, we want to inform you that Section 6.2 is unacceptable. Please refer to the FDA Guidance for Industry Adverse Reactions. Resubmit to me, as a free-standing document, a revised Section 6.2 that meets the AR Guidance.

(b) (4)

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf>

Please submit by COB Monday, June 10<sup>th</sup> at the latest.

Thanks!

Kim Shiley, RN, BSN  
Regulatory Health Project Manager  
Division of Bone, Reproductive, and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
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office: 301-796-2117  
fax: 301-796-9897  
[kimberly.shiley@fda.hhs.gov](mailto:kimberly.shiley@fda.hhs.gov)

**From:** Shah, Snehal N. [mailto:SShah@noven.com]  
**Sent:** Wednesday, June 05, 2013 6:44 PM  
**To:** Shiley, Kimberly  
**Subject:** RE: NDA 204516: Response to Agency's Labeling Comments (Brisdelle USPI and MedGuide)

Dear Kim,

Attached is Noven's response to the Agency's May 31, 2013 labeling comments on the USPI and Medication Guide. The attached label accepts the Agency's proposed revisions and incorporates the Agency's recommendations/ comments in tracked changes with annotations in the comments field. All Agency recommendations have been accepted and implemented with the exception of the following Noven modifications/ proposals with our justification provided below:

(b) (4)

Additionally, as requested by the Agency, for the postmarketing adverse reactions (section 6) a methodology document outlining Noven's approach for populating this section and summary tables are provided so the Agency can verify the adverse reactions reported.

We greatly appreciate the Agency's consideration of the above proposed wording for inclusion in the label and would be glad to discuss further in a teleconference if needed. Thanks for all your help and please let me know if you have any questions.

Kind Regards,

**Snehal Shah, Pharm.D.**  
Regulatory Affairs  
Noven Pharmaceuticals, Inc.  
Phone: (212) 287-0971

 (b) (6)  
[sshah@noven.com](mailto:sshah@noven.com)

**From:** Shiley, Kimberly [mailto:Kimberly.Shiley@fda.hhs.gov]  
**Sent:** Friday, May 31, 2013 12:32 PM  
**To:** Shah, Snehal N.  
**Subject:** NDA 204516

Greetings Snehal,

I have several documents for your team. First is an email courtesy copy of the letter for Labeling Discussion Comments being sent to Noven today.

Also, the word version of the labeling PI and MG. These are our initial labeling comments. We need for you to **return the labeling by COB Friday, June 7th** to me via email. If you accept our edits, please ACCEPT track changes. Any revisions should be made with track changes.

Please review the attached Selected Requirements of Prescribing Information (SRPI) document. Your labeling should address all formatting elements; the attached PI and MG may not reflect these requirements in our comments at this time. The link also provides information regarding PLR Requirements for the PI.

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

If you have any questions, please let me know.

*Kim Shiley, RN, BSN*  
Regulatory Health Project Manager  
Division of Bone, Reproductive, and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
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/s/  
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KIMBERLY A SHILEY  
06/12/2013



NDA 204516

## INFORMATION REQUEST

**From:** Shiley, Kimberly  
**Sent:** Monday, June 03, 2013 3:41 PM  
**To:** Shah, Snehal N. (SShah@noven.com)  
**Cc:** Cato, Marcus  
**Subject:** NDA 204516, Information Request, Carton & Container

Greetings Snehal,

We are reviewing the April 26, 2013 carton and container labels submission and have the following comments and information requests. We request a prompt written response (COB Friday, June 7 requested) in order to continue our evaluation of your NDA.

### A. All Labels and Labeling

1. The finished dosage form is a component of the established name. Thus, we recommend that you relocate 'Capsules' to appear next to 'Paroxetine' and revise the presentation of 'Capsules' to have the same prominence (i.e., font size, color, and style) as Paroxetine.
2. Relocate the product strength (i.e., 7.5 mg) to follow the dosage form. Additionally, increase the prominence of the strength statement by increasing the font size. Thus, after revisions, the presentation of the proprietary name, established name, dosage form, and the product strength should appear as:

#### **Brisdelle**

(Paroxetine) Capsules

7.5 mg

3. Remove or reduce the prominence of the flower type graphic that appears above the proprietary name as it competes in prominence with the proprietary name.
4. Remove (b) (4) that appear on all the labels as they distract from important information such as proprietary name, established name, dosage form, and product strength.

5. Reduce the prominence of the manufacturer's logo so that it does not compete with the prominence of the proprietary name.

B. (b) (4)

(b) (4)

C. Blister Label (trade)

1. Remove the statement (b) (4) that appears next to the proprietary name. This statement appears promotional and clutters the label.
2. Delete the statement (b) (4) from the principal display panel as this statement already appears on the panel with the storage information.
3. Revise the presentation of the established name, dosage form, and product strength where they appear on all the panels of the blister label to appear as:

(Paroxetine) Capsules  
7.5 mg per capsule

4. Relocate the NDC to appear in the top third portion of the label per 21 CFR 207.35(b)(3)(i).
5. Delete the (b) (4) statement and the (b) (4) statement (i.e., (b) (4) that appear on the panel with the storage information. This information already appears on the principal display panel and clutters the area around the proprietary name, established name, and product strength.
6. Revise the blister pack design (b) (4) with Day 1, Day 2, Day 3, ..., Day 30. (b) (4)
7. Remove (b) (4)
8. Delete the statements (b) (4) as well as the listed under these statements. (b) (4)

D. Blister Labels (professional sample)

1. See comments C1 through C3.
2. Revise the blister pack design to replace (b) (4) with Day 1, Day 2, Day 3, ..., Day 7. (b) (4)
3. Delete the (b) (4) statements that appear above the manufacturer's information on the panel with the storage information. This information already appears on this panel as well as the principal display panel, and clutters the label.

*Kim Shiley, RN, BSN*  
Regulatory Health Project Manager  
Division of Bone, Reproductive, and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
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[kimberly.shiley@fda.hhs.gov](mailto:kimberly.shiley@fda.hhs.gov)

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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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KIMBERLY A SHILEY  
06/04/2013



NDA 204516

**LABELING PMR/PMC DISCUSSION COMMENTS**

Noven Therapeutics  
Attention: Snehal Shah, Pharm.D.  
Director, Regulatory Affairs  
Empire State Building  
350 Fifth Avenue, 37th Floor  
NY, NY 10118

Dear Dr. Shah:

Please refer to your August 28, 2012 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brisdelle (paroxetine) capsules, 7.5 mg.

We also refer to our November 9, 2012, letter in which we notified you of our target date of June 1, 2013 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 November 19, 2012, we received your November 19, 2012 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

If you have any questions, call me, at (301) 796-2117.

Sincerely,

*{See appended electronic signature page}*

Kim Shiley, R.N., B.S.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive, and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE: Labeling

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

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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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KIMBERLY A SHILEY  
05/31/2013



NDA 204516

## INFORMATION REQUEST

**From:** Shah, Snehal N. [mailto:SShah@noven.com]  
**Sent:** Wednesday, April 24, 2013 4:43 PM  
**To:** Shiley, Kimberly  
**Cc:** Jennings, Kerri-Ann; Escobar, Monica  
**Subject:** RE: NDA 204-516: Follow-up on Ongoing Activities and RHDAC Meeting Document

Thanks Kim and Kerri-Ann,

We will make the changes as stated below and submit revised packaging as soon as possible. Also for the equivalency statement, as stated in the Agency's November 09, 2012 Filing Communication Letter the Agency's recommended wording, "**Each capsule contains 9.69 mg paroxetine mesylate equivalent to 7.5 mg paroxetine base.**" Is the equivalency statement still necessary based on the revisions proposed below? If it is required we propose it to be revised to "**Each capsule contains paroxetine mesylate equivalent to 7.5 mg of paroxetine.**" Noven proposes this revision to be consistent with the equivalency statements on the packaging of the reference listed drugs for the 505b2 NDA 204-516; Paxil (paroxetine hydrochloride) and Pexeva (paroxetine mesylate). Additionally, having consistent labeling amongst paroxetine products may avoid confusion around the dose of paroxetine and medication errors We can discuss this further at the teleconference tomorrow, if needed, and thanks for all your help!

Kind Regards,

**Snehal Shah, Pharm.D.**  
Regulatory Affairs  
Noven Pharmaceuticals, Inc.  
Phone: (212) 287-0971  
(b) (6)  
[sshah@noven.com](mailto:sshah@noven.com)

**From:** Shiley, Kimberly [mailto:Kimberly.Shiley@fda.hhs.gov]  
**Sent:** Wednesday, April 24, 2013 3:36 PM  
**To:** Shah, Snehal N.  
**Cc:** Jennings, Kerri-Ann  
**Subject:** RE: NDA 204-516: Follow-up on Ongoing Activities and RHDAC Meeting Document

Hi Snehal,

The following changes are needed:

- 1) The established name of the product is paroxetine.\* Change all instances (b) (4) to "paroxetine."
- 2) Include "protect from humidity" or equivalent statement on carton/container for both configurations.

3) Change storage conditions to "Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F)" for all configurations.

\*In consideration of the USP Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations, addressed in USP <1121> and becoming effective May 1, 2013, the established name of the drug product is recommended to be "paroxetine."

Thanks,

*Kim Shiley, RN, BSN, BSBA*  
Regulatory Health Project Manager  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
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office: 301-796-2117  
fax: 301-796-9897  
[kimberly.shiley@fda.hhs.gov](mailto:kimberly.shiley@fda.hhs.gov)

From: Shah, Snehal N. [mailto:SShah@noven.com]

Sent: Wednesday, April 24, 2013 2:46 PM

To: Shiley, Kimberly

Subject: RE: NDA 204-516: Follow-up on Ongoing Activities and RHDAC Meeting Document

No problem Kim. Thanks and we can touch-base tomorrow.

Kind Regards,

**Snehal Shah, Pharm.D.**

Regulatory Affairs

Noven Pharmaceuticals, Inc.

Phone: (212) 287-0971

(b) (6)

[sshah@noven.com](mailto:sshah@noven.com)

From: Shiley, Kimberly [mailto:Kimberly.Shiley@fda.hhs.gov]

Sent: Wednesday, April 24, 2013 2:36 PM

To: Shah, Snehal N.

Subject: RE: NDA 204-516: Follow-up on Ongoing Activities and RHDAC Meeting Document

Hi Snehal,

I need to speak with CMC reviewers tomorrow. Please hold off on sending labels today.

Thanks

*Kim Shiley, RN, BSN, BSBA*  
Regulatory Health Project Manager  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III

**Center for Drug Evaluation and Research**  
10903 New Hampshire Avenue  
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office: 301-796-2117  
fax: 301-796-9897  
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**From:** Shah, Snehal N. [mailto:SShah@noven.com]  
**Sent:** Wednesday, April 24, 2013 1:56 PM  
**To:** Shiley, Kimberly  
**Subject:** RE: NDA 204-516: Follow-up on Ongoing Activities and RHDAC Meeting Document

Hello Kim,

The established name is: [REDACTED] (b) (4) We received feedback in the Agency's November 09, 2012 Filing Communication letter on how to display the established name and the revised labels will reflect this feedback. Please let me know if you have any further questions.

Kind Regards,

**Snehal Shah, Pharm.D.**  
Regulatory Affairs  
Noven Pharmaceuticals, Inc.  
Phone: (212) 287-0971  
[REDACTED] (b) (6)  
[sshah@noven.com](mailto:sshah@noven.com)

**From:** Shiley, Kimberly [mailto:Kimberly.Shiley@fda.hhs.gov]  
**Sent:** Wednesday, April 24, 2013 1:43 PM  
**To:** Shah, Snehal N.  
**Subject:** RE: NDA 204-516: Follow-up on Ongoing Activities and RHDAC Meeting Document

**Quick question before you submit C&C labels: Is your established name paroxetine?**

*Kim Shiley, RN, BSN, BSBA*  
**Regulatory Health Project Manager**  
**Division of Reproductive and Urologic Products**  
**Office of Drug Evaluation III**  
**Center for Drug Evaluation and Research**  
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office: 301-796-2117  
fax: 301-796-9897  
[kimberly.shiley@fda.hhs.gov](mailto:kimberly.shiley@fda.hhs.gov)

**From:** Shah, Snehal N. [mailto:SShah@noven.com]  
**Sent:** Wednesday, April 24, 2013 1:20 PM  
**To:** Shiley, Kimberly  
**Subject:** RE: NDA 204-516: Follow-up on Ongoing Activities and RHDAC Meeting Document

Thanks for the update!

Kind Regards,

**Snehal Shah, Pharm.D.**  
Regulatory Affairs  
Noven Pharmaceuticals, Inc.  
Phone: (212) 287-0971  
 (b) (6)  
[sshah@noven.com](mailto:sshah@noven.com)

**From:** Shiley, Kimberly [mailto:Kimberly.Shiley@fda.hhs.gov]  
**Sent:** Wednesday, April 24, 2013 1:15 PM  
**To:** Shah, Snehal N.  
**Subject:** RE: NDA 204-516: Follow-up on Ongoing Activities and RHDAC Meeting Document

**Hi Snehal,**

Further feedback is, we are not prepared to discuss whether your submission "has addressed any outstanding issues around the efficacy of paroxetine" prior to completion of the review process.

We have the information needed to complete the review and will request anything additional, if needed. A meeting is not needed at this time.

*Kim Shiley, RN, BSN, BSBA*  
Regulatory Health Project Manager  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
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office: 301-796-2117  
fax: 301-796-9897  
[kimberly.shiley@fda.hhs.gov](mailto:kimberly.shiley@fda.hhs.gov)

**From:** Shiley, Kimberly  
**Sent:** Wednesday, April 24, 2013 11:52 AM  
**To:** 'Shah, Snehal N.'  
**Subject:** RE: NDA 204-516: Follow-up on Ongoing Activities and RHDAC Meeting Document

**Hi Snehal,**

Please submit formally. I do not have answers to questions; the NDA is still under review. If I am provided anything by my team, I will let you know.

*Kim Shiley, RN, BSN, BSBA*  
Regulatory Health Project Manager  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

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**office: 301-796-2117**  
**fax: 301-796-9897**  
[kimberly.shiley@fda.hhs.gov](mailto:kimberly.shiley@fda.hhs.gov)

**From:** Shah, Snehal N. [mailto:SShah@noven.com]  
**Sent:** Wednesday, April 24, 2013 11:46 AM  
**To:** Shiley, Kimberly  
**Subject:** RE: NDA 204-516: Follow-up on Ongoing Activities and RHDAC Meeting Document

Dear Kim,

Following the March 04, 2013 Reproductive Health Drugs Advisory Committee (RHDAC) meeting Noven has given considerable thought regarding the feedback provided by the RHDAC. We have prepared a brief (4 page) document summarizing the issues discussed at the RHDAC and their relevance to the review of NDA 204-516. We believe this document will be helpful to the Agency and we would greatly appreciate if you can forward it to your review Team. Please let me know if this email is acceptable or if you need me to submit this document to the NDA or IND so it can be considered by the Agency during the ongoing review of NDA 204-516. The document does not contain any new data so it should not constitute a major amendment, but I want to confirm with you. Thanks for all your help and I look forward to speaking to you soon regarding this document and any information you may be able to provide on our previous questions, in the email below.

Kind Regards,

**Snehal Shah, Pharm.D.**  
Regulatory Affairs  
Noven Pharmaceuticals, Inc.  
Phone: (212) 287-0971  
 (b) (6)  
[sshah@noven.com](mailto:sshah@noven.com)

**From:** Shah, Snehal N.  
**Sent:** Wednesday, April 17, 2013 3:27 PM  
**To:** 'Shiley, Kimberly'  
**Subject:** NDA 204-516: Follow-up on Ongoing Activities

Dear Kim,

I hope all is well and you enjoyed your leave and time in the Navy. I wanted to follow-up with you on a few items:

Statistical Information Request (Severity Score Calculation)

- Noven's March 26 submission provided data from Study N30-003 and Study N30-004 for the new severity score calculation as requested in the Agency's March 20 request. Has the Agency had the opportunity to review this data and does the Agency agree the results of this analysis address any outstanding issues around the efficacy of paroxetine mesylate for treatment of VMS?

Post Advisory Committee Discussions

- Can the Agency please provide any information on the outcome of internal discussions regarding the March 4, 2013 Advisory Committee and implications to the ongoing review of NDA 204-516? Noven would greatly appreciate a meeting with the Agency to understand their perspective on the Adcom and if there is anything Noven can do to work with the Agency to facilitate the NDA review.

Packaging (Carton and Container Labels)

- Noven has prepared packaging labels with updated artwork and the proprietary name Brisdelle. Can you please advise on when they should be submitted to the NDA for review?

Any information on the above questions would be greatly appreciated and thanks for all your help, as always!

Kind Regards,

**Snehal Shah, Pharm.D.**  
Regulatory Affairs  
Noven Pharmaceuticals, Inc.  
Phone: (212) 287-0971

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[sshah@noven.com](mailto:sshah@noven.com)

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/s/  
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KIMBERLY A SHILEY  
04/26/2013



NDA 204516

**INFORMATION REQUEST**

From: Shah, Snehal N. [mailto:SShah@noven.com]  
Sent: Wednesday, March 20, 2013 3:57 PM  
To: Shiley, Kimberly  
Cc: Bell, Samantha  
Subject: RE: NDA 204516, statistical information request

Dear Kim and Samantha,  
We will provide these analyses by March 26, as requested. Also Kim please have a great time on your leave and thank you for your military service!

Kind Regards,

Snehal Shah, Pharm.D.  
Regulatory Affairs  
Noven Pharmaceuticals, Inc.  
Phone: (212) 287-0971  
[REDACTED] (b) (6)  
sshah@noven.com

From: Shiley, Kimberly [mailto:Kimberly.Shiley@fda.hhs.gov]  
Sent: Wednesday, March 20, 2013 3:19 PM  
To: Shah, Snehal N.  
Cc: Bell, Samantha  
Subject: NDA 204516, statistical information request

Greetings Snehal,

Could you please respond by COB March 26, 2013. Because I will be on leave, please reply to Samantha Bell, who will be covering me between March 25 – 28, 2013.

For study 003 and 004,

1. Provide analysis data set for the daily severity score in the same format as ADHS.xpt. This severity score should be derived as

[REDACTED] (b) (4)

2. Provide analysis results for this new derived severity score using the pre-specified analysis methods, i.e. rank-ANCOVA, with observed data only and LOCF imputation respectively.

Thank you.

Kim Shiley, RN, BSN, BSBA  
Regulatory Health Project Manager  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Bldg 22, Room 5377  
office: 301-796-2117  
fax: 301-796-9897  
[kimberly.shiley@fda.hhs.gov](mailto:kimberly.shiley@fda.hhs.gov)

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/s/  
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KIMBERLY A SHILEY  
03/20/2013



NDA 204516

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Noven Therapeutics  
Empire State Building  
350 Fifth Avenue, 37th Floor  
New York, NY 10118

ATTENTION: Snehal Shah, Pharm. D.  
Director, Regulatory Affairs

Dear Dr. Shah:

Please refer to your New Drug Application (NDA) dated and received, August 28, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Paroxetine Mesylate Capsules, 7.5 mg.

We also refer to your correspondence dated and received December 26, 2012, requesting review of your proposed proprietary name, Brisdelle. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Brisdelle, 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 December 26, 2012, 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, call Marcus Cato, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3903. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Kimberly Shiley at (301)796-2117.

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  
03/15/2013



NDA 204516

**FILING COMMUNICATION**

Noven Therapeutics  
Attention: Snehal Shah, Pharm.D.  
Director, Regulatory Affairs  
Empire State Building  
350 Fifth Avenue, 37<sup>th</sup> Floor  
New York, NY 10118

Dear Dr. Shah:

Please refer to your New Drug Application (NDA) dated and received August 28, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for paroxetine mesylate capsules, 7.5 mg.

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 June 28, 2013.

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, mid-cycle, 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 June 1, 2013.

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

Clinical:

1. Based on a preliminary review of the study reports, it appears that Study N30-003 did not meet the prespecified efficacy endpoint for hot flush severity at Week 12. It also appears that sensitivity analysis you conducted to demonstrate the clinical meaningfulness of the change in hot flush frequency did not reach statistical significance at Week 12 in Study N30-003.

Statistical:

2. In Study N30-003, the response variable used in your Receiver Operator Curve (ROC) analysis is not consistent with that specified in the protocol and agreed-to by the Division.

Subjects were categorized as “satisfied” and “unsatisfied” based on answers to the Patient Global Improvement (PGI) questionnaire at Weeks 4 and 12, respectively. (b) (4)

(b) (4)

(b) (4)

(b) (4)

which is not appropriate.

(b) (4)

3. In your submitted program “t14-2-1-1-5a.sas” for Study N30-003, the approach used to find the cutoff for change from baseline in hot flush frequency by using [ (b) (4) ] was incorrect.

The sample code for ROC analysis is

(b) (4)

(b) (4)

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. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

To address the review issues # 2 and 3 above, we request that you submit the following information:

1. For Study N30-003, re-conduct the responder analysis to demonstrate clinical meaningfulness as described above. In the logistic regression model used for the ROC analysis, use the binary variable defined by the PGI response, i.e., satisfied vs. unsatisfied, as the response variable directly at Week 4 and Week 12, respectively. Provide these analyses based on both the cut-offs used to define "satisfied" (b) (4)

[REDACTED] . Submit the updated statistical programs for this analysis.

2. If the responder analysis done to demonstrate clinical meaningfulness in Study N30-004 has the above two issues, re-conduct the responder analysis as suggested for N30-003. Submit the statistical programs of this analysis for Study N30-004.

Chemistry, Manufacturing and Controls:

3. The established name for the drug substance should be displayed as [REDACTED] (b) (4) on both the package insert (PI) and the carton/container labels when displayed in conjunction with the proprietary name.
4. The equivalency statement on the carton/container labels should read: "Each capsule contains 9.69 mg paroxetine mesylate equivalent to 7.5 mg paroxetine base."

Biopharmaceutics:

5. Provide a dissolution method development report in the NDA including the following information:
  - a. Solubility data for the drug substance covering the pH range.
  - b. Detailed description of the dissolution method and the developmental parameter (equipment/apparatus selection, *in vitro* dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the most appropriate method. The testing conditions used for each test should be clearly specified.
  - c. The complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time.

- d. Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as validation data for the dissolution method and analytical method.

Labeling:

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

1. The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents (TOC) must match the headings and subheadings in the Full Prescribing Information (FPI).

Comment: BOXED WARNING is missing; subheading 9.2 should be changed to Abuse; add 9.3 Dependence; subheading 12.4 Special Populations should be changed to 12.6; 12.5 Drug Interactions is not listed in the TOC and should be changed to 12.7. Subheading 12.4, by guidance, is reserved for Microbiology and 12.5 for Pharmacogenomics.

2. The same title for the Boxed Warning that appears in the Highlights (HL) and FPI must also appear bolded at the beginning of the TOC in UPPER-CASE letters.

Comment: WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

We request that you resubmit labeling that addresses these issues by November 30, 2012. 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.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **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. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

*{See appended electronic signature page}*

Hylton V. Joffe, M.D., M.M.Sc.  
Director  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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HYLTON V JOFFE  
11/09/2012



NDA 204516

**NDA ACKNOWLEDGMENT**

Noven Therapeutics  
Attention: Snehal Shah, Pharm.D.  
Director, Regulatory Affairs  
Empire State Building  
350 Fifth Avenue, 37<sup>th</sup> Floor  
New York, NY 10118

Dear Dr. Shah:

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: paroxetine mesylate capsules, 7.5 mg

Date of Application: August 28, 2012

Date of Receipt: August 28, 2012

Our Reference Number: NDA 204516

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 October 27, 2012, in accordance with 21 CFR 314.101(a).

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 Reproductive and Urologic Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph., M.P.A.  
Chief, Project Management Staff  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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MARGARET M KOBER  
10/19/2012  
Chief, Project Management Staff



IND 076636

**MEETING MINUTES**

Noven Therapeutics, LLC.  
Attention: Shawn Elizabeth Lucini, Pharm.D.  
Sr. Director, Regulatory Affairs, Empire State Building  
350 Fifth Avenue, 37<sup>th</sup> Floor  
NY, NY 10118

Dear Dr. Lucini:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for paroxetine mesylate.

We also refer to the meeting between representatives of your firm and the FDA on May 29, 2012. The purpose of the meeting was to discuss your proposed development plan for a submission of paroxetine capsules for a 505(b)(2) NDA. The proposed indication is for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause.

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

If you have any questions, call George Lyght, R.Ph., PharmD., Sr. Regulatory Project Manager at (301) 796-796-0948.

Sincerely,

*{See appended electronic signature page}*

Lisa Soule, M.D.  
Clinical Team Leader  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** May 29, 2012, 3:00 PM – 4:00 PM  
**Meeting Location:** 10903 New Hampshire Avenue, Bldg. 22, Room 1309  
Silver Spring, MD 20903

**Application Number:** IND 076636  
**Product Name:** paroxetine mesylate  
**Indication:** The treatment of moderate to severe vasomotor symptoms (VMS) due to menopause.

**Sponsor/Applicant Name:** Noven Pharmaceuticals, Inc.

**Meeting Chair:** Lisa Soule, M.D.  
**Meeting Recorder:** George Lyght, R.Ph., PharmD.

**FDA ATTENDEES**

Julie Beitz, M.D., Director, Office of Drug Evaluation III (ODEIII), & Acting Director,  
Division of Reproductive and Urologic Products (DRUP)  
Audrey Gassman, M.D., Acting Deputy Director, DRUP  
Lisa Soule, M.D., Clinical Team Leader, DRUP  
Ronald Orleans, M.D., Medical Officer, DRUP  
Chongwoo Yu, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology  
Mahboob Sobhan, Ph.D., Statistical Team Leader, Office of Biometrics (OB)  
Donna Christner, Ph.D., CMC Lead, Office of New Drug Quality Assessment  
Leslie McKinney, Ph.D., Pharmacology/Toxicology Reviewer, DRUP  
Margaret M. Kober, M.P.A., R.Ph., Chief, Project Management Staff, DRUP  
George Lyght, R.Ph., PharmD., Sr. Regulatory Health Project Manager, DRUP

**SPONSOR ATTENDEES**

Sailaja Bhaskar, Ph.D., Executive Director  
Cristina Castelli, Ph.D., Director, Clinical Pharmacology  
Jeffrey Eisenberg, President and CEO  
Monica Escobar, Ph.D., Sr. Manager, CMC Regulatory Affairs  
Bruce Friedman, R.Ph., M.S., VP, Technical Operations  
Joel Lippman, M.D., Executive VP Product Development & CMO  
Shawn Lucini, PharmD., Sr. Director, Regulatory Affairs  
Snehal Shah, PharmD., Director, Regulatory Affairs

(b) (4)

## **BACKGROUND**

Noven Therapeutics is developing paroxetine mesylate for the treatment of vasomotor symptoms (VMS) due to menopause. The Sponsor is planning an NDA submission for the product as a 505(b)(2) application. This meeting was to obtain further advice and guidance on their plan for submission.

## **DISCUSSION**

Preliminary responses to the meeting questions were provided to the Sponsor on May 25, 2012. Additional discussion at the meeting is also presented below.

### **SPONSOR'S QUESTIONS AND DIVISION'S RESPONSES**

#### **1.1. 505(b)(2) Bridging Strategy**

##### **Question 1:**

*As approval of this NDA would rely on other applications (specifically, Noven's NDA 21-299 for Pexeva (paroxetine mesylate) and GlaxoSmithKline's NDA 20-031 for Paxil (paroxetine hydrochloride), for which Noven does not have right of reference), this NDA is planned be filed under Section 505(b)(2). As such, Noven plans to reference the Pexeva NDA and rely on FDA's findings of safety related to aspects of the Paxil NDA. **Does FDA agree with Noven's proposed bridging strategy as outlined below?***

##### **Division Response:**

The bridging strategy as outlined in Table 2 appears to be acceptable.

General 505(b)(2) information:

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf>).

If the Sponsor intends to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, it must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). The Sponsor should establish a "bridge" (e.g., via comparative bioavailability data) between its proposed drug product and each listed drug upon which it proposes to rely to demonstrate that such reliance is scientifically justified. If the Sponsor intends to rely on literature or other studies for which it has no right of reference but that are necessary for approval, it also must establish that reliance on the studies described in the literature is scientifically appropriate. The Sponsor is encouraged to identify

each section of its proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

If the Sponsor intends to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which FDA consider to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), the Sponsor should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that is the subject of an NDA approved under section 505(c) of the FD&C Act (in other words, an application approved under section 505(j) of the Act (i.e., ANDA, generic drug) may not be cited as a listed drug relied upon). the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before the Sponsor's application is submitted, such that its proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, the Division may refuse to file the Sponsor's application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

**Additional Clinical Pharmacology Comments:**

- Pexeva labeling discusses potential drug interactions and use in specific populations using a higher dose of paroxetine (i.e., 20 mg or higher) for different indication(s). The Sponsor should justify in its NDA submission the applicability of this information to the proposed lower dose (7.5 mg) for the indication of VMS.
- Reference is made to the Agency's untitled letter issued on July 26, 2011 and the Information Request letters issued on October 18, 2011 and April 9, 2012 to Cetero Laboratories (Houston, TX) regarding the reliability of studies conducted between April 1, 2005, and August 31, 2009 at Cetero Laboratories (Houston, TX). If the bioanalysis of any studies in the NDA was conducted at this facility during the specified period, the Sponsor should address the Agency's concerns as outlined at:  
<http://www.fda.gov/Drugs/DrugSafety/ucm265559.htm>

**Additional Discussion at the Meeting:**

The Sponsor confirmed that the information and justification requested by the Division will be included in the NDA submission.

**1.2. Nonclinical**

**Question 2:**

*As agreed with FDA in the pre-IND meeting held on April 19, 2007 and confirmed in the End of Phase 2 meeting held on September 20, 2010, no new nonclinical studies were conducted in support of this NDA. The nonclinical safety profile of paroxetine has been established in studies to support approval of Paxil (GlaxoSmithKline NDA 20-031). Additional studies that have been conducted by Noven to demonstrate that the paroxetine mesylate salt has a similar nonclinical*

*safety profile to the paroxetine hydrochloride salt have been submitted within the Pexeva NDA 21-299. Noven therefore proposes to include a Nonclinical Overview in Module 2.4 of the LDMP NDA summarizing these previously generated data at a high level and not to include Nonclinical written and tabulated summaries in Module 2.6 nor any Nonclinical study reports in Module 4. Does FDA agree with this proposal?*

**Division Response:**

Yes.

**1.3. Clinical**

**Question 3:**

*Does FDA agree with the proposed approach for pooling data for the Integrated Summary of Safety (ISS) and the Integrated Summary of Efficacy (ISE)?*

**Division Response:**

For the ISS, pooling the data from the two phase 3 pivotal trials (N30-003, N30-004) and from the supporting phase 2 trial (N30-002) is acceptable.

For the ISE, pooling the data from the two pivotal trials (N30-003, N30-004) is also acceptable.

**Question 4:**

*The NDA filing will contain data from one PK study (N30-005) and associated analytical methods. Therefore, Noven proposes not to include a Summary of Biopharmaceutic Studies and Associated Analytical Methods in Module 2.7.1 or a Summary of Clinical Pharmacology Studies in Module 2.7.2. Is this proposal acceptable to FDA?*

**Division Response:**

No. The bioanalytical method validation and study reports should be included in Module 2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods) and a summary of the PK study should be included in Module 2.7.2 (Summary of Clinical Pharmacology Studies) in the NDA submission.

A hyperlink to the Summary of Biopharmaceutic Studies and Associated Analytical Methods could be included in Module 2.7.2 (Summary of Clinical Pharmacology Studies) of the NDA submission to facilitate the review. Reference is made to the Agency's recent publication on the utilization of electronic resources in the NDA/BLA regulatory review of bioanalytical data (Au et al., Bioanalysis. 2011; 3 (13):1441-1445).

**Additional Discussion at the Meeting:**

The Division clarified that the methods validation and study report information included in Modules 2.7.1 and 2.7.2 could consist of a hyperlink to Module 5, which would include the full information.

**Question 5:**

*Does FDA agree with Noven's plans for the inclusion of datasets within the NDA?*

**Division Response:**

Yes.

**Additional Biometrics Comments:**

1. The Sponsor should submit the SAS programs used to generate the efficacy analysis datasets from raw datasets.
2. The Sponsor should be aware that the current version of CDER Common Data Standards Issues Document recommends that the file size of the standardized datasets not exceed 1 gb. If datasets are greater than 1 gb in size, split the datasets into smaller datasets no larger than 1 gb in size. Refer to <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM254113.pdf>.

This document is updated periodically; therefore, it is important that the Sponsor refer to the CDER data standards website at <http://wcms.fda.gov/FDAgov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM248635> to ensure that it is using the most up-to-date version.

**Question 6:**

*Does FDA agree with the proposal for narratives to be included in the NDA submission?*

**Division Response:**

Yes.

**Question 7:**

*Does FDA agree with the proposal for eCRFs to be included in the NDA submission?*

**Division Response:**

Yes.

**1.4. CMC**

**Question 8:**

*Although the final decision will be a review issue based on data submitted in the NDA, does FDA agree in principle that the body of stability data intended to be submitted in the NDA would be sufficient to support a 36 month shelf life for the drug product?*

**Division Response:**

According to ICH Q1E, shelf life extension beyond real time data can be granted to cover up to twice the amount of available data, but not to exceed 12 months of extension. Unless data are compelling, the Division normally follows the Q1E guidelines. In addition, the NDA should be complete upon submission, so the Division recommends that the 18 month data be submitted in the original application.

**Question 9:**

*The LDMP clinical program has utilized drug product manufactured at Norwich, which is one of the two proposed commercial drug product manufacturing sites. Noven intends to qualify another drug product manufacturer (b)(4) based on comparative drug product dissolution data, as well as comparative release and stability (long term and accelerated) stability data. Although this is not a post-approval change, Noven believes that qualification of (b)(4) essentially represents a Level 3 Change as defined by the SUPAC Guidance for Immediate Release Solid Oral Dosage Forms. Does FDA agree that comparative dissolution data and comparative long term and accelerated stability data are sufficient to qualify (b)(4) for the manufacture of paroxetine mesylate capsules?*

**Division Response:**

The Division agrees that the manufacturing site change would be classified as a SUPAC-IR Level 3 manufacturing change and that the proposed studies are reasonable to support qualification of both sites as manufacturing sites for the capsules.

**Additional CMC Comments:**

The Sponsor is reminded of the CMC comment conveyed in the letter to this IND dated 10-Dec-2007 concerning the need to address the presence of potential (b)(4) impurities at a level of not more than (b)(4) for chronic use. Provide data to demonstrate that (b)(4) impurities are either not formed in the drug substance or drug product, or that they are controlled below the required level. Refer also to the letter to NDA 21-299 dated 09-Nov-2007 that also addressed this issue.

**Additional Discussion at the Meeting:**

The Sponsor noted that it had submitted a response to the (b)(4) comments to the IND and the Pexeva NDA in March 2008. The Division asked that this information be included in the current NDA when it is submitted as well.

**1.5. General**

**Question 10:**

*Noven intends to submit the NDA in eCTD format. The electronic submission will be prepared by (b)(4) in accordance with current eCTD guidances and specifications. (b)(4) filed an acceptable eCTD pilot with the Center on June 2, 2004 (Pilot No. 900024). Does FDA agree with the documents and data planned for inclusion in this NDA?*

**Division Response:**

Yes.

**Question 11:**

*Since all studies will be complete at the time of filing, with no new or ongoing studies planned for LDMP at this time, Noven does not plan to submit a 4 month safety update. Does FDA agree?*

**Division Response:**

No. The 4-month safety update is a required feature of an NDA submission that should include reviews of the current literature and a summary of postmarketing safety information. The Periodic Safety Update Report (PSUR) might be sufficient to address the postmarketing safety information provided the cut-date for the information in that report is reasonably close to the cut-date for the 4-month safety update.

**Additional Discussion at the Meeting:**

The Sponsor stated that the annual PSUR for Pexeva will have a July 2012 cut-off, and the NDA is expected to be submitted in August. The Division asked that a literature review be conducted with a cut-off date closer to the 4-month safety date of December (e.g., through November 2012). It is likely that the PSUR from July 2012 will be sufficient for the postmarketing safety submission, although if the Division identifies any signals of concerns, it may request a subsequent safety update.

**Question 12:**

*Since VMS associated with menopause does not occur in children, Noven proposes to submit a waiver from Pediatric Research Equity Act (PREA) requirements. Does FDA agree?*

**Division Response:**

The Sponsor should submit a waiver request, justified on the basis that the disorder does not occur in the pediatric population. The waiver request will be discussed by the Pediatric Review Committee during the NDA review cycle.

**Question 13:**

*Does FDA have any additional points for Noven's consideration regarding this proposed NDA filing?*

**Division Response:**

The Sponsor is encouraged to submit a Reviewer's Guide in Section 1.2 in the NDA filing in order to assist in the review and navigation of this application.

The Sponsor is also requested to submit the SAS programs used to conduct efficacy analyses for Studies N30-003 and N30-004.

**ADDITIONAL TOPICS DISCUSSED AT THE MEETING:**

The Sponsor acknowledged the OSI-requested datasets and asked if submission of this material in the initial NDA were required. The Division stated that this information is not required to be complete at the time of NDA submission, but is most helpful in determining sites to be inspected if it is submitted early in the review cycle.

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

### **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

### **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

**OSI PRE-NDA REQUEST**

The Office of Scientific Investigations (OSI) requests that the items detailed in Attachments 1 and 2 be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI-requested items should be placed within an eCTD submission (Attachment 3, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
Meeting Minutes	FDA	June 28, 2012

## **Attachment 1**

### **OSI PRE-NDA REQUEST**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 3, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

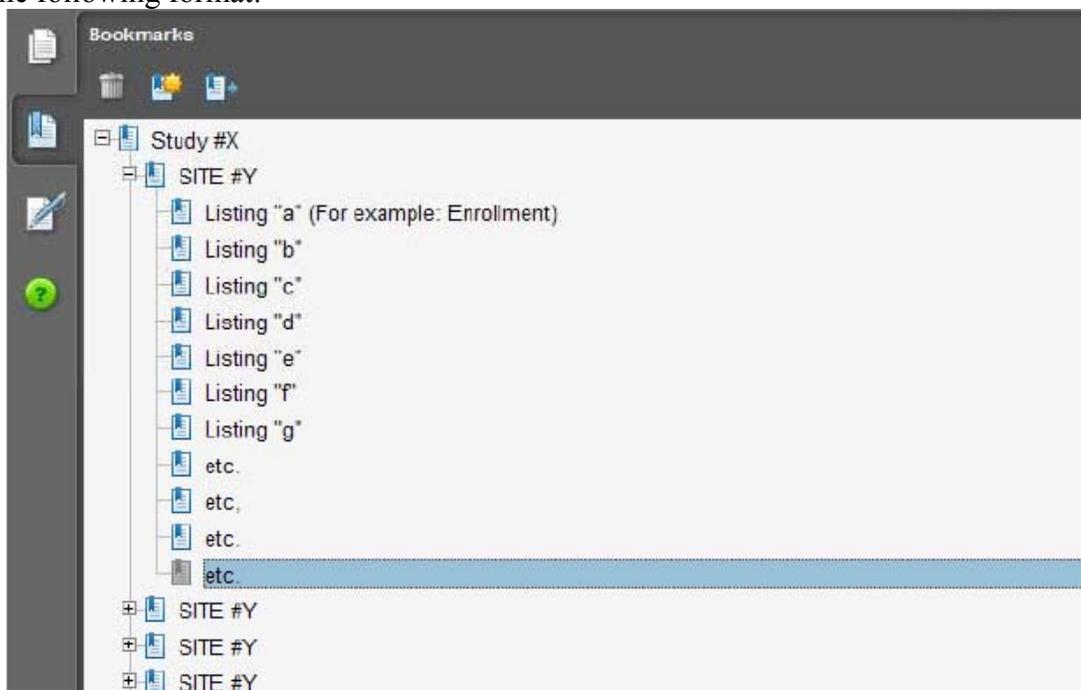
#### **I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
  - a. Number of subjects screened for each site by site
  - b. Number of subjects randomized for each site by site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
  - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
  - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
  - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
  - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

## II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
  - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
  - b. Subject listing for treatment assignment (randomization)
  - c. Subject listing of drop-outs and subjects that discontinued with date and reason
  - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### **III. Request for Site Level Dataset:**

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

## **Attachment 2**

### 1. Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

#### 1.1. INTRODUCTION

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

#### 1.2. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

#### **Site-Specific Efficacy Results**

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

## Attachment 3

### Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study  (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



<sup>1</sup> Please see the OSI Pre-NDA Request document for a full description of requested data files

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

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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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LISA M SOULE  
06/25/2012



IND 076636

**MEETING MINUTES**

Noven Therapeutics, LLC.  
Attention: Tanveer Ahmad, Ph.D  
Senior Director, Regulatory Affairs  
11960 S.W. 144<sup>th</sup> Street  
Miami, FL 33186

Dear Dr. Ahmad:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for paroxetine mesylate.

We also refer to the teleconference between representatives of your firm and the FDA on February 14, 2011. The purpose of the meeting was to discuss the Division's December 13, 2010, Special Protocol-No Agreement letter for Protocol N30-003.

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

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Health Project Manager at (301) 796-0948.

Sincerely,

*{See appended electronic signature page}*

Lisa Soule, M.D.  
Clinical Team Leader  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type A

**Meeting Category:** Special Protocol meeting

**Meeting Date and Time:** February 14, 2011 @ 10: 45 AM  
**Meeting Location:** Teleconference

**Application Number:** IND 076636

**Product Name:** paroxetine mesylate

**Indication:** Treatment of vasomotor symptoms associated with menopause

**Sponsor/Applicant Name:** Noven Therapeutics, LLC

**Meeting Chair:** Lisa Soule, M.D.

**Meeting Recorder:** George Lyght, R.Ph.

**FDA ATTENDEES**

Scott Monroe, M.D., Director, Division of Reproductive and Urologic Products (DRUP)  
Lisa Soule, M.D., Clinical Team Leader, DRUP  
Ronald Orleans, M.D., Clinical Reviewer, DRUP  
Mahboob Sobhan, Ph.D., Statistician, Team Leader, Division of Biometrics III @ DRUP  
Jia Guo, Ph.D., Statistician, Division of Biometrics III @ DRUP  
George Lyght, R.Ph., Senior Regulatory Health Project Manager, DRUP

**SPONSOR ATTENDEES**

Sailaja Bhaskar Ph.D– Executive Director, Clinical Operations, Noven Pharmaceuticals  
Joel Lippman M.D – Executive Vice President Product Development and Chief Medical Officer, Noven Pharmaceuticals  
Ms Joanna Waugh – Vice President Regulatory Affairs and Pharmacovigilance, Noven Pharmaceuticals

(b) (4)

## BACKGROUND

Noven submitted their Special Protocol Assessment (SPA) for the phase 3 Clinical Protocol N30-003 on October 27, 2010. The Division issued a Special Protocol-No Agreement letter to the SPA on December 13, 2010. Noven then requested a Type A meeting to discuss comments included in the SPA-No Agreement letter. The meeting was rescheduled based on the Sponsor's request to postpone the originally scheduled date.

## DISCUSSION

In the meeting package for the meeting, Noven provided responses to the Division's December 13, 2010 letter for discussion. There were no specific questions asked by the Sponsor. The following points were discussed:

1. The Division noted that it was generally in agreement with the protocol changes proposed by the Sponsor in response to the Division's SPA comments.
2. The meeting package does not suffice as a substitute for an SPA request; rather, the Sponsor should request a new SPA review when it submits the revised protocol following the current teleconference guidance.
3. The Sponsor clarified that only the IVRS/IWRS system is used for data recording and collection; there is no paper diary. Subjects are encouraged to enter hot flush data in real time, and have access to the system 24/7. Sites are provided with compliance information so they can contact subjects who do not enter data at least once daily. The Division expressed concern about the feasibility of ensuring that subjects enter all hot flushes, and about how the Sponsor would determine if duplicate data were entered. The "validation" data provided in the meeting package does not address these issues, and it is unclear on what basis the Sponsor has concluded that the system allows accurate and complete data recording. The Sponsor will need to address these concerns in the NDA submission; failure to do so in an adequate manner will be a significant review issue.
4. The Sponsor will clarify areas in the protocol that refer to "hot flashes and awakenings" to reflect the fact that only hot flushes are to be counted as the primary outcome measure.
5. Regarding the planned receiver operating characteristic (ROC) methodology, the Division prefers that the Sponsor establish the cutpoint for determining a "satisfied" subject by dichotomizing subjects between 2/3 ("much better vs. "a little better") (b) (4) on the seven-point scale. If the Sponsor retains the 3/4 cutoff, they should also provide an analysis based on a 2/3 cutpoint as a sensitivity analysis, and responders should be defined as those subjects who had a hot flush reduction of > (b) (4) the number associated with treatment "satisfaction."
6. The Division and Sponsor agreed that the responder analysis is not a primary outcome, but is a supportive analysis, to be done if the reduction in hot flushes is not at least 2 hot flushes/day greater than that observed in the placebo arm.
7. The Division recommended that the ROC curve be established using all subjects, (b) (4) The specific ROC methodology and responder definition will be described in the Statistical Analysis Plan; it will be acceptable for the protocol to state only in general terms that such analyses will be done.

8. The Sponsor clarified that they plan to use LOCF imputation for missing data, but was agreeable to conducting a MMRM analysis as a sensitivity analysis as recommended by the Division.
9. The Division noted that changes to Protocol 004 have been submitted based on the recent discussion regarding evaluation of suicidality. Following receipt of the Division's comments on those revisions, Protocol 003 should be harmonized so that the same suicidality assessments and follow-up procedures are implemented.

**ACTION ITEM**

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
Minutes to be conveyed in 30 days	FDA	March 16, 2011

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/s/  
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LISA M SOULE  
03/15/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 076636

**MEETING MINUTES**

Noven Pharmaceuticals Inc.  
Attention: Tanveer Ahmad, Ph.D.  
Senior Director, Regulatory Affairs  
11960 S.W. 144<sup>th</sup> Street  
Miami, FL 33186

Dear Dr. Ahmad:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for paroxetine mesylate.

We also refer to the meeting between representatives of your firm and the FDA on September 20, 2010. The purpose of the meeting was to seek guidance on your ongoing phase 3 development plans.

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, call George Lyght, R.Ph., Sr. Regulatory Health Project Manager at (301) 796-0948.

Sincerely,

*{See appended electronic signature page}*

Lisa Soule, M.D.  
Clinical Team Leader  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B

**Meeting Category:** End of Phase 2

**Meeting Date and Time:** September 20, 2010 – 2:30 pm – 3:30 pm  
**Meeting Location:** CDER, WO 22, Room 1315  
Silver Spring, MD 20993

**Application Number:** 076636

**Product Name:** paroxetine mesylate

**Indication:** Treatment of vasomotor symptoms associated with  
menopause

**Sponsor:** Noven Therapeutics, LLC

**Meeting Chair:** Lisa Soule, M.D.

**Meeting Recorder:** George Lyght, R.Ph.

**FDA ATTENDEES**

Scott Monroe, M.D., Director, Division of Reproductive and Urologic Products (DRUP)  
Lisa Soule, M.D., Clinical Team Leader, DRUP  
Ronald Orleans, M.D., Clinical Reviewer, DRUP  
Chongwoo Yu, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology  
(OCP) @ DRUP  
Angelica Dorantes, Ph.D., Team Leader, OCP, Office of New Drug Quality Assessment  
(ONDQA), Biopharmaceutics  
Mahboob Sobhan, Ph.D., Statistician, Team Leader, Division of Biometrics III @ DRUP  
Jia Guo, Ph.D., Statistician, Division of Biometrics III @ DRUP  
Leslie McKinney, Ph.D., Pharmacology Reviewer, DRUP  
Margaret M. Kober, R.Ph., M.P.A., Chief, Project Management Staff, DRUP  
George Lyght, R.Ph., Senior Regulatory Health Project Manager, DRUP

**SPONSOR ATTENDEES**

Jeffrey Eisenberg, President and CEO  
Sailaja Bhaskar, Ph.D., Senior Director, Clinical Operations

Joel Lippman, M.D., Executive Vice President, Clinical Development, & CMO  
Marina Komaroff, Senior Biostatistician  
Amaury Sanchez, Manager, Regulatory Affairs  
Tanveer Ahmad, Ph.D., Senior Director, Regulatory Affairs  
Monica Escobar, Ph.D., Senior Manager, Regulatory Affairs  
(b) (4)

## **BACKGROUND**

On June 2, 2010, Noven Therapeutics, LLC requested an End of Phase 2 meeting with the Division of Reproductive and Urologic Products to discuss their ongoing development plans for paroxetine mesylate. The sponsor is currently conducting a single phase 3 study (N30-004) to demonstrate the safety and efficacy of a 7.5 mg/day dose of paroxetine mesylate for the treatment of vasomotor symptoms associated with menopause.

## **DISCUSSION**

Preliminary responses to the meeting questions were provided to the Sponsor on September 17, 2010. Additional discussion at the meeting is also presented below.

### **Sponsor's Questions and the Division's Responses**

#### **Question 1 Nonclinical:**

*The safety of paroxetine mesylate in daily doses up to 60 mg/day has been demonstrated (PEXEVA NDA 21-299). As agreed to in prior discussions (FDA Pre-IND Meeting Minutes, 17 April 2007) additional nonclinical studies are not planned. Noven plans to reference the nonclinical data submitted in the approved PEXEVA NDA 21-299. Does the Agency agree that no additional nonclinical studies will be required for the approval of the NDA?*

#### **Division Response:**

Yes. However, we remind you of our previous December 2007 advice:

“During the development of the drug product, it should be assured that (b) (4) potentially produced by the drug substance manufacturing process (b) (4) are less than (b) (4) per person per day for the current clinical study and (b) (4) per person per day for the chronic use.”

#### **Question 2 Clinical:**

(a) *Would a reduction of 1.4 hot flashes per day meet the definition of a clinically significant reduction in hot flashes with a non-hormonal product?*

#### **Division Response:**

If the product does not achieve a reduction of at least two hot flushes per day above the placebo response, the clinical meaningfulness of the observed treatment effect should be demonstrated. This may be done through a responder analysis and using a global satisfaction questionnaire to establish a cut point for vasomotor symptoms (VMS) frequency that distinguishes between those women (regardless of treatment assignment) who are and are not satisfied with their treatment.

Women would then be classified as responders if their reduction in hot flushes exceeded this cut point. A product with a clinically meaningful treatment effect would have a statistically significantly greater response rate in the treatment arm than in the placebo arm.

**Additional Discussion at the Meeting:**

The Sponsor noted that their first phase 3 study is underway and has enrolled about 144 subjects to date.

The Division provided further guidance about how to anchor a clinically meaningful reduction in VMS and then conduct a responder analysis to determine whether the active treatment arm demonstrated a statistically significantly higher response rate. The Division clarified that neither DRUP nor the Sponsor would select the responder criterion; rather it would be determined by the subjects. The Sponsor proposed using the Numerical Rating Scale (NRS) questionnaire, which is administered at baseline, 4, 12 and 24 weeks, to assess overall treatment satisfaction. The Sponsor will submit an amended Statistical Analysis Plan (SAP) for the ongoing study that will include the scale and a detailed description of the proposed methodology.

The Sponsor is currently using the NRS in the ongoing trial, although it has not been described in the protocol as supporting a determination of clinical meaningfulness. The Sponsor could amend the SAP to add this analysis, as the NRS is already being administered at the Week 24 evaluation. If the Division, upon review of the NRS, determined that it was not an appropriate anchoring questionnaire, evaluation of clinical meaningfulness by a more appropriate instrument that would be used only in the second trial would likely suffice to demonstrate that the reduction in hot flush frequency was clinically meaningful.

- (b) *Does the Agency agree that data from the proposed phase 3 study, assuming positive results, will qualify as a registration study?*

**Division Response:**

The Division is unable to agree to the proposed phase 3 protocol at this time. However, from a clinical perspective, the trial design appears generally appropriate; pending agreement on the final protocol of this phase 3 clinical trial, the proposed trial is likely to qualify as a registration study. See additional comments in responses to Questions 2 (d) and 3. However, a single, “pivotal” phase 3 trial may not be adequate to provide sufficient data for approval of paroxetine mesylate for the indication of treatment of moderate to severe VMS associated with the menopause (see response to Question 2(c)).

**Additional Discussion at the Meeting:**

(b) (4)  
[Redacted]  
The Division cannot provide concurrence until the statistical and clinical issues noted in these comments are resolved. The Sponsor is encouraged to submit a revised protocol as a Special Protocol Assessment (SPA) request.

The Sponsor agreed to conduct two phase 3 studies, one of which will continue to 24 weeks to evaluate the persistence of benefit. They propose testing the hypothesis that the treatment effect at Week 24 does not differ from that at Week 12, rather than testing a hypothesis of improvement

from baseline to Week 24. The Sponsor is concerned that drop-outs from baseline to Week 24 will result in a final evaluable population that is not the randomized, intent-to-treat population, and may require much imputation by last observation carried forward (LOCF).

**Post-meeting comment:** For persistence of benefit, the Sponsor should not use LOCF imputation, but should restrict the analysis to observed data at Week 24.

The Division had a number of concerns about the comparison of Week 24 to Week 12 – this would be closer to a non-inferiority analysis, where the Type 2 error would need to be tightly controlled to avoid falsely concluding that no difference exists between the treatment effects at the two time periods. The study would need to have acceptable power. The Division would have to agree upon an appropriate non-inferiority margin to ensure that sufficient preservation of treatment benefit was maintained. In addition, the Sponsor's proposed analysis does not allow for comparison to a placebo group; with VMS representing a waxing, waning and frequently remitting condition, in the absence of a placebo control, any change over time will be difficult to interpret.

The Sponsor noted that the Division had agreed to this approach in a guidance letter (February 2009). The Division will discuss this further internally and try to provide more definitive guidance in the near future. There are a number of potential approaches to evaluating persistence of benefit; one option might be to conduct a blinded, randomized withdrawal trial from Weeks 12 to 24.

- (c) *The Company is seeking approval for use of an already marketed chemical entity at a lower dose level (7.5 mg/day). Does the Agency agree that positive results from our proposed phase 3 study, together with additional supportive data from the phase 2 trial, and existing market and literature support of tolerability and safety at much higher doses are sufficient for approval of Mesafem for the treatment of VMS associated with menopause?*

**Division Response:**

No. For a first-in-class product like this for the VMS indication, two adequate and well-controlled safety and efficacy studies will be required, as discussed in the PreIND meeting held in April 2007. Submission of a single study meeting a very stringent statistical criterion for success (e.g.,  $p < 0.0025$ ) might be sufficient, but it is unlikely that the sample size of such a study would be less than that needed for two independent studies.

In addition, as noted in our advice letter of April 2008, the persistence of treatment benefit beyond 12 weeks should be demonstrated for nonhormonal treatments for VMS. One of the studies will need to evaluate the four co-primary endpoints at Week 24 of treatment; failure to demonstrate a statistically significant superiority to placebo will be a significant review issue.

**Additional Discussion at the Meeting:**

The Sponsor noted that it had selected the 7.5 mg dose based on published literature showing efficacy for VMS symptoms for 10-25 mg doses of the approved paroxetine mesylate product. There does not appear to be a dose-response in the published literature, so the Sponsor selected a dose lower than that approved for psychiatric indications in order to have a dose that would likely show efficacy while also being safe and well-tolerated.

(d)

(b) (4)

**Division Response:**

(b) (4)

**Question 3 Statistical:**

- (a) *In response to our Amendment dated 26 October 2007, the Agency indicated that analysis of covariance is acceptable for analyzing the co-primary variables. Does the Agency still concur with Noven to use analysis of covariance with baseline values as covariates for the primary and co-primary variables?*

**Division Response:**

Yes. Using an ANCOVA is acceptable for analyzing the four co-primary endpoints. However, clarify whether this is the intended analysis method to be used, as neither the protocol nor the SAP makes reference to an ANCOVA. Rather, they refer to a repeated measures model using the REML (estimated maximum likelihood) method with a first order autoregression AR(1) covariance structure, and week, treatment group, and baseline value(s). The repeated measurement model is recommended for sensitivity analysis of missing data handling in addition to last observation carried forward (LOCF). Clarify the rationale for using AR(1). If there is no supporting information for AR(1) covariance structure, unrestricted structure should be considered. Both the protocol and SAP should describe the primary approach in detail, including all applicable covariates, factors, covariance structure, missing data handling, etc.

- (b) *Noven is planning to readjust the sample size when approximately 60% of the desired number of subjects have been randomized and completed 4 weeks of treatment. Analysis will be performed by a blinded (to the treatment arm) and independent statistician in order to maintain the integrity of the study. Is this strategy acceptable to the Agency?*

**Division Response:**

Yes. The sample size readjustment procedure is acceptable; however, clarify whether the same effect size of 1.4 (used to estimate the original sample size) would still be used to re-estimate the sample size.

**Additional Discussion at the Meeting:**

The Sponsor noted that the interim analysis proposed would only be used to up-size the trial if warranted by new variability estimates; the trial would not be down-sized under any condition.

(c) *Does the Agency agree with the proposed statistical plan of analysis?*

**Division Response:**

No. Please see response to Question 3(a) and the additional statistical comments below.

1.  (b) (4)  
We recommend that the analysis present the mean number of moderate and severe hot flashes per day  (b) (4).
2. Provide a week by week analysis of the change from baseline in mean hot flash frequency and mean hot flash severity for Weeks 1 through 3 and Weeks 5 through 11.
3. Clarify the variables used for the severity of moderate to severe hot flashes at Week 4 and Week 12 analysis. Section 9.2.2.1 on page 25 of the SAP states that: "Mixed model will be used to compare the two treatment groups at the specific visit and the total number of moderate and the mean number of moderate and severe hot flashes that are recorded in the Run-In Period will be used to calculate the baseline severity score."
4. Clarify which analyses will use LOCF imputation.
5. To be consistent with the protocol, the SAP should state that the primary efficacy analysis population is the mITT population.

 (b) (4)

**Question 4 Regulatory:**

*Given the established safety profile for paroxetine mesylate, if the Company submits comparative dissolution data between the paroxetine mesylate capsule and the currently approved PEXEVA tablet and the data show no difference between the capsule and the tablet formulations, does the Agency accept the dissolution data in lieu of the single dose PK study?*

**Division Response:**

No, submission of *in vitro* dissolution data in lieu of *in vivo* bioavailability (BA) data is not

acceptable. The Sponsor should characterize the single and multiple-dose PK of paroxetine using the to-be-marketed (TBM) formulation at the TBM dose strength.

**Additional Discussion at the Meeting:**

The Sponsor noted that the PK characteristics of paroxetine mesylate are well-established and described in the approved product's labeling. The Clinical Pharmacology reviewer expressed concern that dose proportionality cannot be assumed for different formulation products (the approved product is a tablet, while the proposed product is a capsule). Labeling for the proposed product would need to reflect data for the proposed product. There may be several routes to satisfy this requirement, including collection of PK data in phase 3.

The Sponsor acknowledged that dissolution data would not be acceptable in lieu of a single dose PK study, and agreed to conduct such a study. However, they do not believe a multiple dose PK study is needed. The biopharmaceutics reviewer noted that CFR 320.21(a)(1) requires "evidence measuring the *in vivo* bioavailability of the drug product that is subject of the application." The Office of Clinical Pharmacology will determine whether a multiple dose PK study is required to address this, noting that it is important to understand the steady-state PK of the TBM formulation. Based on the information currently available, the Office of Clinical Pharmacology recommends that the Sponsor conduct a single- and multiple-dose PK study. The Sponsor can elect to conduct a separate study or choose to include a PK subgroup in the phase 3 study. The Sponsor may also submit additional information or their justification of how they plan to address this matter without a multiple dose study.

**Question 5 Regulatory:**

*According to the North American Menopause Society, there are approximately 40 million women in the United States of menopausal age; as many as 25% of menopausal women are seeking alternative therapies to relieve VMS, either due to a preference to avoid hormonal therapy or because estrogen is not an option for them. Hence, no satisfactory alternative treatment exists (for a detailed review, please see the White Paper provided in **Appendix 5**). Due to the present state of affairs, would the Agency grant a priority review designation to this NDA?*

**Division Response:**

Priority status is determined at the time of NDA submission. If the product would offer a significant improvement over marketed products available at that time, the Division would likely grant priority review status. For further information on what would constitute significant improvement, refer to <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082000.pdf>.

**Additional Clinical Comments:**

- The Sponsor must conduct a formal evaluation of suicidality and suicidal ideation in the clinical trials. Given the date of approval for Pexeva, it does not appear likely that a prospective assessment of suicidality meeting current standards was conducted. Consult the September 2010 Guidance for Industry, Suicidality: Prospective Assessment of Occurrence

in Clinical Trials, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf>

**Additional Discussion at the Meeting:**

The Sponsor noted that they are using the Suicidality Tracking Scale in the ongoing study, and have previously used it in phase 2. They will evaluate how well it maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA) as mentioned in the new guidance. They will also submit a plan for using this scale in the new protocol to be reviewed under SPA. The Division noted that it would likely consult the Division of Psychiatry Products (DPP) about the acceptability of this scale, and asked that information be submitted to the IND prior to submitting the SPA, in order to allow enough time for consultative advice from DPP.

- If the product were approved for marketing, the labeling would likely include the class labeling for antidepressant drugs, including the boxed warning for suicidality, as well as other relevant class warnings and precautions, regardless of the indication or the specific premarketing findings on suicidality and neuropsychiatric events.
- The Sponsor is strongly encouraged to submit the final phase 3 protocols for review and comment by the Division prior to study initiation. A Special Protocol Assessment request is recommended.

**ACTION ITEMS:**

Action Item/Description	Owner	Due Date
Minutes to be conveyed in 30 days	FDA	October 20, 2010

**Advice to Sponsor:**

- submit an amended Statistical Analysis Plan (SAP) for the ongoing study
- submit information on the Suicidality Tracking Scale and Sponsor's evaluation of how closely it maps to the Columbia Classification Algorithm for Suicide Assessment, prior to submitting a Special Protocol Assessment to allow the Division sufficient time to request consultation from DPP
- submit a new phase 3 protocol for a 12-week study, along with SAP and case report forms (CRFs), with request for a SPA
- submit a protocol for a single dose PK study
- submit a protocol for a multidose PK study or additional justification for not conducting a multidose PK study

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/s/

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LISA M SOULE  
10/20/2010