

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201655Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 201655

SUPPL #

HFD # 170

Trade Name OPANA ER

Generic Name oxymorphone HCl extended-release tablets

Applicant Name Endo Pharmaceuticals, Inc.

Approval Date, If Known December 9, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

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

505(b)(1)

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.

This product approval is based upon comparative BA studies of the 5 mg and 40 mg strengths of the old (NDA 021610) and new (this NDA) formulations of OPANA ER.

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

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

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

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

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

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 011707 OPANA (oxymorphone HCl) Injection
NDA# 021610 OPANA ER (oxymorphone HCl extended-release) Tablets
NDA# 021611 OPANA (oxymorphone HCl) Tablets

2. Combination product. Not a Combination Product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

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

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

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

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

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

YES

NO

If yes, explain:

=====
Name of person completing form: Lisa Basham
Title: Senior Regulatory Health Project Manager
Date: 11/17/11

Name of Office/Division Director signing form: Bob A. Rappaport, M.D.
Title: Division Director

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

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

/s/

LISA E BASHAM
12/09/2011

BOB A RAPPAPORT
12/09/2011

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 201655 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DAAAP PDUFA Goal Date: 12/13/11 Stamp Date: 6/13/2011

Proprietary Name: OPANA ER

Established/Generic Name: Oxymorphone HCl Extended-Release

Dosage Form: Tablets

Applicant/Sponsor: Endo Pharmaceuticals, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: management of moderate to severe ^{(b)(4)} pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

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

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pediatric patients in this/these pediatric subpopulation(s).

ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

* Other Reason: _____

Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

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

Indication #2: _____**Q1:** Does this indication have orphan designation?

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

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

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

(Revised: 6/2008)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

1.3. Administrative Information

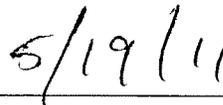
3. DEBARMENT CERTIFICATION

Endo Pharmaceuticals Inc. 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.



Ivan Gergel, MD

Endo Pharmaceuticals Inc.
Executive Vice President,
Research and Development



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 201655 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: OPANA ER Established/Proper Name: Oxymorphone HCl Dosage Form: Extended-Release Tablets		Applicant: Endo Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Lisa Basham		Division: DAAAP
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>12/13/11; Action taken on 12/9/11</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input type="checkbox"/> None CR 1/7/11
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

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

❖ Application Characteristics ²	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 5 (new formulation)</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 <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input checked="" type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

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

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

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) CR 1/7/11 AP 12/9/11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Yes: FINAL submitted 11/30/11
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	No
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	No

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

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	No
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	No
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	No
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Yes-final submitted 11/9/11
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	<div style="background-color: #cccccc; padding: 2px;">(b) (4)</div> 12/23/10 (review 12/22/10) OPANA ER 10/3/11 (review 10/3/11)
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 12/16/10 & 9/2/11 <input checked="" type="checkbox"/> DRISK 12/22/10 & 10/3/11 <input checked="" type="checkbox"/> DDMAC PI: 12/22/10 MG: 12/22/10 <input type="checkbox"/> SEALD <input checked="" type="checkbox"/> CSS 9/30/11 <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	12/21/10
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action

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

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Does not meet criteria for PREA required pediatric studies</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included, but application does not trigger PREA
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Yes
❖ Internal memoranda, telecons, etc.	None; REMS memo in Risk Management Section
❖ 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 4/6/09
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	PIND 5/22/09; Post-Action 2/15/11
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1 st Cycle: 1/7/11 2 nd Cycle: 12/9/11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1 st cycle: 12/22/10 2 nd cycle: 11/30/11
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	CDTL only
• Clinical review(s) (<i>indicate date for each review</i>)	CDTL only
• 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 checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See page 6 of Division Director's 2 nd Cycle Summary Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not applicable 1 st cycle: 12/21/10 2 nd cycle: 9/30/11

⁵ Filing reviews should be filed with the discipline reviews.

<ul style="list-style-type: none"> ❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) <p>LA/ER CLASS REMS Materials LA/ER Class REMS memo 4/18/11 Pre-approval LA/ER Class REMS Notification 4/18/11 Industry Meeting Invitation 5-6-11</p>	<p>11/21/11 memo 1/10/11</p> <p><input type="checkbox"/> None 12/9/10; 8/31/11; 10/3/11; 11/30/11</p>
<ul style="list-style-type: none"> ❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>) 	<p><input checked="" type="checkbox"/> None requested</p>
Clinical Microbiology <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) 	<p><input type="checkbox"/> None</p>
<p>Clinical Microbiology Review(s) (<i>indicate date for each review</i>)</p>	<p><input type="checkbox"/> None</p>
Biostatistics <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) 	<p><input type="checkbox"/> None</p>
<p>Statistical Team Leader Review(s) (<i>indicate date for each review</i>)</p>	<p><input type="checkbox"/> None</p>
<p>Statistical Review(s) (<i>indicate date for each review</i>)</p>	<p><input type="checkbox"/> None</p>
Clinical Pharmacology <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) 	<p><input checked="" type="checkbox"/> None</p>
<p>Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)</p>	<p><input checked="" type="checkbox"/> None</p>
<p>Clinical Pharmacology review(s) (<i>indicate date for each review</i>)</p>	<p><input type="checkbox"/> None 12/15/10; 1/6/11; 11/3/11</p>
<ul style="list-style-type: none"> ❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>) 	<p><input type="checkbox"/> None 12/20/10; 1/5/11; 9/20/11</p>
Nonclinical <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Pharmacology/Toxicology Discipline Reviews 	
<ul style="list-style-type: none"> • ADP/T Review(s) (<i>indicate date for each review</i>) 	<p><input checked="" type="checkbox"/> None</p>
<ul style="list-style-type: none"> • Supervisory Review(s) (<i>indicate date for each review</i>) 	<p><input checked="" type="checkbox"/> None</p>
<ul style="list-style-type: none"> • Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<p><input type="checkbox"/> None 9/7/10</p>
<ul style="list-style-type: none"> ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) 	<p><input checked="" type="checkbox"/> None</p>
<ul style="list-style-type: none"> ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) 	<p><input checked="" type="checkbox"/> No carc</p>
<ul style="list-style-type: none"> ❖ ECAC/CAC report/memo of meeting 	<p><input type="checkbox"/> None Included in P/T review, page</p>
<ul style="list-style-type: none"> ❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>) 	<p><input checked="" type="checkbox"/> None requested</p>

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 9/8/10; 10/27/10; 7/19/11
❖ Microbiology Reviews		<input type="checkbox"/> Not needed 10/5/10; 10/14/10
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> CMC Biopharmaceutics		<input type="checkbox"/> None 12/8/10
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		See page 74 of 9/8/10 CMC review
<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) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>		Date completed: 11/15/10 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per 9/8/10 CMC review, page 71)

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

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/s/

LISA E BASHAM
12/13/2011

Basham, Lisa

From: Basham, Lisa
Sent: Monday, November 14, 2011 1:45 PM
To: 'Chapman, Tara'
Subject: A few more minor changes to the MG...
Attachments: Few more MG changes sent 11-14-11.doc

Hey there,

A couple more changes....

Lisa Basham, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
11/14/2011

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, November 02, 2011 4:34 PM
To: 'Chapman, Tara'
Subject: 11-2-11 REMS Comments

Attachments: fda comments 11.1028 + rems clean Endo version 10 12 11.doc; fda comments 11.1028 + rems-supp-docs 10 12 11 clean.doc

Tara,

We agree with your proposed changes in the October 17, 2011 submission via email communication through Ms. Lisa Basham. Provided below are our additional comments/revisions. Please refer to the attached documents.

REMS Document:

- Goals
Remove the underline formatting from the following phrase:
“The goals of the OPANA ER REMS are:”
- Education Confirmation Form
Is the spacing between the words in the website URL correct? If not, please revise.

Please refer to the attached document below for tracked changes and comments on the REMS document.



fda comments
11.1028 + rems cl..

REMS Supporting Document:



(b) (4)



fda comments
11.1028 + rems-su..

Resubmission Guidelines:

If you do not have any specific questions for the Agency during this review, please remove all comments from the REMS materials (including the comment about adding page numbers in the table of contents when the Training Guide is finalized).

If you agree with the proposed change, please resubmit clean versions of the following, via e-mail:

- One Word file containing the REMS document + all appended materials (clean version) [if any way possible, please try to import snap shots of website in the Word document... This will assist in expediting our review.]
- One Word file containing the Supporting Document (clean version)
- 1 PDF file containing REMS document + all appended materials including Opana ER REMS website
 (b) (4)

If you have any questions, please let us know as soon as possible, so that we can provide final input on your proposed REMS. Otherwise, we will let you know when to provide your final submission through the Gateway.

Lisa Basham, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
11/02/2011

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, November 02, 2011 5:40 PM
To: 'Chapman, Tara'
Subject: OPANA ER MG sent 11-2-11
Attachments: MG with DRISK changes sent to Endo 11-2-11.doc

As discussed, here is the MG with changes proposed by DRISK.

Lisa Basham, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
11/02/2011

Basham, Lisa

From: Basham, Lisa
Sent: Thursday, October 20, 2011 10:59 AM
To: 'Chapman, Tara'
Subject: 10-20-11: One more comment on 7.5 mg labels for NDA 201655

Improve the clarity of the 7.5 mg strength expression. The decimal is too close to the 5, thus, 7.5 mg may be mistaken for 75 mg.

Please adjust and resend informally via email so that we can look over before submitting formally to the NDA.

Thanks!

Lisa Basham, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
10/20/2011

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, October 12, 2011 2:43 PM
To: 'Chapman, Tara'
Subject: Additional DMEPA coments for NDA 201655 C&C labels 10-12-11

Hi Tara! Here are a few more comments on the C&C labels. Please make these changes to both the 60-count and 100-count bottles and EMAIL them to me first. Once we determine that they are fine, you can submit formally.

1. Decrease the space between *Opana* and *ER*. We acknowledge our previous comments asked to add space, however in the current presentation the root name, *Opana* is too far apart from the modifier, *ER*.
2. Increase the font size of the strength presentation. If the circular background shape is limiting the font size, consider utilizing a rectangular background shape.
3. Increase the prominence of the instructions, *Swallow Tablets Whole. Tablets Are Not To Be Cut, Broken, Chewed, Crushed or Dissolved*. Create space on the side panel by decreasing the prominence of manufacturer information.

Thanks!!

Lisa Basham, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
10/12/2011



NDA 201655

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, Pennsylvania 19317

ATTENTION: Tara Chapman, PharmD.
Director, Regulatory Affairs

Dear Dr. Chapman:

Please refer to your New Drug Application (NDA) resubmission dated June 13, 2011, received June 13, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone Hydrochloride Extended-release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg and 40 mg.

We also refer to your July 8, 2011 correspondence, received July 8, 2011, requesting review of your proposed proprietary name, Opana ER. We have completed our review of the proposed proprietary name, Opana ER and have concluded that it is acceptable.

The proposed proprietary name, Opana ER, 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 July 8, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Lisa Basham at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Kellie Taylor, PharmD, MPH

Deputy 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/

AZEEM D CHAUDHRY
09/30/2011

KELLIE A TAYLOR
10/03/2011

Basham, Lisa

From: Basham, Lisa
Sent: Friday, September 30, 2011 11:01 AM
To: 'Chapman, Tara'
Subject: 9/30/11 REMS comments for NDA 201655
Attachments: rem_s + fda comments 11.0929.doc

Tara,

We have updated the language in your REMS document to reflect your proposed changes via email communication on Friday, September 23, 2011. Please refer to the attached REMS document for our additional revisions and comments.

Please update your REMS Supporting Document to reflect the changes proposed in your REMS document.

If you agree with the proposed change, please resubmit the following, via e-mail:

- One Word file containing the REMS document + all appended materials (clean version)
- One Word file containing the Supporting Document (clean version)

If you have any questions, please let us know as soon as possible so that we can provide final input on your supplement. Otherwise, we will let you know when to provide your final submission through the gateway.

Lisa Basham, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
09/30/2011

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, September 21, 2011 9:39 AM
To: 'Chapman, Tara'
Subject: 9-21-11 REMS comment for NDA 201655 (OPANA ER)

Attachments: rems + FDA comments 2011.0921.doc

We have reviewed your submission (dated Sept 7, 2011) and accept your proposed changes. We have one additional revision to your REMS document. Please modify the goals of your REMS to read as follows (*note: this revision is also reflected in tracked changes in the attached document*):

I. GOAL(S):

The goals of the OPANA ER REMS are:

1. To inform patients and healthcare professionals about the potential for abuse, misuse, overdose and addiction associated with the use of OPANA ER
2. To inform patients and healthcare professionals about the safe use of OPANA ER

If you agree with our proposed change, please re-submit clean versions of all REMS documents and materials in WORD format.



rems + FDA
mments 2011.0921.

Lisa Basham, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
09/21/2011



NDA 201655

DISCIPLINE REVIEW LETTER

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Tara Chapman, Pharm.D.
Director, Regulatory Affairs

Dear Dr. Chapman:

Please refer to your July 7, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OPANA ER (Oxymorphone) Extended-Release Tablets.

We also refer to your submission dated June 13, 2011, which contained your resubmission in response to our January 7, 2011, Complete Response Letter, and your July 8, 2011, request for proprietary name review.

Our review of your proposed container labels is complete and we have identified the following deficiencies:

1. Revise the presentation of the proprietary name to title case to appear as *Opana ER*. Additionally, add more space between *Opana* and *ER*. Currently, Opana ER looks like one word instead of the root name, *Opana*, and modifier, *ER*.
2. Increase the prominence of the strength presentation, *x mg*, by increasing the font size.
3. Submit container labels for the 100-tablet count bottle after completing the above revisions.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
09/15/2011



NDA 201655

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Robert A. Barto, MBA
Vice President, Regulatory Affairs

Dear Mr. Barto:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OPANA ER (Oxymorphone Hydrochloride) Extended-Release Tablets.

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

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

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

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

searching available documentation to determine which NDAs are impacted by the above findings.

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

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

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

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

If you have any questions, call Lisa Basham, Sr. Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SARA E STRADLEY
09/07/2011
on behalf of Parinda Jani



NDA 201655

FILING COMMUNICATION

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Robert A. Barto, MBA
Vice President, Regulatory Affairs

Dear Mr. Barto:

Please refer to your new drug application (NDA) dated and received July 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Oxymorphone Extended-Release Tablets.

We also refer to your submission dated July 23, 2010.

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 **Priority**. Therefore, the user fee goal date is January 7, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 17, 2010.

We request that you submit the following information:

1. In drug liking study EN3288-109, we note that you have recruited subjects experienced with chewing opioid products. We could not ascertain if the subjects were provided specific instructions on how to chew the treatments/tablets. Indicate details of

instructions provided to subjects with regard to rate of chewing or duration of chewing and if the individual subjects followed those instructions.

2. Since the lower strengths (5 mg to 15 mg) are not proportionally similar to the 40 mg strength, provide dissolution profile comparisons (f2 testing) using the 5 mg strength as the reference.
3. Provide the quantitative composition of the seven different (b) (4) coating systems used for the drug product, or provide letters of authorization (LOAs) to permit review of a (b) (4) drug master file (DMF) that includes this information. LOAs should specifically refer to the submission dates and location of the composition information.
4. Include a test for microbial limits (USP<61>, <62>) in the release specifications for this product. USP <1111> provides recommendations for acceptable limits. The information provided in the NDA does not address the microbiological load or in-process control. The appropriate ingredients should also be tested for bioburden as part of the microbiological control of this manufacturing process.

Over time it is possible that the product may take on water and support growth. This issue should be addressed in the stability plan. Annual testing is recommended.

5. The results of the bioavailability study EN3288-108 demonstrate a shorter Tmax and a substantial increase in Cmax of oxymorphone in plasma following administration of EN3288 ((b) (4) cut (b) (4)) relative to intact EN3288. Such changes in Tmax and Cmax may be indicative of an increased abuse potential. In addition, it is known that, following administration of the currently approved Opana ER in fed subjects, the Cmax increases by approximately 50% compared to fasted subjects.

The relative abuse potentials of intact and tampered product should be assessed in order to evaluate the abuse deterrence of the original product formulation. Results from a human abuse liability study are needed in order to support labeling claims about (b) (4) (b) (4). This study should be conducted in fed and fasted, opioid-experienced, non-dependent subjects to evaluate and compare the pharmacodynamic response (subjective effects) observed with an increase in Cmax and decrease in Tmax following administration of EN3288, when cut (b) (4), relative to intact EN3288 in the two groups.

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

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

If you have any questions, call Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, MD
Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201655	ORIG-1	ENDO PHARMACEUTICA LS INC	Oxymorphone HCl (b) (4) extended-release tablet

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/s/

SHARON H HERTZ
09/02/2010
Signing for Bob Rappaport, M.D.

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, August 31, 2011 3:11 PM
To: 'Chapman, Tara'; Barto, Bob
Subject: REMS comments for NDA 201655

Attachments: rems and materials + FDA Comments 2011.0831.doc; rems-website + FDA comments 2011.0831.pdf; rems-supp-docs + FDA Comments 2011.0831 .pdf

Hi Tara, The following are our comments on the REMS for NDA 201655. Some minor C&C comments will be coming soon.

Following are FDA's comments on your proposed REMS, appended materials and Supporting Document, submitted to NDA 201655, on January 6, 2011, and June 13, 2011. Please incorporate the changes and submit all revised materials within 1 week.

The comments provided are based on the draft Product Labeling. Your REMS document and all REMS materials will need to be updated to be consistent with the final agreed upon PI.



rems and materials + FDA Comments 2011.0831.doc; rems-website + FDA comments 2011.0831.pdf; rems-supp-docs + FDA Comments 2011.0831 .pdf

1. **REMS Document**

See attached document for tracked changes and comments of the proposed REMS document.

2. **Other REMS Materials**

a. *Website Screen Shots*

- i. Append screen shots of the REMS website to your REMS document
- ii. See edits/comments provided in the attached document.

b. *DHCP Letter, Dear Pharmacist Letter, and Healthcare Professional (HCP) Training Guide*

- i. See edits/comments provided in the attached document

b. Healthcare Professional (HCP) Training Guide

- i. See edits/comments provided in the attached document

3. **REMS Supporting Document**

Make the minor edits to the document as noted in the tracked changes and revise the REMS Supporting Document to be consistent with all changes made to the REMS document.

4. **Re-submission Requirements and Instructions**

- a. Submit the revised proposed REMS with all appended materials and the REMS Supporting Document.
- b. Formatting requirements:
 - i. Provide a WORD document with tracked changes and a clean WORD version of all revised materials and documents.
 - ii. Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.
 - iii. Date and paginate all REMS documents to facilitate review and document control.

Lisa Basham, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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immediately following this page

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/s/

LISA E BASHAM
08/31/2011



NDA 201655

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Robert A. Barto, MBA
Vice President, Regulatory Affairs

Dear Mr. Barto:

We acknowledge receipt on June 13, 2011, of your June 13, 2011, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for OPANA ER (oxymorphone hydrochloride) Extended-Release Tablets.

We consider this a complete, class 2 response to our January 7, 2011, action letter. Therefore, the user fee goal date is December 13, 2011.

If you have any questions, call me at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LISA E BASHAM
06/23/2011



Department of Health and Human Services

Food and Drug Administration
10903 New Hampshire Ave
Building 51
Silver Spring, MD 20993

Via Electronic Mail

May 6, 2011

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Robert A. Barto
Senior Director, Regulatory Affairs

Dear Mr. Barto:

As stated in our letter of April 19, 2011, FDA has determined that a REMS is necessary for long-acting (LA) and extended-release (ER) opioid medications to ensure the benefits of the drugs continue to outweigh the risks of adverse outcomes of addiction, unintentional overdose, and death that result from inappropriate prescribing, misuse, and abuse of these products. Within 120 days from the issuance of the letter, you are required to submit a proposed REMS containing the elements described in the letter.

To provide an opportunity to discuss any questions or concerns with us well in advance of the REMS submission due date, you are invited to a meeting that will be held from 10:00 AM to 12:00 Noon on May 16, 2011. This meeting will only be open to sponsors with approved or pending applications for an LA or ER opioid. The meeting will be held in Room 9201 at the Kirkland Center of the National Labor College, located at 10000 New Hampshire Avenue, Silver Spring, MD 20903. The Kirkland Center has abundant free parking. Information about the Kirkland Center, including directions, can be found at <http://www.acc-kirklandconferencecenter.com/index.cfm>.

Because space is limited, each sponsor is limited to sending three representatives to attend the meeting in person. We will set up an operator assisted teleconference so that additional members of your staff will be able to listen to, but not speak at, the meeting.

Please send the names and titles of the staff who will represent you at the May 16 meeting to Michie Hunt at michie.hunt@fda.hhs.gov by close of business Monday, May 9. We require a list of attendees because we will be checking arrivals against a list of names at the door. There will be no exceptions to the rule limiting each company to three representatives at the meeting. You must also provide the names of those who will be participating in the meeting by phone so we can notify the operator of those authorized to participate. Please provide Ms. Hunt with the names and email addresses of the staff whom you wish to participate in the call by close of

business Monday, May 9. She will then place their names on the screening list, which the operator will check before allowing entry into the call. She will also send your staff members the call-in number and passcode.

We encourage you to submit written questions to us in advance of the meeting so that we will be able to consider the questions and be prepared to respond at the meeting. You may address your written questions to Ms. Hunt. In order to give us time to consider your questions in advance of the meeting they should be submitted to Ms. Hunt by close of business Tuesday, May 10.

If you have any additional questions about the meeting, please address them to Ms. Hunt by email or at 301-796-3504.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SHARON H HERTZ on behalf of BOB A RAPPAPORT

05/06/2011

Signing for Bob Rappaport, M.D.



NDA 201655

PRE-APPROVAL REMS NOTIFICATION

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Tara Chapman, Pharm.D.
Director, Regulatory Affairs

Dear Ms. Chapman:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oxymorphone Hydrochloride Extended-Release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

We also refer to the stakeholder, industry, and public meetings, and Advisory Committee meeting held on February 10, March 3, May 4 and 5, May 27 and 28, 2009, and July 22 and 23, 2010, respectively, at which discussions took place concerning a risk evaluation and mitigation strategy (REMS) for the class of long-acting and extended-release opioid products. FDA has analyzed the advice and comments provided during these meetings and has determined the necessary elements of the class-wide REMS.

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for certain long-acting and extended-release opioid products, including Oxymorphone Extended-Release Tablets, to ensure that the benefits of the drug continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The elements of the REMS are described below.

In the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for all members of the class.

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Oxymorphone Extended-Release Tablets would pose a serious and

significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Oxymorphone Extended-Release Tablets. FDA has determined that Oxymorphone Extended-Release Tablets is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Oxymorphone Extended-Release Tablets. FDA has also determined that Oxymorphone Extended-Release Tablets is a product for which patient labeling could help prevent serious adverse events. The Medication Guide should have both common content applicable to all extended-release and long-acting opioids, as well as product specific information that is necessary for safe and effective use of the drug.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Oxymorphone Extended-Release Tablets.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a Communication Plan are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including, at a minimum, the following:

1. The sponsor must ensure that training is provided to prescribers who prescribe Oxymorphone Extended-Release Tablets. An outline of the content for this information is described in Appendix A. The training must include successful completion of a knowledge assessment and proof of successful program completion. To assure access to Oxymorphone Extended-Release Tablets and minimize the burden on the healthcare delivery system, FDA expects that the training will be conducted by accredited, independent continuing medical education (CME) providers, to the extent practicable.
2. The sponsor must provide to prescribers information that the prescriber can use to educate patients in the safe use, storage, and disposal of opioids. An outline of the content for this information is described in Appendix B.
3. The sponsor must inform prescribers of the existence of the REMS and the need to successfully complete the necessary training.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 6 months, 12 months, and annually after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

As required under section 505-1(g)(3)(A) of the FDCA, assessments of an approved REMS must assess the extent to which the elements to assure safe use are meeting the goals of your REMS and whether the goals or elements should be modified. Your assessment plan should include the following elements along with the methodology for each element:

1. an assessment of how many prescribers of long-acting and extended-release opioids have successfully completed the training. The assessment should specify performance goals for how many prescribers can be expected to be trained within a certain period, e.g., 50% of prescribers trained within 6 months; 70% within twelve months. We recommend that you consult with accredited CME providers to determine what can be realistically be achieved through an aggressive education program and propose goals accordingly.
2. an independent audit of the quality of the content of the educational materials used by the CME providers to provide the education. The audit should evaluate the quality of the content against the content approved by FDA as part of the REMS as well as against the Accreditation Council for Continuing Medication Education (ACCME) standards for CME.
3. an evaluation of healthcare providers' awareness and understanding of the serious risks associated with these products (for example, through surveys of healthcare providers) and specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.
4. an evaluation of patients' understanding of the serious risks of these products.
5. a surveillance plan that includes monitoring for misuse, abuse, overdose, addiction, death and any intervention to be taken resulting from signals of these metrics. Surveillance needs to include information on changes in abuse, misuse, overdose addiction, and death for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency rooms, addiction treatment centers, poison control call centers). As much as possible, the information should be drug-specific.
6. an evaluation of drug utilization patterns. Include methodology for monitoring patterns of prescribing to identify changes in access to these products.
7. an evaluation of changes in prescribing behavior of prescribers, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills. Provide the methodology for this analysis.

FDA strongly recommends that sponsors make provision in the single shared system for joint assessments of the effectiveness of the REMS.

In order to continue our evaluation of this NDA, upon resubmission, you will need to include the revised proposed REMS.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a model for the proposed REMS (see Appendix C).

Additionally, all relevant proposed REMS materials, including educational materials, should be appended to the proposed REMS. FDA expects that the content of the educational materials will follow the attached outline, and contain more specific content on the proposed topics than is contained in the outline. FDA will review and approve the content of the training. However, FDA understands that CME providers will take the approved content and develop specific materials for training (e.g., slides, internet-based training). Accordingly, FDA does not expect the sponsor to provide and attach to the REMS the specific materials that will be used to train prescribers.

Once FDA finds the content of the REMS acceptable and determines that the application can be approved, we will include the approved documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining how the REMS will be implemented. The same supporting document may be submitted by each member of the single, shared system.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

For administrative purposes, designate the proposed REMS submission “**PROPOSED REMS for NDA 201655/S-###**” and all subsequent submissions related to the proposed REMS “**PROPOSED REMS-AMENDMENT for NDA 201655.**” If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
REMS Appendices A, B, and C

APPENDIX A: CONTENT OF EDUCATION PROGRAM

The training for prescribers required by the elements to assure safe use must contain the following content:

1. General information for safe opioid prescribing
 - a. Patient selection and assessment
 - i. Determine goal of therapy
 - ii. Assessment of the risk of abuse, including history of substance abuse and serious mental illness
 - iii. When relevant, determining if patient is opioid tolerant
 - b. Considerations when prescribing opioids
 - i. Pharmacokinetics and potential for overdose
 - ii. Addiction, abuse, and misuse
 - iii. Intentional abuse by patient or household contacts
 - iv. Interactions with other medications/substances
 - c. Managing patients taking opioids
 - i. Establishing goals for treatment and evaluating pain control
 - ii. Use of Patient Provider Agreements (PPAs)
 - iii. Adherence to a treatment plan
 - iv. Recognizing aberrant behavior
 - v. Managing adverse events
 - d. Initiating and modifying dosing of opioids for chronic pain
 - i. As first opioid
 - ii. Converting from one opioid to another
 1. Converting from immediate-release to extended-release and long-acting products
 2. Converting from one extended-release and long-acting product to another
 - iii. Titrating to effect/tolerability
 - iv. How to deal with missed doses
 - e. Maintenance
 - i. Reassessment over time
 - ii. Tolerance
 - f. Monitoring patients for misuse and abuse

- i. Utilization of prescription monitoring programs to identify potential abuse
 - ii. Understanding the role of drug testing
 - iii. Screening and referral for substance abuse treatment
 - g. How to discontinue opioid therapy when it is not needed any longer
- 2. Product Specific Information
 - a. Pharmacokinetic characteristics
 - b. Product specific toxicity
 - c. Requirements for opioid tolerance for certain long-acting and extended-release products
 - d. Individual product information modules
 - i. Fentanyl transdermal system
 - ii. Hydromorphone ER
 - iii. Methadone (For the treatment of moderate to severe pain not responsive to non-narcotic analgesics)
 - iv. Morphine ER
 - v. Oxycodone ER
 - vi. Oxymorphone ER
 - vii. Buprenorphine (for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time)
 - viii. New products
- 3. Patient counseling
 - a. Information about prescribed opioid
 - b. How to take opioid properly
 - i. Adherence to dosing regimen
 - ii. Risk from breaking, chewing, crushing certain products
 - c. Reporting adverse effects
 - d. Concomitant use of other CNS depressants, alcohol, or illegal drugs
 - e. Discontinuation of opioid
 - f. Risks associated with sharing, i.e., overdose prevention
 - g. Proper storage in the household
 - i. Avoiding accidental exposure

- h. Avoiding unsafe exposure by preventing theft and proper disposal
- i. Purpose and content of Patient Provider Agreement

APPENDIX B: PATIENT EDUCATION

Materials to provide to patients as part of patient counseling must include:

1. How to take opioid properly
 - a. Adherence to dosing regimen
 - b. Risk from breaking, chewing, crushing certain products
 - c. Symptoms of overdose
2. Reporting adverse effects
3. Concomitant use of other CNS depressants, alcohol, or illegal drugs
4. Discontinuation of opioid
5. Risks associated with sharing
6. Proper storage in the household
 - a. Avoiding accidental exposure
7. Avoiding unsafe exposure by preventing theft and proper disposal
8. Purpose and content of Patient Treatment Agreement
9. Links to Web sites with more information about topics 1 through 8

APPENDIX C: REMS TEMPLATE

Initial REMS Approval: XX/XXXX

Most Recent Modification: XX/XXXX

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL:

Reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release (ER) and long-acting (LA) opioids while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

II. REMS ELEMENTS:

A. Medication Guide or PPI

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

B. Communication Plan

A communication plan is not required.

C. Elements To Assure Safe Use

1. The sponsor must ensure that training is provided to prescribers who prescribe DRUG. An outline of the content for this information is described in Appendix A. The training must include successful completion of a knowledge assessment and proof of successful program completion. To assure access to DRUG and minimize the burden on the healthcare delivery system, FDA expects that the training will be conducted by accredited, independent continuing medical education (CME) providers, to the extent practicable.
2. The sponsor must provide to prescribers information that the prescriber can use to educate patients in the safe use, storage, and disposal of opioids. An outline of the content for this information is described in Appendix B.
3. The sponsor must inform prescribers of the existence of the REMS and the need to successfully complete the necessary training.

D. Implementation Plan

An implementation plan is not required.

E. Timetable for Submission of Assessments

COMPANY will submit REMS Assessments to the FDA no less frequent than 6 months, 12 months, and annually after the REMS is initially approved from the date of approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

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/s/

SHARON H HERTZ on behalf of BOB A RAPPAPORT
04/18/2011
Signing for Bob Rappaport, M.D.



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

MEMORANDUM

DATE: April 18, 2011

TO: File,

NDA	Tradename	Established Name
6134	Dolophine Tablets	(methadone hydrochloride) 5 mg and 10 mg
19516	MS CONTIN Tablets	(morphine sulfate controlled-release) 15, 30, 60, 100, 200 mg
19813	DURAGESIC	(fentanyl transdermal system) 1.25, 2.5, 5, 7.5, 10 mg
19977	Oramorph SR Tablets	(morphine sulfate sustained-release) 15, 30, 60, 100 mg
20616	KADIAN Capsules	(morphine sulfate extended-release) 10, 20, 30, 50, 60, 80, 100, 200 mg
21610	OPANA ER Tablets	(oxymorphone hydrochloride extended-release) 5, 7.5, 10, 15, 20, 30, 40 mg
21260	AVINZA Capsules	(morphine sulfate extended-release) 30, 45, 60, 75, 90, 120 mg
(b) (4)		
200533 (pending)	Nucynta ER Tablets	(Tapentadol Extended-Release) 50, 100, 150, 200, 250 mg
201655 (between cycles)	tradename pending	Oxymorphone HCl Extended-Release Tablets, 5, 7.5, 10, 15, 20, 20, 40
20553 (discontinued)	OxyContin Tablets	(oxycodone hydrochloride controlled-release)
21044 (discontinued)	PALLADONE Capsules	(hydromorphone hydrochloride extended-release) 12, 16, 24, 32 mg

From: Laura Governale, Pharm.D., MBA
Acting Deputy Director for Safety

Through: Bob Rappaport, M.D.
Division Director

RE: Risk Evaluation and Mitigation Strategy (REMS) Requirements

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity.

The use of prescription opioid drug products has nearly doubled in the past decade, and with that increase in use, there has been a concordant rise in the abuse and misuse of prescription opioid drug products, resulting in increased reports of serious adverse outcomes such as death, overdose and addiction. The spectrum of behaviors contributing to these problems include inappropriate prescribing such as improper dosing, patient selection, and patient counseling, as well as inappropriate patient behaviors such as improper use, storage and disposal of prescription drug opioid products.¹ Extended-release (ER) and long-acting (LA) opioid products pose unique risks to patients due to their pharmacokinetic properties, duration of use, and the amount of active ingredient contained in the drug product in comparison to their immediate-release opioid counterparts. The amount of opioid contained in an extended-release tablet can be much more than the amount of opioid contained in an immediate-release tablet because extended-release tablets are designed to release the opioid over a longer period of time. Long-acting opioids can take many hours to be cleared out of the body. Improper use of any opioid can result in serious side effects including overdose and death and this risk is magnified with long-acting and extended-release opioids. As it is important that these products are prescribed and used safely among the intended population, FDA has determined that a REMS is necessary to address the issues of unintentional overdose, addiction, and death resulting from inappropriate prescribing, misuse and abuse of ER and LA opioid drug products.

After consultations with the Office of New Drugs, the Office of Surveillance and Epidemiology, and members of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management committees on July 2010, we have determined that a class-wide REMS is necessary to ensure that the benefits of ER and LA opioid drug products outweigh their risks. In reaching this determination, we considered the following:

¹<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM217510.pdf>

- A. Approximately 24-33% of Americans suffer from chronic, non-cancer pain such as arthritis, lower back pain, and fibromyalgia.² In year 2009, an estimated (b) (4) unique patients received a dispensed prescription for an ER/LA opioid product from outpatient retail pharmacies.³
- B. ER and LA opioid products are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The majority of use for ER/LA opioid products is associated with “diseases of the musculoskeletal system and connective tissue” (ICD-9 codes 710-739) which include chronic pain conditions such as arthritis and back pain.⁴
- C. ER and LA opioid products are an important part of the armamentarium of drugs used to treat chronic pain. Some advantages of these types of formulations over the short-acting opioids are: 1) less frequent dosing; 2) better control of pain achieved through more stable drug levels; 3) improved patient compliance; and 4) less opioid side-effects.⁵ It is important to note that patients respond differently to different opioid drug substances and some patients develop tolerance to an opioid after chronic exposure. Physicians use a technique known as “opioid rotation” whereby they switch patients from one opioid to another if patients develop tolerance and cannot get adequate pain relief from any given opioid. Therefore, having different opioids available as modified-release formulations provides important pain relief options for these patients.
- D. The expected duration of treatment with ER and LA opioids will be from weeks to months or longer. Data from outpatient prescription claims databases suggest that ER and LA opioid products are typically prescribed for approximately 30-days at a time, whereas immediate-release opioid products are prescribed for 13-21 days at a time.⁶
- E. ER and LA opioid drug products such as OxyContin have distinguished themselves among the class of opioid pain medications with their disproportionately high rate of serious adverse outcomes including deaths, unintentional overdose and addiction, in comparison to immediate-release opioid products.¹ The goal of the REMS would be to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of ER and LA opioids while maintaining patient access to these medications. Serious adverse outcomes of concern including addiction, unintentional overdose, and death have been reported for each of the currently marketed products listed in the table above and in association with approved formulations of the drug substances in the products under review.

² Nelson, R. *Lancet* 362(9390): 1129, 2003.

³ SDI, Total Patient Tracker. Year 2009, Extracted, June 2010.

⁴ SDI, Physician Drug and Diagnosis Audit, Year 2009, Extracted June 2010

⁵ Balch RJ, et al. Extended-release morphine sulfate in treatment of severe acute and chronic pain. *Journal of Pain Research* 2010:3 191-200.

⁶ SDI, Vector One®: National. Years 2000 – 2009, Extracted June 2010.

- F. ER and LA opioid products contain one of the following active drug substances such as oxycodone, morphine, fentanyl, buprenorphine, methadone, and hydromorphone; none of these active drug substances are new molecular entities.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that ER/LA opioid products pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of ER/LA opioid products. FDA has determined that ER/LA opioid products are products that have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, ER/LA opioid products for which patient labeling could help prevent serious adverse events related to the use of these products.

The elements of the REMS will be a Medication Guide, Elements to Assure Safe Use, an implementation plan, and a timetable for submission of assessments of the REMS.

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/s/

KATHERINE S WON
04/18/2011

SHARON H HERTZ on behalf of BOB A RAPPAPORT
04/18/2011
Signing for Bob Rappaport, M.D.



NDA 201655

MEETING MINUTES

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Tara Chapman, Pharm.D.
Director, Regulatory Affairs

Dear Dr. Chapman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone Hydrochloride Extended-Release Tablets, 5mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

We also refer to the meeting between representatives of your firm and the FDA on February 15, 2011. The purpose of the meeting was to discuss resolution of the deficiencies noted in our January 7, 2011, Complete Response letter.

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 me at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham, M.S.
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

SPONSOR MEETING AGENDA

MEETING DATE/TIME: February 15, 2011 (4:00-5:00 PM)
LOCATION: Teleconference
APPLICATION: NDA 201655/Oxymorphone HCl Extended-Release Tablets
INDICATION: relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.
STATUS OF APPLICATION: Complete Response
SPONSOR: Endo Pharmaceuticals Inc.
TYPE OF MEETING: Type A/Post Action
MEETING CHAIR: Ellen Fields, MD; Clinical Team Leader, Division of Anesthesia and Analgesia Products (DAAP)
MEETING RECORDER: Lisa Basham, Senior Regulatory Health Project Manager

FDA Attendees	Title
Bob Rappaport, MD	Division Director
Sharon Hertz, MD	Deputy Division Director
Leslie K. Ball, MD, CAPT, USPHS	Director, Division of Scientific Investigations
Ellen Fields, MD, MPH	Clinical Team Leader
Martin Yau, Ph.D.	Acting Team Leader; Bioequivalence Team, DSI
Sam Haidar, Ph.D.	Chief, GLP and Bioequivalence Branch, DSI
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer
Lisa Basham, MS	Senior Regulatory Health Project Manager

Sponsor Attendees	Title
Irma Benedek, PhD	Sr. Director, Clinical Pharmacology
Tara Chapman, PharmD	Director, Regulatory Affairs
Yusong Chen, PhD	Sr. Director, Quantitative Sciences
Paula Clark	Director, Regulatory Affairs
Frank Diana, PhD	Vice President, Pharmaceutical Development
Bill Fiske, PhD	Sr. Director, Drug Metabolism and PK
Richard Reeve, MSc	Sr. Director, Qualitative Assurance
Debbie Travers	Director, Project Management
Silvia Dickhut	International Project Leader; Grunenthal

BACKGROUND: NDA 201655 received a Complete Response letter from the Agency on January 7, 2011. Endo Pharmaceuticals requested a Type A meeting on January 14, 2011. The background package was received on January 27, 2011. Preliminary responses to the sponsor's questions were sent on February 11, 2011. The sponsor contacted Lisa Basham on February 14, 2011, to change the meeting format from a face-to-face meeting to a teleconference. Furthermore, the sponsor informed the Agency that they would like some clarification on our responses to questions 1 and 3. Their requests for clarification are shown below the FDA responses to those questions, in italicized text. Discussion during the teleconference is show in normal text.

1. *Per the January 7, 2011 Complete Response Letter, Endo plans to reassay blood samples from study EN3288-103. Additional studies that were included in the original NDA filing (July 7, 2010) will not be subject to reassay and, since not noted in the letter as deficiencies, are interpreted to be accepted to support the application. Does the Agency concur?*

FDA RESPONSE:

Yes, provided that the reassay of blood samples as planned from study EN3288-103 yields results and conclusions consistent with those noted previously. If there is substantial difference from the original analysis a new bioequivalence study may be required.

*Endo's request for clarification received February 14, 2011:
In the response to Question 1, Endo would like to clarify the statement "results and conclusions consistent with those noted previously". Endo interprets this statement to mean that the results of the sample reanalysis for EN3288 meet the bioequivalence criteria versus the reference OPANA ER. Does the Agency concur?*

DISCUSSION:

The Agency confirmed that the primary outcome of interest is the confirmation of bioequivalence of OPANA ER and EN3288. In addition, the Agency briefly described the summary of the BE analysis from Study 103 and mentioned that the new statistical analysis should be consistent with the previous analysis in terms of ratio of geometric least square means (GLSM) and 90% confidence intervals. Also, the Agency indicated that the GLSM for C_{max} and AUC from the previous analysis should be tabulated along with the new data. Any major differences should be explained in the study report. The sponsor requested confirmation that, in the event that the results are not reproducible, Study 103 is the pivotal study to be repeated. The Agency confirmed this.

2. *Endo plans to use frozen (b)(4) back-up samples from Study EN3288-103 for sample reassay at (b)(4). Does the Agency concur?*

FDA RESPONSE:

Yes, you may proceed to re-assay back-up samples that have been stored at (b)(4) (b)(4) Documentation for the handling of those samples, particularly for storage conditions and the number of freeze-thaw cycles the samples have gone through, should be in place.

DISCUSSION: No discussion necessary.

3. *The sample reassay will be conducted by* [REDACTED] (b) (4)

[REDACTED]
[REDACTED] *Does the Agency concur that these steps will adequately address the inspectional findings at* [REDACTED] (b) (4) *to allow the reassay of samples to support the study being relied upon to establish bioequivalence of the proposed drug product to the reference product?*

[REDACTED] (b) (4)

[REDACTED] (b) (4)

DISCUSSION: The Agency expressed concurrence with the strategy described above and emphasized the continued need to heed the advice presented above in bullets 2 through 6. It was noted, however, that blinding will not likely be necessary with neat samples.

4. *Stability testing will be completed by (b) (4) to confirm long-term frozen stability of the bioanalytical samples. Does the Agency concur with this approach?*

FDA RESPONSE:

Yes, you may proceed to re-assay back-up samples that have been stored at (b) (4) (b) (4) provided that long-term stability in plasma was validated for the period of storage of back-up samples at (b) (4) (b) (4)

DISCUSSION: No discussion necessary.

5. *If for any reason the number of reassayed samples is not sufficient for statistical analysis or the samples are not viable for sample reassay, Endo will conduct a pharmacokinetic study to establish bioequivalence of oxymorphone hydrochloride extended-release 40 mg tablets with OPANA ER 40 mg tablets under fasted conditions using adequately validated analytical methodology. Does the Division concur that the basis for approval can be established with this proposed repeat pharmacokinetic study?*

FDA RESPONSE:

Yes, we concur with your proposal.

DISCUSSION: No discussion necessary.

6. *Additional finished product stability data will be available at the time of resubmission. Endo would like to propose extension of the expiration dating period for this drug product based on ICH Q1E. Will the Agency accept stability data in the response to the Complete Response Letter?*

FDA RESPONSE:

Yes, we will accept updated stability data in the response along with updated graphical presentations and analyses to support the extension of the expiration dating period following the recommendations of ICH Q1E.

DISCUSSION: No discussion necessary.

If you have any questions, call me at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham, M.S.
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LISA E BASHAM
03/03/2011



NDA 201655

MEETING PRELIMINARY COMMENTS

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Tara Chapman, Pharm.D.
Director, Regulatory Affairs

Dear Dr. Chapman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone Hydrochloride Extended-Release Tablets, 5mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

We also refer to your January 12, 2011, correspondence, received January 14, 2011, requesting a meeting to discuss your proposed strategy for responding to our January 7, 2011, Complete Response letter.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 15, 2011, from 4-5 PM at 10903 New Hampshire Avenue, Silver Spring, MD, 20993, Bldg 22, room 1315, between Endo Pharmaceuticals, Inc. and the Division of Anesthesia and Analgesia Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

For ease of reference, your questions are reproduced below in italicized text, followed by our responses in bold text.

1. *Per the January 7, 2011 Complete Response Letter, Endo plans to reassay blood samples from study EN3288-103. Additional studies that were included in the original NDA filing (July 7, 2010) will not be subject to reassay and, since not noted in the letter as deficiencies, are interpreted to be accepted to support the application. Does the Agency concur?*

FDA RESPONSE:

Yes, provided that the reassay of blood samples as planned from study EN3288-103 yields results and conclusions consistent with those noted previously. If there is substantial difference from the original analysis a new bioequivalence study may be required.

2. *Endo plans to use frozen (b)(4) back-up samples from Study EN3288-103 for sample reassay at (b)(4). Does the Agency concur?*

FDA RESPONSE:

Yes, you may proceed to re-assay back-up samples that have been stored at (b)(4). Documentation for the handling of those samples, particularly for storage conditions and the number of freeze-thaw cycles the samples have gone through, should be in place.

3. *The sample reassay will be conducted by (b)(4). Does the Agency concur that these steps will adequately address the inspectional findings at (b)(4) to allow the reassay of samples to support the study being relied upon to establish bioequivalence of the proposed drug product to the reference product?*



4. *Stability testing will be completed by (b) (4) to confirm long-term frozen stability of the bioanalytical samples. Does the Agency concur with this approach?*

FDA RESPONSE:

Yes, you may proceed to re-assay back-up samples that have been stored at (b) (4) at (b) (4) provided that long-term stability in plasma was validated for the period of storage of back-up samples at (b) (4)

5. *If for any reason the number of reassayed samples is not sufficient for statistical analysis or the samples are not viable for sample reassay, Endo will conduct a pharmacokinetic study to establish bioequivalence of oxymorphone hydrochloride extended-release 40 mg tablets with OPANA ER 40 mg tablets under fasted conditions using adequately validated analytical methodology. Does the Division concur that the basis for approval can be established with this proposed repeat pharmacokinetic study?*

FDA RESPONSE:

Yes, we concur with your proposal.

6. *Additional finished product stability data will be available at the time of resubmission. Endo would like to propose extension of the expiration dating period for this drug product based on ICH Q1E. Will the Agency accept stability data in the response to the Complete Response Letter?*

FDA RESPONSE:

Yes, we will accept updated stability data in the response along with updated graphical presentations and analyses to support the extension of the expiration dating period following the recommendations of ICH Q1E.

If you have any questions, call me at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham, M.S.
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LISA E BASHAM
02/11/2011

For Internal Use Only

Meeting Request Granted Form**

(Use this form to document the meeting granted via telephone.)

Complete the information below and check form into DFS.

Application Type	P-IND	IND	X NDA
Application Number	201655		
DATE Sponsor informed of meeting granted	1/14/11		
Sponsor was informed of:			
• date/time & meeting location	X Yes	No	
• expected FDA attendees	X Yes	No	
• meeting briefing package due date	X Yes (date: ASAP)	No	
• number of copies	X Yes	No	
	Other: Meeting Scheduled for 2/15/11		
Project Manager	Lisa Basham		

Any follow-up letter must be checked into DFS as an advice letter, **NOT as a meeting request granted letter.

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/s/

LISA E BASHAM
01/25/2011



NDA 201655

DISCIPLINE REVIEW LETTER

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Robert A. Barto
Vice President, Regulatory Affairs

Dear Mr. Barto:

Please refer to your New Drug Application (NDA) dated July 7, 2010, received July 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (Oxymorphone Hydrochloride Extended-Release) Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

Our review of your submission by the Controlled Substance Staff is complete, and we have the following comments.

The Controlled Substance Staff reviewed the *in vitro* manipulation and chemical extraction studies, a clinical pharmacokinetic (bioavailability) study (EN3288-108), human abuse potential studies (EN3288-109), and two bench top attractiveness studies (EN3288-901 and EN3288-902), and have the following conclusions regarding (b) (4) tablets, and have concluded that:

- (b) (4) provides limited resistance to physical and chemical manipulation for abuse. (b) (4) extended-release mechanism can be overcome by cutting, chewing, or grinding. Intake of (b) (4) with food or alcohol increases blood levels of oxymorphone. (b) (4) tablets provide some resistance to crushing (b) (4)
- Studies were not conducted to demonstrate that ground (b) (4) tablets can be abused intranasally. However, the difficulty in crushing (b) (4) tablets (b) (4) as observed in the *in vitro* studies makes it less likely that, relative to OPANA ER, individuals will intranasally abuse (b) (4) manipulated using these tools. The bench top study (EN3288-902) demonstrated the difficulty in forming an intranasal preparation (b) (4). However, the *in vitro* studies and study EN3288-902 did not address the grinding of (b) (4) tablets for possible abuse by intranasal administration.

- (b) (4) tablets are more difficult to cut than are OPANA ER tablets. However, (b) (4) tablets can be cut (b) (4) compromising the extended-release properties of the product.
- An *in vitro* study that it might be easier to prepare a solution for injection when using (b) (4) than when using OPANA ER. Exposure of a crushed (b) (4) 40 mg tablet (b) (4) (b) (4) of the label claim of extracted oxymorphone HCl. However, the bench top manipulation study, Study EN 3288-901, showed that both formulations behaved similarly.
- Grinding the (b) (4) tablets severely compromises the controlled release of oxymorphone HCl, as demonstrated by the high percentages of label claim of oxymorphone HCl (b) (4). These percentages of label claim (b) (4) represent extraction levels ranging from (b) (4) (b) (4) of oxymorphone for a 40 mg (b) (4) tablet. Considering that at equianalgesic doses, oral oxymorphone is (b) (4) more potent than oral oxycodone when physiological opioid effects (miosis, hypotension, analgesia) are compared, the extracted amounts of oxymorphone are equivalent in its opioid effects of analgesia, miosis, and respiratory depression to (b) (4) of oral oxycodone respectively.
- (b) (4) manipulated (b) (4) tablets or OPANA ER tablets might be difficult, (b) (4) (b) (4)
- Clinical abuse liability study EN3288-109 demonstrates that mastication of (b) (4) 40 mg tablets compromises the controlled-release mechanism of (b) (4)
- Based on the results of pharmacokinetic study EN3288-108 and abuse liability study EN3288-109, it is likely that the ingestion of a (b) (4) 40 mg tablet cut (b) (4) (b) (4) will produce substantial and statistically significant subjective reinforcing effects above those produced by the ingestion of intact (b) (4) 40 mg tablets. In addition, food increases the absorption of oxymorphone, thus increasing the likeability of oxymorphone containing products, including (b) (4)

RECOMMENDATIONS

Based on review of the relevant studies and the above conclusions, the Controlled Substance Staff recommends the following:

- The product label should not include language asserting that (b) (4) provides resistance to crushing, (b) (4)

- You need to conduct a study post approval, to determine if [REDACTED] ^{(b) (4)} could be administered intranasally, if such a study can be conducted safely. This study is relevant considering that the intranasal route seems to be the most prominent route of abuse of OPANA ER, followed by the oral and intravenous routes as reported by adult individuals (18 years or older) entering treatment (Addiction Severity Index-Multimedia Version (ASIMV) 2009- Data presented at the FDA joint meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committee held October 21-22, 2010 in Gaithersburg, Maryland).

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
01/04/2011

Basham, Lisa

From: Basham, Lisa
Sent: Thursday, December 30, 2010 3:34 PM
To: 'Chapman, Tara'
Subject: 12-30-10 REMS comments

Tara,

Please refer to your response, dated December 17, 2010 (eCTD Sequence No. 0016).

1. Regarding our request (Discipline Review Letter; December 10, 2010) for screen shots of your website, you indicate that, "screen shots are not available." Clarify when the screen shots will be available.
2. In your cover letter you indicate that you have provided, "the details of what will be provided on each web page;" however, the information provided is not sufficient to evaluate your proposed web site.

Provide more detail in your "Sitemap Explanation," and consider providing mock-ups of each page.

Examples of additional detail include, but are not limited to:

- a. On your "Landing page" provide the actual 'background information' text.
- b. On your "Education Program" page/link, clarify whether the text from the letters and training guide will be included on a separate page and/or if there will be links to pdf-versions. Also, if instructional text will be included to help HCPs navigate the various materials, provide that text.

Lisa Basham, MS

Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
01/03/2011



NDA 201655

DISCIPLINE REVIEW LETTER

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Robert A. Barto
Vice President, Regulatory Affairs

Dear Mr. Barto:

Please refer to your New Drug Application (NDA) dated July 7, 2010, received July 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (Oxymorphone Hydrochloride Extended-Release) Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

Our Division of Scientific Investigations (DSI) inspection of the analytical portions of Study EN3288-103, conducted at (b) (4), is complete, and we have identified the following deficiencies:

Study EN3288-103 should not be accepted for review at this time (b) (4)

(b) (4)

If you have any questions, call Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure
Redacted copy of the FDA 483

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/s/

PARINDA JANI
12/28/2010



NDA 201655

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

ENDO Pharmaceuticals Inc
100 Endo Boulevard
Chadds Ford, Philadelphia 19317

ATTENTION: Tara Chapman, PharmD
Associate Director, Regulatory Affairs

Dear Dr. Chapman:

Please refer to your New Drug Application (NDA) dated July 7, 2010, received July 7, 2010, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Oxymorphone Hydrochloride Extended-release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

We also refer to your July 23, 2010, correspondence, received July 23, 2010, requesting review of your proposed proprietary name, (b)(4). We have completed our review of the proposed proprietary name, (b)(4) and have concluded that it is acceptable.

The proposed proprietary name, (b)(4) will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 23, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abolade (Bola) Adeolu, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4264. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Lisa Basham at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Denise Toyer, PharmD,
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DENISE P TOYER
12/23/2010



NDA 201655

DISCIPLINE REVIEW LETTER

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Robert A. Barto
Vice President, Regulatory Affairs

Dear Mr. Barto:

Please refer to your New Drug Application (NDA) dated July 7, 2010, received July 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (Oxymorphone Hydrochloride Extended-Release) Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

We also refer to your submission dated July 23, 2010.

Our review of the proposed carton and container labels is complete, and we have identified the following deficiencies:

A. Container Label (All strengths)

1. Revise the presentation of the proprietary name and strength to ensure the proprietary name is the most prominent feature on the label. Currently, the colored circle that surrounds the strength makes it more prominent than the proprietary name.
2. Increase the prominence of the established name. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3. Increase the font size and weight of *mg* on the principal display panel.
4. Delete (b) (4)
5. Delete (b) (4)
6. Increase the prominence of the second set of digits (product code) in the NDC number by increasing the font size so they are more prominent than the rest of the NDC number.

7. Add the word *cut* to the list of actions that must be avoided that appear on the left side panel.
8. Revise the following statements on the left side panel by changing from all uppercase letters to improve readability.
 - Swallow Tablets Whole. Tablets Are Not To Be Cut, Broken, Chewed, Crushed, or Dissolved
 - Dispense Accompanying Medication Guide To Each Patient.Note, we find it acceptable to keep these statements in bold font.
9. Decrease the font size of the *Rx only* statement.

B. Container Label (7.5 mg and 15 mg)

Revise the font color of the strength from white to black to provide better contrast with the background color. Currently, the presentation of the white font on both the yellow (7.5 mg tablet) and peach (15 mg tablet) background colors do not provide sufficient contrast and are difficult to read.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa E. Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
12/22/2010



NDA 201655

DISCIPLINE REVIEW LETTER

Endo Pharmaceuticals
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Tara Chapman
Director, Regulatory Affairs

Dear Ms. Chapman:

Please refer to your July 7, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone Extended-Release Tablets.

Our review of your proposed Risk Evaluation and Mitigation Strategy (REMS) is complete, and we have identified the following deficiencies. The comments provided are based upon the draft package insert (PI). Your REMS document and all REMS materials will need to be updated to be consistent with the final agreed-upon PI. Please incorporate the changes and submit all revised materials within 1 week.

1. REMS Document

See **Appendix A** for tracked changes and clean versions of the REMS document.

2. Medication Guide

Specific comments on the content of the Medication Guide will be provided under separate cover.

3. Other REMS Materials

- a. Add an 'education confirmation' form to your REMS (see **Appendix A**, tracked changes version of the REMS).

The purpose of the form is to confirm and track Health Care Professionals' (HCP) completion of the REMS training program, and confirm their understanding of the key safety messages. Instruct HCPs to complete the form and return it to you, Endo, after the HCP has reviewed the Training Guide. Inform HCPs that completion of the form will not affect their ability to prescribe oxymorphone HCl ER.

- b. Append screen shots of the REMS website to your REMS document. Since your REMS materials will be maintained on a website (as referenced in your REMS document), the

website has been included as part of the REMS (see **Appendix A**, tracked changes version of the REMS). Specific website recommendations are included below.

- i. We recommend a stand-alone, REMS-dedicated website.
 - ii. We recommend that you include a prominent link on the product website's homepage for REMS materials. We remind you that any component of a REMS proposal must be reviewed and approved by the FDA, including any post-approval modifications. Because of this requirement, we recommend creating a single-click, prominent direct link off the main website that includes REMS-specific materials. This link will direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. The REMS-related webpage(s) should not be a means to promote oxymorphone HCl ER or any other Endo product. Only the separate webpage(s) and /or link will be considered a component of the REMS.
 - iii. The landing page of the separate REMS link should contain background information on the REMS, as well as safety information, the REMS goals, along with links to the REMS materials.
 - iv. This page should include a prominent header to communicate the risks associated with oxymorphone HCl ER and addressed through the REMS.
- c. Revisions were made to the following documents:
- Dear Healthcare Professional Letter
 - Dear Pharmacist Letter
 - TRADEMARK Healthcare Professional Training Guide
- See **Appendix B** for tracked changes versions of these documents

4. Supporting Document

Revise the REMS Supporting Document to be consistent with all changes made to the REMS document.

5. Re-submission Requirements and Instructions

- a. Submit the revised proposed REMS with all appended materials and the REMS Supporting Document.
- b. Formatting requirements:
 - i. Provide a WORD document with tracked changes and a clean WORD version of all revised materials and documents.
 - ii. Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.
 - iii. Date and paginate all REMS documents, to facilitate review and document control.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPENDICES

Appendix A: Tracked changes and clean versions of the REMS

Appendix B: Redline versions of REMS Materials

- DHCP Letter
- Dear Pharmacist Letter
- TRADEMARK Healthcare Professional (HCP) Training Guide

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/s/

LISA E BASHAM
12/10/2010
For Parinda Jani



NDA 201655

INFORMATION REQUEST

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317
Attention: Robert A. Barto, MBA
Vice President, Regulatory Affairs

Dear Mr. Barto:

Please refer to your July 7, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone Extended-Release Tablets.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- 1. The following dissolution acceptance criteria is recommended for all the strengths of Oxymorphone extended-release tablets:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Oxymorphone HCl	ER Tablet	II (paddle)	50	phosphate buffer, pH 4.5	900, 37 °C ± 0.5 °C	1 hour: (b) (4) (b) (4) 2 hours (b) (4) 8 hours: (b) (4)

These values are based on the mean dissolution profiles (b) (4) variation of the clinical batches and on stability testing for all the strengths. Please revise your dissolution specifications accordingly.

If you have any questions, call Swati Patwardhan, Regulatory Management Officer, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
11/23/2010



NDA 201655

DISCIPLINE REVIEW LETTER

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Robert A. Barto, MBA
Vice President, Regulatory Affairs

Dear Mr. Barto:

Please refer to your July 7, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone Extended-Release Tablets.

We also refer to your submission dated September 14, 2010.

Our review of the microbiology section of your submission is complete, and we have identified the following deficiencies:

ICH Q6a states “it is advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination or proliferation.” Adequate information has been provided that the finished dosage form will not support growth but the introduction of contaminants during the manufacturing process has not been adequately addressed. The product specification should state that the product meets the requirements of USP <61>, <62>, and <1111> if tested. The batch release criteria should identify the specific manufacturing process tests and criteria used to assess the finished product as microbiologically suitable for release. These tests and criteria should include, for example:

- Microbial limits data for critical raw materials,
- Microbiological environmental monitoring data for critical processing steps, and
- In-process control parameters **37 pages of draft labeling** that may affect product quality microbiology. h b ithh ld i f ll

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Swati Patwardhan, Regulatory Management Officer, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI

10/08/2010

I concur



NDA 201,655

DISCIPLINE REVIEW LETTER

Endo Pharmaceuticals, Inc.
Attention: Robert A. Barto, MBA
Vice President, Regulatory Affairs:
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Mr. Barto,

Please refer to your July 7, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone Extended-Release Tablets.

Our review of the CMC section of your submission is complete, and we have identified the following deficiencies:

1. We remind you to provide the quantitative composition of the seven different (b) (4) coating systems used for the drug product, or provide letters of authorization (LOAs) allowing our review of a (b) (4) master file that includes this information. LOAs should specifically refer to the submission dates and location of the composition information.
2. Provide details about how manufacturing changes at (b) (4) will be reported to the NDA.
3. Indicate the maximum storage time that the finished dosage form will be held in bulk packaging at (b) (4). In addition, provide stability data to justify the maximum hold period or indicate if registration batches were held for this period prior to final packaging and entry into the stability program.
4. Provide justification for the absence of an in-process test for dissolution.
5. Specify the viscosity range for the polyethylene oxide (b) (4) that is used in all drug product formulations.
6. Provide copies of representative infrared spectra of the seven (b) (4) coating systems that are obtained from (b) (4).
7. In section P.4.6 it is stated that each (b) (4) colorant formulation "is approved by FDA for pharmaceutical use." Elaborate on how this has been confirmed.

8. Provide a justification for the absence of a test with acceptance criterion for (b) (4) in the drug product, (b) (4) in the proposed container closure system.
9. Additional comments may be forthcoming regarding the absence of microbial testing of the drug product.
10. Provide assurance that the supplier of the various reference standards, (b) (4) has confirmed the identity of the (b) (4) (b) (4) reference standard (e.g., NMR, IR, MS). This was not clear from the certificate of analysis that you have provided for this standard.
11. As for the final packaging configuration, provide a detailed description of the bulk packaging used for storage at PMRS and for shipment to (b) (4) for final packaging. Identify the materials of construction of the bulk packaging components and provide their specifications. This information should support that this container closure system is constructed with materials that are compatible with the drug product and are safe for the intended use. Reference to information in master files may be made by providing letters of authorization that include specific reference to the master file submission date and the particular pages where the pertinent information can be found.
12. Provide test results for (b) (4) of the drug product on stability in order to allow our evaluation of the adequacy of the container closure system, (b) (4)
13. Provide, if available, pictures of the 40 mg tablets before and after the fading that takes place during storage under accelerated storage conditions (40°C/75%RH), so the extent of the fading can be gauged. Provide a comparative picture of the 15 mg strength tablets.
14. Modify your post-approval stability protocol for annual batches to include drug product in the bulk container that is to be used for shipment to the contract packager (b) (4) (b) (4). Refer to section VI.B of the Agency guidance for industry entitled Container Closure Systems for Packaging Human Drugs and Biologics (1999).
15. There may be additional revisions requested for your post-approval stability protocol depending on your response regarding the tablet (b) (4) data and your justification for not including a test for (b) (4) in the drug product specification.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee

reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Swati Patwardhan, Regulatory Management Officer, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-201655

ORIG-1

ENDO
PHARMACEUTICA
LS INC

Oxymorphone HCl (b) (4)
extended-release tablet

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/s/

PRASAD PERI
09/16/2010



NDA 201655

NDA ACKNOWLEDGMENT

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Robert A. Barto, MBA
Vice President, Regulatory Affairs

Dear Mr. Barto:

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

Name of Drug Product: Oxymorphone Hydrochloride Extended-Release tablets, 5, 7.5, 10, 15, 20, 30, and 40 mg.

Date of Application: July 7, 2010

Date of Receipt: July 7, 2010

Our Reference Number: NDA 201655

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 September 5, 2010, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

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

If you have any questions, call Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-201655

ORIG-1

ENDO
PHARMACEUTICA
LS INC

Oxymorphone HCl (b) (4)
extended-release tablet

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/s/

PARINDA JANI
07/20/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Pre-NDA Meeting
Minutes
4-6-09

Food and Drug Administration
Silver Spring, MD 20993

IND 104250

Endo Pharmaceuticals
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Tara Chapman
Associate Director, Regulatory Affairs

Dear Ms. Chapman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone HCl [REDACTED] (b) (4) Extended-Release Tablets.

We also refer to the meeting between representatives of your firm and the FDA on April 6, 2009. The purpose of the meeting was to discuss your proposed NDA submission for Oxymorphone HCl [REDACTED] (b) (4) Extended-Release Tablets.

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, please call me at 301-796-1175.

Sincerely,

{See appended electronic signature page}

Lisa Basham, MS
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

SPONSOR MEETING AGENDA

MEETING DATE/TIME: April 6, 2010/12 PM
LOCATION: White Oak Campus
 10903 New Hampshire Ave
 Bldg 22, Room 1315
 Silver Spring, MD 20903
APPLICATION: IND 104,250
STATUS OF APPLICATION: Active
PRODUCT: Oxymorphone HCl (b) (4), Extended-Release Tablets
INDICATION: analgesia
SPONSOR: Endo Pharmaceuticals, Inc.
TYPE OF MEETING: Type B (Pre-NDA); teleconference
MEETING CHAIR: Ellen Fields, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
MEETING RECORDER: Lisa Basham, Regulatory Project Manager

FDA Attendees	Title
Bob A. Rappaport, MD	Director, DAARP
Ellen Fields, MD	Clinical Team Leader
Dionne Price, PhD	Statistics Team Leader
Dan Mellon, PhD	Supervisory Pharmacologist
Srikanth Nallani, PhD	Clinical Pharmacology Review
Nick Olmos-Lau, MD	Clinical Reviewer
Zhihong Li, Ph.D.	Clinical Pharmacology Reviewer
Elizabeth Bolan, PhD	Preclinical Pharmacology Reviewer
Danae Christodoulou, PhD	CMC Lead, ONDQA
Lisa Basham, MS	Regulatory Project Manager
Attendees	Title
<i>Endo Pharmaceuticals</i>	
Tara Chapman, PharmD	Associate Director, Regulatory Affairs
Paula Clark	Director, Regulatory Affairs
Sou-Chan Chang, PhD	Director, Pharmaceutical Development
Frank Diana, PhD	Vice President, Pharmaceutical Development
Ivan Gergel, MD	Executive Vice President, Research and Development
Sandeep Gupta, PhD	Sr. Vice President, Discovery and Early Development
Robyne Kelemen, PhD	Director, Regulatory Affairs/CMC
Dana Shuey, PhD	Senior Director, Toxicology and Safety Pharmacology
Debbie Travers	Director, Project Management
Liann Yuh, PhD	Vice President, Biostatistics and Programming
Liz Nouaime	Manager, Regulatory Affairs, CMC
<i>Grunenthal</i>	
Silvia Dickhut	International Project Leader, New Therapeutic Entities
Keith Ryan	Director, Regulatory and Safety Affairs

(b) (6)

Note: Your questions are reproduced below in italicized font. Our responses, provided prior to the meeting, follow in bold font. Your comments on our responses, also provided prior to the meeting, are shown following our responses in italicized font. Discussion during the meeting is normal text.

Chemistry, Manufacturing, and Controls

1. *Endo proposes to use the following dissolution method for oxymorphone HCl (b) (4) extended-release tablets:
USP <711> Apparatus 2 (paddles) at 50 rpm
900 mL of pH 4.5 Phosphate buffer at 37°C*

Dissolution studies have been conducted at various conditions, including, but not limited to various changes in pH, agitation, and apparatus.

The selected dissolution parameters are the same as used for testing of OPANA® ER (oxymorphone HCl) Extended-Release Tablets. Does the Division concur with this approach?

FDA RESPONSE:

Yes, the proposed dissolution testing conditions appear to be appropriate.

ENDO RESPONSE:

No discussion necessary.

Clinical

2. *The NDA will be based on bioequivalence (BE) to OPANA ER. Endo proposes to not integrate the safety data as an Integrated Summary of Safety (ISS) since the studies are single dose and the subjects are healthy volunteers who are naltrexone blocked in most studies. Does the Division concur?*

FDA RESPONSE:

All safety data obtained from clinical studies, even in naltrexone-blocked volunteers, must be included in the submission. It is not necessary to pool the data from these studies. These data can be included in either Module 2, the clinical safety summary, or Module 5, the ISS.

ENDO RESPONSE:

No discussion necessary.

3. *Since Endo is not conducting safety and efficacy studies, we propose to not provide an Integrated Summary of Efficacy (ISE). Does the Division concur?*

FDA RESPONSE:

Do not omit the ISE from your NDA submission. However, you may simply include a statement to the effect that you are referencing the findings of efficacy for Opana ER.

ENDO RESPONSE:

No discussion necessary.



Electronic Submission

5. *Endo intends to file the upcoming NDA in eCTD format. Endo will provide a Table of Contents with proposed placement of items in the NDA within the eCTD structure.*
- a. *Two studies (EN3288-901 and EN3288-902) in which participants tamper with tablets, but do not ingest study drug are being conducted. Endo proposes to place those studies in Module 5.3.5.4. Endo also proposes to not include SAS transport files of the subject level data. The CSR appendices will contain listings of the subject level data. Does the Division concur?*

FDA RESPONSE:

Yes. Both studies can be placed in Module 5.3.5.4

ENDO RESPONSE:

No discussion necessary.

- b. *Studies EN3288-901 and EN3288-902 (proposed in Module 5.3.5.4) include video footage of study subjects manipulating oxymorphone HCl (b) (4) extended-release tablets and OPANA ER tablets for intravenous and intranasal abuse. Endo proposes to include this video footage as part of the NDA submission. Does the Division concur with this video footage being included in the NDA? If so, please confirm the most effective way for Endo to provide this footage to the Division.*

FDA RESPONSE:

We do not accept video files. In lieu of the videos, submit a text summary of the footage.

ENDO RESPONSE:

No discussion necessary.

- c. *A battery of standardized in vitro studies designed to test the physical and physiochemical properties of the formulation have been conducted. Endo proposes to summarize the results in Module 2.3 (Quality Overall Summary) and provide the detailed design and report in Module 3.2.P.2.2.3 (Physiochemical and Biological Properties). Does the Division concur with this placement in the eCTD structure?*

FDA RESPONSE:

Yes. The in vitro study can be summarized in Module 2.3 with the design and report placed in Module 3.2.P.2.2.3

ENDO RESPONSE:

No discussion necessary.

- d. *All data sets in Module 5.3.1.2 will be provided in CDISC and SDTM v3.1.1 and ADaM v2.0 standards will be followed. Does the Division have any additional data requirements for the eCTD filing?*

FDA RESPONSE:

We do not have additional data requirements.

ENDO RESPONSE:

No discussion necessary.

- e. *Are there any additional eCTD requirements the Division would like Endo to be aware of before submitting the NDA?*

FDA RESPONSE:

No

ENDO RESPONSE:

No discussion necessary.

Regulatory

6. *Endo will propose an interim Risk Evaluation and Mitigation Strategy (REMS) program, pending approval of the class-wide opioid REMS. Does the Division agree with this approach?*

FDA RESPONSE:

Yes. A REMS must be included in your NDA submission consisting of physician education as an element to assure safe use and a medication guide. We suggest that your proposed REMS include two parts: a “Proposed REMS” and a “REMS Supporting Document.” All relevant proposed REMS communication materials should be appended to the proposed REMS and all materials should be submitted as WORD documents. Education provided as part of a REMS should emphasize the safety messages important for the safe use of the product. Product marketing materials generally are not appropriate to educate about product risks.

ENDO RESPONSE:

No discussion necessary.

7. *OPANA[®] (oxymorphone HCl) Tablets and OPANA ER have post-marketing commitments for the Pediatric Research Equity Act (PREA). There are currently studies ongoing to fulfill these commitments. Endo proposes to not have additional PREA requirements for this formulation of oxymorphone. Does the Division concur?*

FDA RESPONSE:

Since your product does not represent a new indication, dosage form, active ingredient, dosing regimen or route of administration, PREA is not triggered and no studies in the pediatric population will be required.

ENDO RESPONSE:

No discussion necessary.

8. *At the time of the May 22, 2009 pre-IND meeting, Endo asked the following question: If a generic OPANA ER (non-tamper-resistant formulation) is approved prior to the approval of the oxymorphone HCl [REDACTED] (b) (4) extended-release tablets, does FDA have policy at their disposal to prevent substitution of the tamper-resistant formulation with a non-tamper-resistant formulation at the pharmacy level (ie, would the Agency consider assigning an alternative therapeutic equivalence (TE) code such as AB1, BC, or no TE code to the tamper-resistant formulation)? An alternative TE code would prevent automatic substitution between the brand, the generic, and the tamper-resistant formulation. At the time of the meeting, the Division indicated that this was under internal discussion. Can the Division provide any further insight at this time?*

FDA RESPONSE:

TE codes are not generally assigned until post approval, and are assigned relative to other products that are available on the market at the time. A final answer cannot be provided at this time.

ENDO RESPONSE:

No discussion necessary.

Nonclinical Comments

- **Due to the development of tolerance to the effects of opioids, there is no maximum daily dose for these products. The Division will consider the maximum theoretical daily dose (MTDD) for an opioid tolerant individual for your drug product when establishing the safety qualification threshold for impurities, degradants, and the safety of the proposed excipients in your drug product. The current thinking in the Division for an MTDD of oxymorphone in an opioid tolerant individual is [REDACTED] (b) (4). If you can provide clear clinical data to support a different MTDD for this product submit your justification for review by the Division.**
- **Any novel excipients must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance document: Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.**
 - **As noted in the document cited above, “the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product**

delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed *level of exposure, duration of exposure, or route of administration.*" (emphasis added).

- For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R2), ICHQ3B(R2)).
 - Adequate qualification must include:
 - Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - Repeat dose toxicology of appropriate duration to support the proposed indication.
 - In module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICHQ3A and Q3B qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.
 - NOTE: We may to refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity containing a structural alert for mutagenicity that exceeds (b) (4).
- Potentially genotoxic impurities or degradation products such as (b) (4) pose an additional risk; therefore, a specification of NMT (b) (4) must be set for genotoxic or potentially genotoxic impurities in the drug substance and drug product unless otherwise adequately justified. Adequate safety qualification for any potential genotoxic impurities identified via a structural alert for mutagenicity must be provided with the NDA submission and must include and *in vitro* bacterial reverse mutation assay (Ames assay) with the isolated impurity, tested up to the limit dose for the assay. Should this qualification produce positive or equivocal results, the impurity specification must be set at NMT (b) (4), or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

- The Division recommends that you consult with your DMF holder to determine the levels of these impurities in the drug substance you are obtaining and if needed, to decrease the limit of these impurities.
- NOTE: We may to refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity containing a structural alert for mutagenicity that exceeds (b) (4)

ENDO RESPONSE:

NOTE: In the first sentence of the paragraph above, Endo interpreted the repeat listing of (b) (4)

Endo has consulted with the DMF No. (b) (4) holder, (b) (4) on oxymorphone hydrochloride impurity specifications. The specified impurities other than (b) (4) impurities and oxycodone meet ICH Q3A(R2) requirements. (b) (4) is a (b) (4) impurity, (b) (4) therefore, Endo will maintain the current specification for (b) (4) at (b) (4) as in DMF No. (b) (4). Oxycodone is an approved analgesic active pharmaceutical ingredient and is specified at NMT (b) (4). There are three (b) (4) impurities, which are (b) (4) impurities, (b) (4) (b) (4) (b) (4) has been determined to not be a genotoxic impurity (b) (4)

The manufacturing, controls and testing for the (b) (4) oxymorphone hydrochloride material have been reviewed by the Agency as noted in an Advice Letter to (b) (4) pertaining to updated DMF No. (b) (4) dated February 22, 2010 (See Advice Letter attachment). Endo is proposing impurity specifications that align with (b) (4) specifications. The comparison of the impurity specifications for the two materials is provided in Table 1.

Table 1: Comparison of Oxymorphone Hydrochloride, USP, Impurity Specifications

(b) (4)

Since this (b) (4) material has just become available from (b) (4), all oxymorphone hydrochloride (b) (4) extended-release tablet batches (EN3288) were made with the original material (b) (4). However, Endo plans to implement the change to the (b) (4) by the time of drug product process validation (total of 11 batches). Endo does not anticipate that implementing use of (b) (4) drug substance will impact the drug product. As recommended in the Advice Letter to (b) (4), Endo will confirm that the change has no material impact on the manufacturability or product performance prior to launch.

The Advice Letter recommends that drug product manufacturers using (b) (4) oxymorphone hydrochloride implement the change to (b) (4) and corresponding specifications and analytical procedures based on (b) (4) validated method as a Changes Being Effected Supplement (CBE 0) to their A/NDAs. Endo is proposing that these (b) (4) specifications and analytical procedures be included in the original NDA submission for oxymorphone hydrochloride (b) (4) (b) (4) extended-release tablets.

Discussion: The Agency noted that the proposed specifications for (b) (4) (b) (4) are acceptable, as this represents reasonable current technological capabilities. However, as technological capabilities improve, ultimately the Agency is working toward reaching the NMT (b) (4) specification for impurities that are genotoxic structural alerts. The Agency also noted that (b) (4) (b) (4) which may be a structural alert for mutagenicity.

The Agency will conduct a computational toxicology analysis of (b) (4) in order to evaluate its potential for mutagenicity. The Agency requested that the sponsor also conduct their own computational toxicology analysis with the compound. This evaluation must be performed prior to NDA submission. The Agency also noted that there have been situations in the past where different programs yielded different results. If the computational toxicology analysis predicts that (b) (4) is not a potential mutagen, the proposed specification of NMT (b) (4) will be considered acceptable. If the analysis predicts that (b) (4) is a potential mutagen, the sponsor would need to reduce the specification to reflect NMT (b) (4) intake or conduct an Ames test. If the Ames test is negative, the compound will be considered qualified as per the FDA 2008 draft guidance *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, December 2008* and the proposed specification of NMT (b) (4) will be acceptable. If the Ames test is positive, the sponsor would need to reduce the specification to reflect NMT (b) (4) intake.

The Agency also requested that the sponsor send the structure, molecular formula and CAS number for (b) (4) to ensure that the Agency and the sponsor analyze the same compound.

POST MEETING NOTE: The sponsor sent this information via email on April 6, 2010 (no CAS number is available). The sponsor also sent their computational toxicology evaluation on April 19, 2010, and it has been reviewed. Our internal computational toxicology analysis concurs with the sponsor's conclusion that (b) (4) is not predicted to be a potential mutagen. The proposed specification of NMT (b) (4) for (b) (4) in the drug substance will be considered acceptable.

The sponsor made reference to (b) (4) updated DMF for drug substance with (b) (4) (b) (4) specs and noted that their NDA batches have been generated using (b) (4) specifications, because the new API process was not available at the time. They plan to use (b) (4) API to manufacture validation batches of the new drug product prior to launch and for commercial launch. The Agency requested clarification that the sponsor's plan is not to include comparative data using the new API in the NDA. The sponsor stated that this is correct. The Agency inquired whether the sponsor will have release data for the validation batches available to submit with the NDA. The sponsor stated that they will not have validation batch release data available. The Agency responded that the drug product impurity and dissolution profiles will need to be evaluated during NDA review to ensure the purity and dissolution performance between products made from the different APIs and noted that the drug product is an extended-release formulation. The sponsor stated there is no change in the impurity profile with the change in API and, consequently, they do not anticipate differences in the dissolution profiles. They continued that (b) (4) has confirmed that the materials are equivalent in that their (b) (4) is the same. The only change in the API, they continued, is in the (b) (4) specifications, but the sponsor plans to confirm this with the validation batches. The Agency asked what data would be available for drug product manufactured with the drug substance (b) (4). The sponsor responded that they would have 12-month stability data for the highest and lowest strengths, and 6-month data for the intermediate strengths. They noted that there is no observed difference between the

strengths in dissolution profiles. The Agency stated that they will provide further guidance in the form of a post-meeting note, but added that extended-release, tamper-resistant formulations need to be assessed for comparability during NDA review.

It was recommended that the sponsor provide release data for the highest and lowest strength batches in the NDA and 3-month stability data, to ensure that the product is performing as predicted. The sponsor made reference to the February 22, 2010, Agency letter to (b) (4) stating that companies with A/NDAs for products using new (b) (4) may submit this change to the A/NDA as a Changes Being Effected Supplement. They noted that the new material has just recently become available to them and that a 3-month lead time would be required to meet the Agency's request, thus making it difficult to provide the requested information in the NDA submission. Therefore, they suggested that they should be able to file as proposed and to amend the application during the review cycle. The Agency reiterated that it is the sponsor's responsibility to provide all of the required information at the time of NDA submission. The sponsor stated that they plan to file the NDA by June 30, 2010.

POST MEETING NOTE:

You have proposed to submit the NDA with 12-month stability data on two batches each of the highest and lowest strengths, and one batch each of all intermediate strengths with six-month data. All the NDA batches have been manufactured with oxymorphone (b) (4) (b) (4). Validation batches will be manufactured with oxymorphone (b) (4) and you propose to submit release data during the review cycle.

After internal discussion, we request the following additional data to support comparability of the drug product:

In addition to the NDA batches manufactured with API (b) (4) (b) (4) provide batch analysis, release data at the time of NDA submission, for one batch each of drug product of the highest and lowest strengths, manufactured from API (b) (4). Three-month stability data under normal and accelerated storage conditions for these two batches may be amended during the NDA review cycle.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-104250	GI-1	ENDO PHARMACEUTICA LS INC	EN3288 (oxymorphone HCl ^{(b) (4)} extended- release tablets)

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

/s/

LISA E BASHAM
04/26/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Pre-IND Meeting
Minutes

5-22-09

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 104,250

Endo Pharmaceuticals
100 Endo Boulevard
Chadds Ford, PA 19317

Attention: Tara Chapman
Associate Director, Regulatory Affairs

Dear Ms. Chapman:

Please refer to your Pre-IND file for Oxymorphone HCl [REDACTED] Extended-Release
Tablets.

We also refer to the meeting between representatives of your firm and the FDA on May 22,
2009. The purpose of the meeting was to discuss your drug development plan for Oxymorphone
HCl [REDACTED] Extended-Release Tablets.

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, please call me at 301-796-1175.

Sincerely,

{See appended electronic signature page}

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

SPONSOR MEETING AGENDA

MEETING DATE/TIME: May 22, 2009/11 AM
LOCATION: White Oak Campus
 10903 New Hampshire Ave
 Bldg 22, Room 1313
 Silver Spring, MD 20903

APPLICATION: Pre-IND 104,250
STATUS OF APPLICATION: Presubmission
PRODUCT: Oxymorphone HCl (b) (4) Extended-Release Tablets
INDICATION: analgesia
SPONSOR: Endo Pharmaceuticals, Inc.
TYPE OF MEETING: Type B (Pre-IND)
MEETING CHAIR: Sharon Hertz, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
MEETING RECORDER: Lisa Basham, Regulatory Project Manager

FDA Attendees	Title
Bob A. Rappaport, MD	Director, DAARP
Sharon Hertz, MD	Deputy Director, DAARP
Rob Shibuya, MD	Clinical Team Leader
Silvia Calderon, PhD	Team Leader, CSS
Jacqueline Spaulding, MD	Clinical Reviewer
David J. Lee, Ph.D.	Clinical Pharmacologist/Reviewer
Danae Christodoulou, PhD	Pharmaceutical Assessment Lead, ONDQA
Jim Tolliver, PhD	CSS Reviewer
Lisa Basham, MS	Regulatory Project Manager
Attendees	Title
<i>Endo Pharmaceuticals</i>	
Bob Barto	Vice President, Regulatory Affairs
Tara Chapman	Associate Director, Regulatory Affairs
Frank Diana	Vice President, Pharmaceutical Development
Bill Fiske	Sr. Director, Drug Metabolism and PK
Ivan Gergel	Executive Vice President, Research and Development
Sandeep Gupta	Sr. Vice President, Discovery and Early Development
Debbie Travers	Director, Project Management
<i>Grunenthal</i>	
(b) (6)	
Silvia Dickhut	International Project Leader, New Therapeutic Entities
Keith Ryan	Director, Regulatory and Safety Affairs

Background: The Sponsor submitted a meeting request on January 7, 2009, which was subsequently granted on January 27, 2009. The meeting was scheduled for May 22, 2009. The meeting package was submitted on April 10, 2009. On May 20, 2009, prior to the meeting date, the Division provided responses to the questions contained in the April 10, 2009, meeting package. The Sponsor provided some follow-up comments on the morning of the meeting. The original questions, contained in the April 10, 2009, meeting package, are presented below in italicized text. Our responses, forwarded on May 20, 2009, are in bolded text. The Sponsor's comments, provided on the morning of the meeting are present below the Division's responses, in italicized text. Discussion during the meeting is presented in normal text and is labeled as such.

Meeting Minutes:

The Sponsor began the meeting by making some opening remarks. They acknowledged that the Division has put considerable thought into the assessment of (b)(4) formulations. They noted that the proposed formulation of oxymorphone, (b)(4), is not tamper-proof. It is designed to release over 12 hours, to protect against medical errors, and to raise the hurdle for the casual abuser to defeat the controlled-release characteristics. The Sponsor inquired where the bar is being set for tamper-resistant products, i.e., do tamper-resistant formulations need to protect the casual abuser, or are they expected to thwart the kitchen chemist? They noted that there are currently no guidelines or criteria for a threshold by which they may gauge the tamper-resistance of their formulation. The Division responded that we are learning as more of these products are being developed. Currently, the Division noted, there are three areas of testing to consider, and depending on the results, the Division will work with the Sponsor on how to convey the results in labeling. The overarching theme is that the Division will not allow labeling that will mislead the patient or practitioner into believing that the drug is safer than other formulations without specific data demonstrating that is it. Without data, the Sponsor will not be able to make claims about or market based upon the drug's (b)(4) tamper-resistance qualities. The three levels of data fall roughly into the following categories:

1. In vitro data: Data from studies designed to evaluate the product's resistance to attempts to defeat the controlled-release properties. These studies should be based on information from abusers, must be scientifically rigorous and blinded. The Sponsor was referred to the May 2008 Advisory Committee to learn what the committee recommended.
2. Pharmacokinetic data: Data from studies that evaluate the effects of different methods of physical manipulation identified in the in vitro studies on the pharmacokinetic profile. These studies can enroll normal volunteers who are naltrexone-blocked for safety.
3. Clinical data: Data from studies of opioid-experienced drug abusers to evaluate the likability and euphorogenic effects of manipulated and intact product compared to oxymorphone that is not tamper resistant.

Depending on the scientific validity of the studies and the study results, the Division will determine what information will be allowed in the label. While the Division may allow language in the label describing the data, the Division will clearly state that these data have not been shown to affect the abuse liability of the drug. The ability to effectively impact abuse must be demonstrated by a post-marketing study. The post-marketing assessment of the impact of a tamper-resistant formulation on abuse will be challenging if the non-tamper resistant formulation continues to be available.

The Division commented that the current thinking on how to demonstrate abuse resistance is evolving and that the Division plans to bring these products before the Advisory Committee for discussion. The Division agrees that even an incremental improvement over current formulations could be beneficial.

Chemistry, Manufacturing, and Controls

Question 1.

Endo and its partner Grünenthal GmbH (Aachen, Germany) are developing an oxymorphone HCl extended-release, (b) (4) oral tablet formulation. This product, planned to be submitted under a new NDA, has the same drug substance as the Endo product OPANA ER (oxymorphone HCl) extended-release tablets, (b) (4)

(b) (4). The product is intended to be marketed in the same seven dosage strengths as OPANA ER (5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg). Endo has an extensive stability database for oxymorphone HCl tablets, including that for OPANA ER (NDA 21-610), which has an approved 36 month shelf-life.

All seven strengths of the oxymorphone HCl (b) (4) extended-release tablets are formulated using the same common excipients (b) (4) (b) (4) material, which is specific to each strength. The (b) (4) tablet weight is the same for all strengths. The amounts of excipients in the (b) (4) tablet are similar for each strength (b) (4)

In accordance with ICH Q1C, Stability Testing for New Dosage Forms (CDER, November, 1996), Endo is planning to provide 6 months of long-term (25°C/60%RH) and 6 months of accelerated (40°C/75%RH) drug product registration stability data on a total of 12 lots of the new formulation at NDA filing. Additional long-term stability data (eg, 9 months) are planned to be provided as minor amendments during the NDA review period.

The stability lots of oxymorphone HCl (b) (4) extended-release tablets are planned to meet the following bracketing design, in accordance with ICH Q1D, Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products, CDER, January 2003:

- 3 batches, 5 mg strength, packed in (b) (4) HDPE bottle (60 tablets/bottle)
- 1 batch, 10 mg strength, packed in (b) (4) HDPE bottle (60 tablets/bottle)
- 1 batch, 20 mg strength, packed in (b) (4) HDPE bottle (60 tablets/bottle)
- 3 batches, 40 mg strength, packed in (b) (4) HDPE bottle (60 tablets/bottle)
- 1 batch each of above, 5 mg, 10 mg, 20 mg and 40 mg strengths, packed in (b) (4) HDPE bottle (100 tablets/bottle).

Endo plans to include batch release data in the NDA for one batch of each of the intermediate strengths, 7.5 mg, 15 mg, and 30 mg tablets. For each of these 3 strengths, Endo plans to provide 3-month stability data during the NDA review period as a minor amendment.

- a. *Does the Division agree with this plan for providing 6 months of long-term and accelerated stability data at the time of NDA filing, and minor amendments with additional stability data during the NDA review period?*

FDA Response:

- No, we do not agree.
- We strongly recommend that you submit 12-month, long-term and 6-month, accelerated stability data for your primary stability batches at the time of NDA submission, or at least in the early part of the review cycle (first three months for a non-priority submission).
- While every effort will be made to review any stability amendments to the NDA, their review will depend on the timeliness of submission, extent of submitted data and available resources. Therefore, per GRMP guidelines, we may not be able to review amendments submitted to the NDA during the review cycle.

Endo's comment: See comment below Question 1b.

DISCUSSION: See discussion following question 1b.

- b. Does the Division concur that this bracketing stability design is acceptable for all the planned commercial dose strengths and package sizes to provide expiration dating for the product?

FDA Response:

- No, we do not agree.
- The proposed bracketing design for your stability protocol does not include all proposed strengths. Since this is a novel formulation and an extended-release dosage form, include all strengths in your bracketing design. As you proposed, you may reduce the number of primary stability batches of intermediate strengths, but you must include both commercial packaging configurations, all strengths and more than one batch at the extremes of 5-mg and 40 mg tablets.
- Note that stability data from your existing OPANA ER product may not be

used as supporting stability data since the two formulations are different.

- **We remind you that expiration dating will be assessed at the time of NDA review, as per ICH Q1E guidelines, based on real time stability data on primary and supporting batches and statistical analysis evaluation, if applicable.**

Endo's Comment:

We believe this product should be considered a New Dosage Form as described in ICH Q1C and that it qualifies for reduced stability testing at submission. We will file as much stability data as available at the time of filing. Please clarify the Division's position on recommending 12-month stability data.

We would like to further discuss our bracketing strategy.

DISCUSSION:

The Division agreed that the product would be considered a New Dosage Form and stated that the Sponsor's proposal would be reasonable under different circumstances. Tamper-resistant formulations are usually granted Priority Review status, which amounts to a 6-month review clock. The Sponsor is advised to include as much stability data as possible with the initial NDA submission because any data received past three months into the review cycle may require a three-month clock extension or may not be reviewed at all depending on available resources.

Regarding the Sponsor's proposed stability protocol and their plan to skip data for the three intermediate strengths (7.5 mg, 15 mg, and 30 mg) the Division stressed that stability data for all strengths of this (b) (4) formulation are critical for determining that the dissolution method is discriminating and robust. It is unclear which intermediate strengths may group with the lower strengths, and which with the higher strengths. Dissolution data from all strengths, generated with a robust method, will support the in vitro (b) (4) studies. The Division stated that it would be reasonable to reduce the amount of batches tested, but not to skip strengths. The Sponsor stated that they will begin stability testing on the other strengths, but that, upon NDA submission, they won't have data from the same time points due to the delayed start for these strengths. For the intermediate strengths, the Sponsor will provide 3-month data. For the others, they will provide 6-9-month data. The Division reminded the Sponsor that the expiry date will be based upon evaluation of data submitted with the NDA.

Question 2.

The tamper-resistant characteristics of the oxymorphone HCl (b) (4) extended-release tablets include high breaking force, formation of a viscous gel after immersion of

tablets in aqueous environment and low extractability of the drug substance in a range of solvents.

Endo plans to conduct a battery of standardized in vitro studies to test the physical and physicochemical tamper-resistant properties of the formulation:

- Resistance to crushing/pulverization
- Resistance to extraction in various solvents
- Resistance to preparation for intravenous and intranasal abuse

a. Does the Division concur that the proposed in vitro studies will adequately assess the physicochemical tamper-resistant properties of the formulation?

FDA Response:

- **Explore and conduct the different possible extraction scenarios using intact (b) (4) tablets over an extended time period, out to at least (b) (4) until most of the API is extracted, with periodic sampling to determine amount extracted. (b) (4)**

Endo's Response:

Please clarify that the "different possible extraction scenarios" mentioned refers to the testing as described in Attachment 3, sections 5.2 and 5.3 of the briefing document. We will take the testing through full extraction of the API (b) (4)

DISCUSSION:

The Division noted that we are referring to studies described in sections 3.5, 3.5.1, 4.3 and 4.4, where the protocols state that the extraction time is (b) (4). The Sponsor clarified that, following the (b) (4), the extraction will be allowed to continue until complete dissolution, to ensure that there is no dose dumping. For tests that are extractions only (5.2 and 5.3), additional extraction points will be considered.

The Division inquired about the test methods used in the study described in section 4.4.1, where the Sponsor describes transfer of the test sample, including medium, into a vessel to simulate oral ingestion after extraction. The Division asked whether this was intended to take the place of pharmacokinetic studies. The Sponsor responded that, since the test sample is taken to complete dissolution in pH 4.5 buffer, this test method should provide an accurate simulation of what could happen in vivo. The Division stated that, even with an in vitro/in vivo correlation, the Division would not accept in vitro data to inform labeling in the place of in vivo PK data. The Sponsor noted that, at (b) (4) of in vitro extraction, there is still an extended-release

component to the formulation that could then be tested in vivo. Running the extraction out past (b) (4) however, will eliminate the ER component and render the test material immediate-release. In this case, there is no point in performing the in vivo study, they continued. The Division stressed the importance of understanding what happens to this formulation when manipulated for (b) (4) i.e., evaluating the immediate-release profile, in terms of PK, after manipulation.

The Division recommended the Sponsor explore who is abusing oxymorphone, and how, and then incorporate that information into the design of studies, as well as into the assessment of the adequacy of the studies for evaluating any incremental improvement this formulation may have over the old formulation. The proposed benefit of an incremental change would require agreement from an Advisory Committee. The Division understands that the formulation will not resist every method of tampering, but stated that the product must be fully evaluated so that the limits of the formulation are well-understood. The Division acknowledged that the chewing-deterrent quality of this formulation may be valuable; however, the clinical relevance of this change should be evaluated in the context of its impact on the most prevalent methods of abuse. The evaluation should be systematically developed and carried out. In vitro data needs to be put in the context of clinical significance by performing in vivo studies.

- **Considering that the amount of (b) (4) (b) (4) conduct studies to determine the relative rate of release of the active pharmaceutical ingredient (API) on all strengths of crushed (b) (4) tablets to determine whether all dosage strengths retain the controlled-release properties after crushing (b) (4) and that dose dumping does not occur.**

Endo's response:

Please clarify why bracketing with the 5 and 40 mg strengths would not be representative of all dosage strengths since this tests the (b) (4). We believe that the 5 and 40 mg strengths, as described in Attachment 3, would be representative of all the strengths based on composition and excipient-DS ratios (Tables 6 and 7).

DISCUSSION:

The Division stated that the dose strengths (b) (4) (b) (4)

Therefore, it will be difficult to evaluate the intermediate strengths based upon data from the 5 mg and 40 mg strengths alone. It was agreed that one intermediate strength would be tested and that the Sponsor would include a justification for the intermediate dose-selection in the NDA.

- **Conduct testing in a blinded manner, preferably by an independent party.**

Endo's Response:

The testing protocol will be conducted under standard operating procedures at an independent laboratory and the tests will be replicated. We are using standardized apparatus and not human testing wherever possible (b) (4)
(b) (4) We believe that there should be no bias since the testing is analytical in nature. Please clarify the rationale for requiring blinding.

DISCUSSION:

The Sponsor stated that blinding would be difficult because the doses are different colors and debossed with the strength. The Sponsor also stated that they do not expect there to be differences between the two strengths. The Division noted that the Sponsor's expectation that there will be no differences between the two strengths is a bias in itself and that the Advisory Committee and the Division are interested in seeing blinded data. If the Sponsor feels that this is not necessary or possible, this rationale should be included in the NDA.

- **Provide data documenting the amount of oxymorphone released if the tablet is chewed after crushing (b) (4)**
Particular attention should be directed at the duration of chewing with multiple time points. Chewing should be conducted in the presence of saliva.

DISCUSSION: No discussion necessary.

- **Provide details regarding the degree of (b) (4) of extraction solutions. Solutions should be (b) (4) and not simply shaken. Provide details including the method of (b) (4) as well as degree and duration of (b) (4)**

DISCUSSION: No discussion necessary.

- **Report study results in a tabular format indicating the most effective conditions of extraction, meaning those that would afford the higher amounts of API extracted for each dosage strength. Further compare the percentages of API extracted from the new formulation to those extracted from the currently available OPANA ER tablets with similar particle size.**

Endo's Response:

Please clarify the rationale behind this request.

DISCUSSION:

The Division explained that the Sponsor should do whatever possible to take the formulation to the breaking point. They should consider all variables (b) (4) () in their attempt to fully characterize this formulation. The Division recommended that the Sponsor consult with abusers or the internet to learn about possible extraction techniques used by abusers.

- **Provide information on any immediate-release component to the formulation.**

DISCUSSION: No discussion necessary.

- **We strongly recommend that you review the recommendations from the Advisory Committee transcripts from the May 2008 and November 2008 ALSDAC meetings as they pertain to conditions of testing and implications for labeling.**

DISCUSSION: No discussion necessary.

- b. *Does the Division concur that descriptions of the physicochemical tamper-resistant properties based on the proposed in vitro studies could be described in the package insert?* [REDACTED] (b) (4)

FDA Response:

- **In vitro studies alone are not sufficient.**
- **Both in vitro studies and in vivo pharmacokinetic studies are required for consideration of whether information will be suitable for labeling. These studies need to be well designed and scientifically rigorous.**
- **Studies need to be extensive with regard to taking into account the array of equipment available for drug extraction, the various time spans for assessing drug extraction, extraction conditions [REDACTED] (b) (4) [REDACTED] that might be used to accomplish drug extraction.**
- **Consideration of the physical property data for placement into the label will be based not only upon the rigor and validity of the studies, but also on other information contained in the NDA and Advisory Committee feedback as well as the current thinking at the time of the NDA submission.**
- **In order to obtain a claim about abuse liability, a large-scale, long-term epidemiologic study will be required.**

Endo's Response: See comment below Q3.

DISCUSSION:

See Question 3 Discussion.

Question 3.

In addition to the in vitro testing described above, laboratory bench top tampering tests with both experienced intravenous and intranasal prescription opioid abusers will be conducted. The purpose of these trials is to gain insight into how actual abusers tamper with non-tamper-resistant extended-release opioid medications and to determine to what extent changes in the physicochemical properties of tablets, such as increased breaking force (crushing strength, hardness), will affect the ability of abusers to extract or pulverize the tamper-resistant tablets. No active product will be ingested during the conduct of these tests.

Does the Division concur that the described laboratory bench top tampering tests provide adequate information to inform the Division about the ability of an experienced abuser to tamper with the oxymorphone (b) (4) tablet?

FDA Response:

- **The proposed studies may provide some useful information but they will not, on their own, provide adequate information to characterize the ability of an experienced abuser to tamper with the product. Bench top tampering tests should be used to identify the most convenient methodology to tamper with the proposed formulation. The information gathered from bench top tampering tests should then be used to design appropriate testing protocols that examine the relative bioavailability of oxymorphone following tampering.**
- **With regard to the proposed bench top studies, it is not clear how subjects will be recruited or to what extent they will represent the general population of prescription opioid abusers.**
- **As stated earlier, it is questionable as to whether a one-hour time limit is adequate for assessing tampering with the tablets.**
- **Information is not provided on the "open-ended questions" that will be used in the studies.**
- **You must determine the methods that are currently being used to abuse OPANA ER, e.g. oral, nasal or parenteral, in order to support the relevance of methods used to test the product for resistance to physical and chemical manipulation.**

Endo's comment:

We interpret the Division's responses as follows: Both in vitro and in vivo data will be required under scientifically rigorous testing conditions as determined most appropriate based on the bench top tampering test results to support the possible inclusion of physical property data in the label. Due to the hardness of the tablet we believe a precaution is necessary against the possibility of breaking teeth (Section 5.2.3, page 21) if there is an attempt to chew the tablet. Please clarify if this type of data inclusion in the label would also require scientifically rigorous in vivo testing as well.

In the proposed in vivo testing, is the Division suggesting that the methods of tampering are representative of a casual abuser or the hard core kitchen chemist? We recognize that it is feasible that extensive (hard core) tampering could defeat the extended-release properties of the formulation.

DISCUSSION:

The Division stated that a warning about breaking teeth would not be included as a warning in the label.

Clinical:

Question 4.

The pivotal bioequivalence studies to be conducted are:

- 40 mg – fasted*
- 40 mg – fed*
- 5 mg – fasted*

Bioequivalence acceptance criteria for the fasted studies will be based on the 90% confidence interval (CI) of maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) within 80% to 125%. The fed study bioequivalence acceptance criteria will be based on the 90% CI of AUC within 80% to 125%. In the fed study, the 90% CI of C_{max} will be described but will not be considered as part of the bioequivalence acceptance criteria.

Does the Division concur that the proposed pivotal bioequivalence studies and bioequivalence acceptance criteria are adequate to support the filing of the NDA?

FDA Response:

Your proposed fasted and fed BE studies comparing the approved product (b) (4) under development at the 5-mg and 40-mg strengths are acceptable (see additional comment below on other strengths). However, for the fed study, 90% CI of C_{max} should be considered as part of the bioequivalence acceptance criteria. If C_{max} fails the bioequivalence criteria, discuss the implications of the C_{max} differences on the safety and efficacy of the product and the implications for labeling related to food.

Additional Clinical Pharmacology comments:

You propose to conduct a BE study with the lowest and highest strengths. If you do not have plans to obtain additional information from the intermediate strengths, you need to submit a Biowaiver Request for the intermediate strengths with appropriate justification and data to support your request. At this time, you have not made clear how you are going to link the intermediate strengths across the two products.

DISCUSSION: No discussion necessary.

Regulatory:

Question 5.

Endo intends to request a priority review for the oxymorphone HCl [REDACTED] (b) (4) extended-release tablet formulation NDA. Does the Division agree that a priority review could be granted?

FDA Response:

You will need to provide a rationale for why a priority review would be appropriate for this product, taking into account the extent of abuse and the ongoing marketing of the original formulation. A decision will be made based on that argument.

DISCUSSION: No discussion necessary.

Question 6.

Endo plans to submit a 505(b)(1) NDA for the oxymorphone HCl [REDACTED] (b) (4) extended-release tablets, based on the bioequivalence program to the currently marketed OPANA ER, as described above. Does the Division concur that Endo can submit a 505(b)(1) application based on the proposed bioequivalence program?

FDA Response:

Yes

DISCUSSION: No discussion necessary.

Question 7.

If the proposed 505(b)(1) for the oxymorphone HCl (b)(4) extended-release tablets consists of the data as described above would FDA consider reducing the PDUFA fee?

FDA Response:

If the data required for approval is bioavailability or bioequivalence only, we would expect a half fee for a new NDA. In other words, if no other safety or efficacy data, whether your own, obtained via right of reference, or obtained from literature, is required for approval, we would expect a half fee. If clinical data is necessary to demonstrate safety or efficacy, a full fee is required.

DISCUSSION: No discussion necessary.

Question 8.

Will FDA permit products with the same active moiety and dosage form to be available simultaneously on the market (b)(4)?

FDA Response:

Provide a rationale to support continued marketing of the non-tamper resistant formulation.

DISCUSSION: No discussion necessary.

Question 9.

If a generic OPANA ER (non-tamper-resistant formulation) is approved prior to the approval of the oxymorphone HCl (b)(4) extended-release tablets, does FDA have policy at their disposal to prevent substitution of the tamper-resistant formulation with a non-tamper-resistant formulation at the pharmacy level (ie, would the Agency consider assigning an alternative TE code such as AB1, BC, or no TE code to the tamper-resistant formulation)? An alternative TE code would prevent automatic substitution between the brand, the generic, and the TRF formulation.

FDA Response:

At this time we have no comment. This is under internal discussion.

DISCUSSION: No discussion necessary.

Additional Nonclinical Comment

As stability data for the final drug product formulation has not been obtained, we remind you that, for the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICHQ3B(R).

- **Adequate qualification must include:**
 - **Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
 - **Repeat dose toxicology of appropriate duration to support the proposed indication.**

DISCUSSION: No discussion necessary.

KEY SUMMARY POINTS:

1. The Sponsor will develop a full array of testing in an effort to fully characterize the physical characteristics of the formulation. They will consult with abusers to focus this effort and will provide justification for the parameters utilized in the tampering studies.
2. Stability data should be generated for all strengths. The number of primary stability batches may be reduced for the intermediate strengths, but both commercial packaging configurations must be included. Expiry date will be based upon the data submitted with the NDA. Updated stability will be reviewed if time and resources permit.
3. The Sponsor will include an intermediate strength in the extraction studies and will provide a justification for selection of that strength.
4. The Division and the AC recommend running blinded assays. The Sponsor should provide a justification if blinding is not utilized.
5. The new formulation should be compared to OPANA ER in tampering studies.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 104250

ENDO
PHARMACEUTICALS
INC

EN3288 (oxymorphone HCl (b) (4)
[REDACTED] extended-release tablets)

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

/s/

LISA E BASHAM
07/06/2009