CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205777Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205777 SUPPL # HFD #

Trade Name TARGINIQ ER

Generic Name oxycodone HCl/naloxone HCl extended-release tablets

Applicant Name Purdue Pharma, L.P.

Approval Date, If Known July 23, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

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

product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Reference ID: 3597945

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

Purdue did not specify

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

Reference ID: 3597945

#(s).

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☒ NO ☐

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

NDA#	NDA 021011	Roxicodone (oxycodone HCl immediate-release tablets)
NDA#	NDA 022272	OXYCONTIN (oxycodone HCl extended-release tablets)
NDA#	NDA 016636	Narcan (naloxone HCl)

*******For additional products refer to the Orange Book.*

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

Reference ID: 3597945

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

Reference ID: 3597945

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:

Study ONU3701: A Randomized, Double-blind, Placebo-controlled, Multicenter Trial with an Enriched Study Design to Assess the Efficacy and Safety of Oxycodone/Naloxone Controlled-Release Tablets (OXN) Compared to Placebo in Opioid-Experience Subjects with Moderate to Severe Pain due to Chronic Low Back Pain who Require Around-the-clock Opioid Therapy

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:

Reference ID: 3597945

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

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

Study ONU3701: A Randomized, Double-blind, Placebo-controlled, Multicenter Trial with an Enriched Study Design to Assess the Efficacy and Safety of Oxycodone/Naloxone Controlled-Release Tablets (OXN) Compared to Placebo in Opioid-Experience Subjects with Moderate to Severe Pain due to Chronic Low Back Pain who Require Around-the-clock Opioid Therapy

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

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

Investigation #1 !
!
IND # 070851 YES ☒ ! NO ☐
! Explain:

Investigation #2 !

Reference ID: 3597945

IND # YES ☐ ! NO ☐
! Explain:

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

Investigation #1 !
!
YES ☐ ! NO ☐
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 E. Basham, MS

Reference ID: 3597945

Title: Senior Regulatory Health Project Manager
Date: 7/7/14

Name of Office/Division Director signing form: Bob Rappaport, MD
Title: Director, DAAAP

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

Reference ID: 3597945

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
07/23/2014

BOB A RAPPAPORT
07/23/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205777 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: TARGINIQ ER Established/Proper Name: oxycodone HCl and naloxone HCl Dosage Form: extended-release tablets		Applicant: Purdue Pharma L.P. Agent for Applicant (if applicable):
RPM: Lisa Basham		Division: DAAAP

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: 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.

❖ Actions	
• Proposed action • User Fee Goal Date is July 23, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] 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.

Reference ID: 3600527

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 4
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☒ CDER Q&As ☒ Other - Blog and Fact Sheet
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Reference ID: 3600527

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date: APPROVAL 7/23/14
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	10/28/14 10/23/14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: ☐ None 2/26/14 DMPP/PLT (DRISK): ☐ None 6/25/14 OPDP: ☐ None 6/24/14 SEALD: ☒ None CSS: ☐ None In NDA review Other: ☐ None PMHS 6/20/14
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	505 (b)(2) Assessment 7/23/14 RPM Filing Review: 5/6/14 ☐ Not a (b)(2) 6/10/14
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

Reference ID: 3600527

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 5/28/14 If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	Yes
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 10/12/12
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 12/17/10
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 7/23/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 7/14/14
PMR/PMC Development Templates *(indicate total number)*	☐ None 9
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	6/19/14 (Filing: 11/18/13)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Page 15 of 6/19/14 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None DCRP 3/20/14 DBVII 3/25/14
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ N/A CSS 6/24/14 (Filing: 12/3/13) Stats Reviews: 2/11/14 (3) and

Reference ID: 3600527

	7/1/14 (2)
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	7/21/14 6/24/14 and 7/23/14 (amended) ☐ None DRISK: 7/22/14 OPDP: 4/7/14
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 6/9/14
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 6/16/14
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 6/18/14 (Filing: 11/4/13)
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 6/24/14 (Filing: 10/29/13)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 7/8/14
❖ ECAC/CAC report/memo of meeting	☐ None 6/12/14 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Reference ID: 3600527

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 6/18/14 (Filing 11/20/13)
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 1/15/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None Biopharmaceutics 6/16/14
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	CMC Review (6/18/14) – page 56
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 4/24/14 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per CMC review – page 7)

[5] 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.

Reference ID: 3600527

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

Reference ID: 3600527

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
07/28/2014

Basham, Lisa

From: Liao, Edward <Edward.Liao@pharma.com>
Sent: Wednesday, July 16, 2014 5:06 PM
To: Basham, Lisa
Subject: Re: Another PMR for your concurrence - TARGINIQ ER

Hi Lisa:
We accept the PMR.
Thanks.
Ed

On Jul 16, 2014, at 4:13 PM, "Basham, Lisa" <Lisa.Basham@fda.hhs.gov<mailto:Lisa.Basham@fda.hhs.gov>> wrote:

Hi Ed,

We recognize that you included an epidemiological study in your NDA submission to evaluate CV risk with OXN. However, there were substantial limitations of this study that impel us to require a PMR to further investigate this safety issue. First, the submitted study began in January 1, 2005, which is approximately four years prior to the October 2008 approval of OXN in the UK. Thus, for over 50% of the study time, no post-market data would have been available for OXN in the UK database. As such, the reliability of this data source for assessing CV safety of OXN is questionable, particularly because only 5% of the study patients were exposed to OXN (2600 exposed to OXN; 35636 exposed to extended release morphine, and 10,990 exposed to controlled release oxycodone). Furthermore, when there is a substantial imbalance in numbers of exposed patients between treatment groups in an observational study, usually statistical methods, such as use of propensity scores or other matching strategy, are implemented to deal with such imbalances to manage confounding. It does not appear that any such methods were used in this study.

Importantly, the PMR language states that an adequate number of patients must be treated for at least six months. We note that only 645 patients were treated in the study for this duration, and we would not deem that as an adequate number of patients. Additionally, we note that the study protocol indicated that patients with a history of cardiovascular disease were excluded from inclusion in the study. We do not think the study would be adequately generalizable if such patients were excluded (we note that based on the demographics table, it appears that a few patients with a history of CV disease were included, and it is not clear why, based on the exclusion criteria).

For these reasons we believe a PMR to assess the risk of serious CV thromboembolic events is warranted.

Thanks,
Lisa

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov<mailto:lisa.basham@fda.hhs.gov>

From: Liao, Edward [mailto:Edward.Liao@pharma.com]
Sent: Wednesday, July 16, 2014 11:12 AM
To: Basham, Lisa

Reference ID: 3594328

Subject: RE: Another PMR for your concurrence - TARGINIQ ER

Hi Lisa:
We have already conducted a study similar to the PMR requested. We refer to Module 5.3.5.3, Evaluation of Cardiovascular Events, Section 6 of the NDA. This section contains an epidemiologic study to evaluate the cardiovascular (CV) risk of OXN using the United Kingdom THE HEALTH IMPROVEMENT NETWORK (THIN) database. The study characterized the incidence rate of ischemic CV events, including MI, cerebrovascular accident, revascularization, angina, thrombosis, and death, in 49226 patients, including 2600 exposed to OXN, 35636 exposed to Morphine ER, and 10990 exposed to Oxycodone CR.

Given that this information is presented in the NDA, what is the rationale for this proposed PMR?

Thanks.
ed

From: Basham, Lisa [mailto:Lisa.Basham@fda.hhs.gov]
Sent: Tuesday, July 15, 2014 4:28 PM
To: Liao, Edward
Subject: RE: Another PMR for your concurrence - TARGINIQ ER

Hi Ed, Here are our responses to your questions:

For Question 1: The term “serious cardiovascular thromboembolic events” refers primarily to acute MI and ischemic stroke. If you want to consider related events (e.g., unstable angina, TIA) in the case definition for your study, you can provide a rationale for that in the protocol, and it will be a matter of review.

For Question 2: This PMR is unrelated to the other PMRs, therefore, we would prefer to have the final protocol submission milestone date be April 2015.

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov<mailto:lisa.basham@fda.hhs.gov>

From: Liao, Edward [mailto:Edward.Liao@pharma.com]
Sent: Tuesday, July 15, 2014 3:44 PM
To: Basham, Lisa
Subject: RE: Another PMR for your concurrence - TARGINIQ ER

Hi Lisa:
We are reviewing this PMR and will get back to you shortly.
We have 2 questions regarding this PMR:

Reference ID: 3594328

1. Can we get some clarity on how the Agency defines thromboembolic events in the PMR below. Does the Agency consider thromboembolic events to include deep vein thrombosis (DVT) and pulmonary embolism, or limited to ischemic cardiovascular events (major events such as stroke and MI or a more expansive category including angina, CABG, etc.). This will be important for study design since thromboembolic events are going to be more common than major CV events and the populations at higher risk are going to differ somewhat.

2. Can the timelines for this PMR match the timelines for the other PMRs – e.g., final protocol due 7/2015 instead of 4/2015?
Thanks.
ed

From: Basham, Lisa [mailto:Lisa.Basham@fda.hhs.gov]
Sent: Tuesday, July 15, 2014 2:23 PM
To: Liao, Edward
Subject: Another PMR for your concurrence - TARGINIQ ER
Importance: High

Hi Ed, One more PMR for you. Please respond as soon as possible indicating your concurrence.

A postmarketing observational cohort study comparing Targiniq ER to other drugs approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The study's outcome is serious cardiovascular thromboembolic events; a concise case definition should be provided. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to Targiniq ER-exposed patients. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in serious cardiovascular thromboembolic risk above the comparator background rate, using a pre-specified statistical analysis method. For the Targiniq ER-exposed and comparator(s)-exposed patients, the study drug initiation period should be clearly defined, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least six months of Targiniq ER exposure at the end of the study.

Final protocol submission: April 2015
Study completion: April 2019
Final study report: November 2019

Warm regards,

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov<mailto:lisa.basham@fda.hhs.gov>

Reference ID: 3594328

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/s/

LISA E BASHAM
07/16/2014

Basham, Lisa

From: Liao, Edward <Edward.Liao@pharma.com>
Sent: Monday, June 23, 2014 1:27 PM
To: Basham, Lisa
Subject: RE: TARGINIQ ER PMRs

Hi Lisa:
We agree with the PMRs for Targiniq ER.
Thanks.
ed

From: Basham, Lisa [mailto:Lisa.Basham@fda.hhs.gov]
Sent: Wednesday, June 18, 2014 3:40 PM
To: Liao, Edward
Subject: TARGINIQ ER PMRs

Hi Ed, The following are the PMRs that will be required of Purdue if TARGINIQ ER should be approved. Please indicate your concurrence. The PREA PMR dates changed slightly form those you proposed because we do not indicate the Study Initiation date but, rather, the Study Completion Date. We have not yet assigned a unique number to the PREA PMR. The other PMRs are those required of the class of ER/LA opioid products and will be numbered the same as those for the class.

Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of oxycodone hydrochloride/naloxone hydrochloride extended-release tablets in patients from ages 7 to less than 17 years pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Final Protocol Submission: December 31, 2014
Study Completion: December 31, 2018
Final Report Submission: June 30, 2019

2065-1 Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.

Reference ID: 3530301

b. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

The following timetable proposes the schedule by which you will conduct these studies:

Final Protocol Submission: 08/2014
Study Completion: 01/2018
Final Report Submission: 06/2018

2065-2 Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

2065-4 Conduct a study to define and validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

Reference ID: 3530301

2065-5 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

The following timetable proposes the schedule by which you will conduct this trial:

Final Protocol Submission: 08/2014
Trial Completion: 08/2016
Final Report Submission: 02/2017

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3530301

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/s/

LISA E BASHAM
06/23/2014

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, June 17, 2014 12:31 PM
To: edward.liao@pharma.com
Cc: Basham, Lisa
Subject: 6-17-14 Clinical request re: NDA 205777

Follow Up Flag: Follow up
Due By: Wednesday, June 18, 2014 1:00 PM
Flag Status: Flagged

Hi Ed. Please see the request below from the clinical team:

> **In the Deaths Section of the Postmarketing safety it is reported that there were 86 cases associated with a fatal outcome. In the Non-fatal SAEs sections it states that a total of 1090 postmarketing SAEs (970 nonfatal and 120 fatal) identified within the worldwide safety database for OXN received through 31-Dec-2012. Clarify whether there were 86 or 120 deaths. The 120-day Safety Update does not provide clarification.**

Please confirm receipt and let me know the timeline for response.

Regards,

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3527367

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/s/

LISA E BASHAM
06/18/2014

Basham, Lisa

From: Basham, Lisa
Sent: Thursday, June 12, 2014 3:16 PM
To: 'Liao, Edward'
Subject: RE: 6/10/14 clinical request TARGINIQ ER NDA 205777

Hi Ed,

Include " physical withdrawal symptoms" in the count in the OW Adverse Reactions table, and combine it with the "drug withdrawal syndrome" category. By splitting the two categories, the occurrence of drug withdrawal is underestimated. You may put an asterisk explaining the combined category.

Thanks,

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

From: Liao, Edward [mailto:Edward.Liao@pharma.com]
Sent: Thursday, June 12, 2014 10:03 AM
To: Basham, Lisa
Subject: RE: 6/10/14 clinical request TARGINIQ ER NDA 205777

Hi Lisa:
Below is our response to this clinical information request.
Please let me know if you have any additional questions. Please let me know if I should I file this response to the NDA.
Thanks.
ed

Table 3 of the proposed label indicates (b)(4) OXN-treated subjects with the adverse event of Drug Withdrawal Syndrome (preferred term). In addition there was (b)(4) OXN-treated subject with the adverse event of Withdrawal Syndrome (preferred term). Therefore, there were a total of (b)(4) OXN-treated subjects identified by the investigator as having opioid withdrawal during the double-blind period. However, since the table is based on preferred terms with frequency ≥ 2%, only the (b)(4) subjects with the adverse event of Drug Withdrawal Syndrome are included in the table.

The verbatim term reported by the investigator for the adverse event of Withdrawal Syndrome noted above was "(b)(4)." By convention, if the verbatim term did not indicate specific etiology (eg, opioid withdrawal, drug withdrawal, etc.) it was coded to the more general preferred term of Withdrawal Syndrome. The (b)(4) cases with the preferred term of Drug Withdrawal Syndrome were reported by the investigators with verbatim terms of opioid withdrawal or similar. Standard adverse event tables were generated using preferred terms as coded. We note

Reference ID: 3523883

that preferred terms relating to opioid withdrawal were combined in the ONU3701 CSR discussion of opioid withdrawal (Section 12.3.5.1), as well as in the Integrated Summary of Safety (Section 7.7.6) using the Standard MedDRA Query (SMQ) for drug withdrawal.

From: Liao, Edward
Sent: Thursday, June 12, 2014 8:56 AM
To: 'Basham, Lisa'
Subject: RE: 6/10/14 clinical request TARGINIQ ER NDA 205777

Hi Lisa:
Acknowleding receipt. We should have a response via email to you shortly.
Thanks.
ed

From: Basham, Lisa [mailto:Lisa.Basham@fda.hhs.gov]
Sent: Tuesday, June 10, 2014 1:17 PM
To: Liao, Edward
Subject: 6/10/14 clinical request TARGINIQ ER NDA 205777

Hi Ed, Please see the clinical request below:

In Table 3 of the proposed label, you report an incidence of 2% TARGINIQ-treated subjects in the double-blind period who experienced Drug withdrawal syndrome. Our calculation is 8/298 (3%). Explain the discrepancy.

Table 3. Incidence of Treatment-Emergent Adverse Events Reported in ≥ 2% of Subjects Taking TARGINIQ: Safety Population (Open-label Titration Period) and Randomized Safety Population (Double-blind Period)

	Open-Label Period	Double-blind Period	
MedDRA System Organ Class Preferred Term	**TARGINIQ (N=1095) (%)**	**Placebo (N=302) (%)**	**TARGINIQ (N=298) (%)**
Drug withdrawal syndrome	1	2	(b) (4)

Please acknowledge receipt and let me know your timeframe for response.

Thanks!

Lisa E. Basham, M.S.
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

Reference ID: 3523883

lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
06/12/2014

EXECUTIVE CAC MEETING MINUTES
Date of Meeting: June 10**, 2014**

Committee: Abby Jacobs, PhD, OND IO, Acting Chair
Paul Brown, PhD, OND IO, Member
Wendelyn Schmidt, PhD, DAIP, Alternate Member
R. Daniel Mellon, PhD, DAAAP, Supervisor
BeLinda A. Hayes, PhD DAAAP, Presenting Reviewer

Author of Draft: BeLinda A. Hayes, PhD

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 205777
Drug Name: Naloxone hydrochloride (b) (4)
Sponsor: Purdue Pharma, L.P.

Background:

Purdue Pharma, L.P. submitted NDA 205777 for Targiniq ER, an extended-release tablet formulation containing oxycodone hydrochloride and naloxone hydrochloride in a fixed 2:1 ratio for the management of (b) (4) pain (b) (4), around-the-clock (b) (4). The naloxone does not contribute to the efficacy; it is present only to deter abuse via the injection or insufflation route of abuse. The Applicant submitted final reports for the rat and mouse carcinogenicity studies conducted with naloxone. The ECAC evaluated a Special Protocol Assessment for the proposed 6-month mouse carcinogenicity study on January 18, 2010. The Applicant did not submit a Special Protocol Assessment for the 2-year rat carcinogenicity study.

Mouse Carcinogenicity Study

In a 26-week carcinogenicity study, Tg.rasH2 mice were orally administered naloxone hydrochloride (b) (4) at dose levels of 25, 75, and 200 mg/kg/day by gavage in sterile water for injection. Naloxone showed no evidence of oncogenic potential. The positive control was urethane, which produced the types and frequencies of tumors expected in this model. The study appeared to be valid and no clinically significant drug-related neoplastic findings occurred under the study conditions.

Rat Carcinogenicity Study

In a 2-year rat carcinogenicity study, Sprague-Dawley rats (60/sex/group) were orally administered naloxone hydrochloride (b) (4) via the diet at doses of 0 (Control 1), 0 (Control 2), 4, 20, and 100 mg/kg/day. Naloxone HCl administered at a dose of 100 mg/kg/day produced excessive mortality with the survival rate in males beginning to decline early. All naloxone-treated male rats were terminated early during Week 101 when the surviving animals in Control Group 1 were reduced to 20 animals. Mortality in females was not altered by the treatment. There were no statistically significant dose-related trends in neoplastic findings (both common and rare neoplasms) observed in either male or female rats. The FDA statistics reviewer concluded that there was no treatment-related mortality in either sex.

The study appeared to be valid and no clinically significant drug-related neoplastic findings occurred under the study conditions.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee concurred that the study was valid and acceptable.
- The Committee concurred that there were no drug-related neoplasms in the study.

Mouse:

- The Committee agreed that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

Abby Jacobs, PhD
Acting Chair, Executive CAC

cc:\
/Division File, DAAAP
/R.D. Mellon, DAAAP
/B.A. Hayes, DAAAP
/L. Basham/PM, DAAAP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
06/12/2014

ABIGAIL C JACOBS
06/12/2014

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, June 10, 2014 1:17 PM
To: edward.liao@pharma.com
Subject: 6/10/14 clinical request TARGINIQ ER NDA 205777

Hi Ed, Please see the clinical request below:

In Table 3 of the proposed label, you report an incidence of 2% TARGINIQ-treated subjects in the double-blind period who experienced Drug withdrawal syndrome. Our calculation is 8/298 (3%). Explain the discrepancy.

Table 3. Incidence of Treatment-Emergent Adverse Events Reported in ≥ 2% of Subjects Taking TARGINIQ: Safety Population (Open-label Titration Period) and Randomized Safety Population (Double-blind Period)

	Open-Label Period	Double-blind Period	
MedDRA System Organ Class Preferred Term	**TARGINIQ (N=1095) (%)**	**Placebo (N=302) (%)**	**TARGINIQ (N=298) (%)**
Drug withdrawal syndrome	1	2	(b) (4)

Please acknowledge receipt and let me know your timeframe for response.

Thanks!

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3521923

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/s/

LISA E BASHAM
06/10/2014

PeRC PREA Subcommittee Meeting Minutes
May 28, 2014

PeRC Members Attending:
Robert Nelson
Jane Inglese
Rosemary Addy
Hari Cheryl Sachs
Wiley Chambers
Tom Smith
Peter Starke
Gregory Reaman
Daiva Shetty
Kristiana Brugger
Ruthanna Davi
Freda Cooner
Lily Mulugeta
Maura O'Leary
Dianne Murphy
Michelle Roth-Cline

Agenda

NDA	205777	Targiniq ER (oxycodone and naloxone) Partial Waiver_Deferral_Plan	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Targiniq ER (oxycodone and naloxone) Partial Waiver_Deferral_Plan

- NDA 205777 seeks marketing approval for Targiniq ER (oxycodone and naloxone) for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
- The application triggers PREA as a new active ingredient.
- The application has a PDUFA a goal date of July 23, 2014.
- *PeRC Recommendations:*
    - The PeRC agreed with a partial waiver for pediatric patients aged birth to less than 7 years because studies would be impossible or highly impracticable.
    - The assessment that studies would be impossible or highly impracticable depends on factors such as the size and complexity of the pediatric studies that would be required for adequate labeling. The PeRC recommended that the Division evaluate how much data would be needed to label this product for pediatric patients down to 2 years of age, and consider as a matter of policy whether this and other similar products could be studied and then labeled for pediatric patients of this age.
    - The PeRC agreed with a deferral for pediatric patients aged 7 to 17 years because adult studies have been completed and the product is ready for approval.

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/s/

JANE E INGLESE
06/09/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205777

GENERAL ADVICE

Purdue Pharma L.P.
Attention: Edward Liao, Pharm.D.
Director, Regulatory Affairs
One Stamford Forum, 201 Tresser Blvd
Stamford CT 06901-3431

Dear Dr. Liao:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Targiniq (oxycodone hydrochloride/ naloxone hydrochloride Extended-release Tablets, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg.

We have the following comments:

> Your application referenced the Drug Master File (DMF) (b) (4), for Naloxone hydrochloride. This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on June 3, 2014.

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796 4013.

Sincerely,

{See appended electronic signature page}

Eric P. Duffy, Ph.D.
Division Director
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ERIC P DUFFY
06/04/2014

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, June 04, 2014 4:20 PM
To: edward.liao@pharma.com
Subject: Targiniq ER: Requested revisions to subsection 9.2 Abuse; Abuse Deterrence Studies

Hi Ed, Below are some requests for revision to subsection **9.2 Abuse; *Abuse Deterrence Studies*** of the proposed PI for TARGINIQ ER.

1. Revise Figure 1 of the proposed PI to reflect that Subject 0091169 had a 0 percent reduction in Drug Liking VAS. In the intranasal study (ONU1003, Session 2) , Subject 0091169 had Emax of Drug Liking VAS of 51, 100, and 100 for ONU40/20 mg, Oxy API 40 mg, and placebo, respectively. Because the subject had Emax of 100 to placebo, based on the calculation formula provided by Chen, Klein and (b) (4) at the 74th CPDD annual meeting, this subject should have 0 percent reduction.

2. Revise Figure 2 of the proposed PI to include Subject 0001155 in the analysis of percent reduction for Emax of Drug Liking VAS considering that this subject is within the completers population and that the analysis of percent reduction should be based on the completers population. In the intravenous study (ONU1003, Session 3), Subject 0001155 had Emax for Drug Liking VAS of 50, 0, and 100 for the positive control (oxycodone 0.07 mg/kg), placebo, and the test drug (oxycodone + naloxone 0.07/0.035 mg/kg), respectively. You may assign a big negative percent reduction, say -999, to this subject in order to include this subject in Figure 2.

3. Revise Table 6 of the proposed PI to include subject 0001016 in the analysis of Emax of Drug Liking for OXY API treatment in Study ONU1008. Although this subject experienced emesis 73 minutes after dosing with OXY API, for the Drug Liking VAS, the subject had already reached Emax (93) at 0.5 hours. Therefore there does not appear to be a reason to exclude this subject. Redo Table 6 to reflect the use of 29 subjects across all treatments in ONU1008.

4. Revise Figure 3 of the proposed PI to include subjects 0001006, 0001079, and 0001108 in the analysis of percent reduction of Emax of Drug Liking VAS. These subjects were part of the completers population in study ONU1008. As noted under bullet 2 above, in the case of having zero in the denominator when calculating the percentage reduction, you may assign a big negative percent reduction to these three subjects.

Reference ID: 3518974

5. Change the last category on the x-axis from [redacted] (b) (4) to " ≥100" for Figures 1, 2, and 3.

6. Modify tables 4, 5, and 6 of the proposed PI by replacing [redacted] (b) (4) [redacted] (b) (4) by standard errors (SE).

Please confirm receipt and provide a timeframe for response. For this request and the one yesterday pertaining to section 12.3, it may make the most sense to simply send WORD documents containing these sections only. We can then cut and paste into our working label, which is currently under revision. Let me know if that makes sense to you too.

Regards,

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3518974

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/s/

LISA E BASHAM
06/04/2014

Basham, Lisa

From:	Basham, Lisa
Sent:	Tuesday, June 03, 2014 5:07 PM
To:	edward.liao@pharma.com
Subject:	TARGINIQ ER draft labeling Section 12.3 for your review and comment
Attachments:	Clinical Pharmacology 12 3 Pharmacokinetics Labeling.docx; Clinical Pharmacology 12 3 Pharmacokinetics Labeling sent 6-3-14.pdf

Hi Ed, Attached are our proposed changes to section 12.3 of the label for TARGINIQ ER. Please respond within a week, if possible. Accept any changes that you agree with and track any additional changes/additions. We will send the rest of the label for your consideration when it is ready.

Please let me know when you expect to be able to return this section of the label with your proposed edits/additions.

Warm regards,

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

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

Reference ID: 3518004

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/s/

LISA E BASHAM
06/03/2014

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, May 28, 2014 3:04 PM
To: edward.liao@pharma.com
Subject: Comments on NDA 205777 Proposed pediatric plan

Hello, Ed,

Your proposed pediatric plan is acceptable.

Provide the following in the final protocol for your proposed PK/safety study in pediatric patients ages 7-17 years of age:

1. The opioid conversion table which will be used during the open-label conversion and titration period of the study

2. An OXN conversion table and a taper schedule for how patients are to be either transitioned from study drug OXN to pre-study opioid, or tapered off OXN if they no longer require analgesia

3. A list of acceptable rescue analgesics and how dosing will be determined

4. Details of the safety assessments and their timing

Additional comments may be forthcoming upon review of the final protocol.

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3514191

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/s/

LISA E BASHAM
05/28/2014

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, May 20, 2014 3:09 PM
To: edward.liao@pharma.com
Subject: Clinical/Stats request re: study ONU 1008 for NDA 205777

Hi Ed, Please respond ASAP to the following request pertaining to Study ONU 1008:

1. Provide the formula you used to calculate the percentage reduction
2. Provide the SAS code for the percentage reduction analysis
3. There are 29 completers in the study (protocol page 47). Clarify why only 26 subjects were included in the percentage reduction analysis in the Figure 3 of labeling.

Please confirm receipt and provide an estimated timeline for your response.

Kind regards,

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3510053

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/s/

LISA E BASHAM
05/20/2014

Basham, Lisa

From: Basham, Lisa
Sent: Thursday, May 15, 2014 4:24 PM
To: edward.liao@pharma.com
Subject: Targiniq ER C&C label comments

Hi Ed, Please see the requested revisions below for the Carton and Container labels for TARGINIQ ER:

A. Ensure that the approved USAN established name is at least ½ the size of the proprietary name per *21 CFR 201.10(g)(2)*.

B. Add the unit of measure, milligram (mg), to the oxycodone hydrochloride component of the strength statement as this is important information that must be displayed and omission may pose confusion as to the amount of ingredient per tablet.

C. Remove the [redacted] (b) (4) from the principal display panel as it will reduce clutter and redundancy with information already contained on the side panel.

D. Relocate the Medication Guide statement to the lower third portion of the principal display panel (PDP) and remove the red-lined box from around the Medication Guide Statement so it does not compete with more important information on the PDP.

Let me know when we can expect submission of revised C&C labels.

Thanks!!

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3507721

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/s/

LISA E BASHAM
05/15/2014

Basham, Lisa

From: Basham, Lisa
Sent: Friday, May 09, 2014 12:17 PM
To: edward.liao@pharma.com
Subject: 5-9-14 clinical request for Targiniq ER

Hi Ed, Please see the clinical request below:

On page 149 of CSR ONU3701, Table 38, clarify whether this table represents subjects who: 1) discontinued study drug and stayed in the study, 2) discontinued study drug and discontinued the study simultaneously, or 3) both categories. Explain where in the submission an AE incidence summary table may be found for these different categories of discontinuation. If such a table is not already included in the submission, please provide one to identify discontinuation AEs for the various discontinuation outcomes by treatment period.

Please confirm receipt and expected timeline for response.

As always, many thanks,

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3504206

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/s/

LISA E BASHAM
05/09/2014

Basham, Lisa

From: Basham, Lisa
Sent: Friday, May 09, 2014 4:33 PM
To: edward.liao@pharma.com
Subject: 5-9-14 clinical request #2

Hi Ed, One more.

In accordance with the February 2013 guidance, *Financial Disclosure by Clinical Investigators*, which states that, "For purposes of this part, an applicant must submit a list of all clinical investigators who conducted covered clinical studies…… identifying those clinical investigators who are full-time or part-time employees of the sponsor of each covered study." You have identified the investigators in your Financial Certification and Disclosure form. Although you acknowledge on the form that no investigators had a financial interest or conflict, you must clarify and clearly designate whether any clinical investigator for the covered clinical studies was a full or part-time employee.

Please confirm receipt and timeline for response.

Thanks and have a great weekend!

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3504475

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/s/

LISA E BASHAM
05/09/2014

Basham, Lisa

From: Basham, Lisa
Sent: Thursday, May 01, 2014 3:19 PM
To: edward.liao@pharma.com
Subject: 5-1-14 Clinical Request for NDA 205777 TARGINIQ ER

Hi Ed, See the clinical request below:

Our internal analysis of TEAEs >/= 2% differs from those in Table 3 of the proposed label for the following MedDRA PTs:

	Double Blind			
	Placebo		OXN	
MedDRA Preferred Term	Agency N=302 (%)	Sponsor N=302 (%)	Agency N=299 (%)	Sponsor N=298 (%)
Headache	6	3	6	3
Nausea	9	5	12	8

Provide a possible explanation for these discrepancies.

Please confirm receipt and let me know the timeframe for response.

Thanks!

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3499452

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/s/

LISA E BASHAM
05/01/2014

Basham, Lisa

From: Basham, Lisa
Sent: Friday, April 25, 2014 1:15 PM
To: edward.liao@pharma.com
Subject: 4-25-14 Clinical Information Request

Hi Ed, Please see the inquiry below re: Targiniq ER.

Clarify why Table 1 *(Conversion Factors of Oral Opioid Analgesics to TARGINIQ Opioid Conversion Factor)* in the proposed label is different from the conversion table used in the key efficacy study, ONU3701 and why you reference your Strategy for Converting to OXN and OxyCR document in Section 2.1 [Initial Dosing, page 5] of the annotated label instead of referencing the conversion table used in Study ONU3701.

Please confirm receipt and estimated time for response.

Have a great weekend!

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3496007

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/s/

LISA E BASHAM
04/25/2014

Basham, Lisa

From: ees_admin@fda.gov
Sent: Thursday, April 24, 2014 4:09 PM
To: Godwin, Francis; Pinto, Julia; Basham, Lisa; Rivera, Luz E (CDER); Salganik, Maria*; Spain, Nancy *; Kyada, Yogesh*
Subject: Overall OC Recommendation NDA 205777/000 Decision: ACCEPTABLE, Decision Date: 04/24/2014, Re-evaluation Date: 03/21/2015

This is a system generated email message to notify you that the
Overall Compliance Recommendation has been made for the above Application.

For general questions about how to use EES in your work, send
an email to EESQUESTIONS (EESQUESTIONS@cder.fda.gov).
To contact the EES technical staff, send an email to
CDER EES Help (EESHELP@fda.hhs.gov). Thank you.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205777 **INFORMATION REQUEST**

Purdue Pharma L.P.
Attention: Edward Liao, Pharm.D.
Director, Regulatory Affairs
One Stamford Forum, 201 Tresser Blvd
Stamford CT 06901-3431

Dear Dr. Liao:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Targiniq (oxycodone hydrochloride naloxone hydrochloride) Extended Release Tablets, 10/5 mg, 20/10 mg, and 40/20 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information requests. We request a written response by **Monday, April 28, 2014,** in order to continue our evaluation of your NDA.

1. Submit revised acceptance specification sheets for naloxone hydrochloride drug substance (supplied by [redacted] (b) (4)) and oxycodone hydrochloride drug substance (supplied by [redacted] (b) (4)) to tighten the proposed acceptance criteria for impurities as follow.

   a. Refer to Specification numbers QS-302217:4 and QS-302959:2, for naloxone hydrochloride. The proposed acceptance criteria for [redacted] (b) (4) [redacted] (b) (4) of NMT [redacted] (b) (4) %, for controls of drug substance from each supplier, are above the ICH Q3A – recommended qualification level of NMT [redacted] (b) (4) %. Tighten the limits to reflect the drug substance stability data.

   b. Refer to Specification number Refer QS-5400:30, for oxycodone hydrochloride. The proposed acceptance criterion for [redacted] (b) (4) impurity of NMT [redacted] (b) (4) % is above the ICH Q3A – recommended qualification level of NMT [redacted] (b) (4) %. Tighten the limit to reflect the drug substance stability data. In addition, tighten the acceptance criterion for total impurities to reflect the drug substance stability data.

2. Submit revised specification sheets for drug product to encompass the release and stability testing on one specification sheet. Specify which attributes are tested on stability and denote any differences in acceptance criteria or methods for stability testing. In addition, include the following changes.

a. Tighten the acceptance criteria for individual and total impurities to reflect the release and stability data obtained for drug product batches representative of the to-be-marketed products. We note that the currently proposed limits substantially exceed the ICHQ3B-recommended qualification thresholds for daily doses above [redacted] (b) (4).

b. Include the release and stability testing for [redacted] (b) (4) as requested in Agency letter dated December 6, 2013. We note that the [redacted] (b) (4) results were not submitted with stability data intended to support the to-be-marketed product. The preliminary data for [redacted] (b) (4) submitted for batches which were tested under "special stability studies" (refer to NDA amendment dated January 22, 2014) may serve as a database for establishing the interim acceptance criteria for the [redacted] (b) (4).

3. Provide statistical evaluation with graphic charts for drug product stability batches which are representative of drug products proposed for marketing, e.g., three recently manufactured batches for each strength. Include data for assays, individual and total impurities, and dissolution. In addition, include data and statistical analysis for the [redacted] (b) (4), if available for the recently manufactured batches.

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796 4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
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
04/10/2014

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, April 01, 2014 2:31 PM
To: edward.liao@pharma.com
Subject: 4-1-14 clinical information request for NDA 205777

Hi, Ed, Please see the request below form the clinical team.

1. We note that Section 6 (Adverse Reactions) section of the label does not include information regarding the incidence of ARs which occurred with an incidence ≥1% and <2%. Include these less common ARs in the label.

2. Describe the prescribing patterns for the EU marketed oxycodone/naloxone product compared to that of OxyContin where both are available, since the approval of oxycodone/naloxone.

Regards,

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3481624

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/s/

LISA E BASHAM
04/01/2014

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, March 26, 2014 4:51 PM
To: edward.liao@pharma.com
Subject: 3-26-14 Request for carc datasets (NDA 205777)

Hi Ed,

See the request below from the statistician reviewing the carcinogenicity studies for NDA 205777.

Please submit ASAP the data of tf and ex domains for rat carcinogenicity study review.

Thanks!

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3478169

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/s/

LISA E BASHAM
03/26/2014

Basham, Lisa

From: Basham, Lisa
Sent: Monday, March 17, 2014 2:08 PM
To: edward.liao@pharma.com
Subject: 3-17-14 Clinical Information Request NDA 205777

Hi Ed, See the clinical information request below.

Provide a table with the total number of OXN deaths grouped by study (specifically separate core studies from extension studies) identified by patient ID, regardless of causality assignment. Provide a separate table with these same variables for the non-OXN deaths. Clarify and reconcile whether the completed tables are consistent with the Individual Subject Narratives' table provided in the ISS Appendix 17.5 and Studies OXN2001/OXN2001S Supplement, as the Supplement contains corrected information not included in the original OXN2001 and OXN2001S clinical study reports.

Thanks!

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
03/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205777 **INFORMATION REQUEST**

Purdue Pharma L.P.
Attention: Edward Liao, Pharm.D.
Director, Regulatory Affairs
One Stamford Forum, 201 Tresser Blvd
Stamford CT 06901-3431

Dear Dr. Liao:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxycodone hydrochloride/ Naloxone hydrochloride Tablets, 10/5, 20/10, and 40/20 mg.

We are reviewing the Biopharmaceutical section of your submission and have the following information requests. We request a written response by **Friday, March 28. 2014,** in order to continue our evaluation of your NDA.

- You have not provided data to support the Level (b)(4) manufacturing site change and the Level (b)(4) drug product batch scale-up for the 20/10 mg strength. Provide dissolution profile comparison data along with f2 values between the 20/10 mg and 40/20 mg strengths in the following media (pH 1.2, 2.5, 4.5, 6.8).

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796 4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
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
03/12/2014

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, March 11, 2014 6:03 PM
To: edward.liao@pharma.com
Subject: 3-11-14 Stats questions NDA 205777

Hi Ed, See the questions/requests below from the stats reviewer for Targiniq ER.

1. On page 55 of protocol [redacted] (b) (4), you used log transformation for the modeling. Placebos are all equal to zero in this study and log (0) is negative infinity. Clarify how you handled this situation, and provide the SAS code for the primary analysis.
2. Clarify why ALO-[redacted] (b) (4) Drug Liking VAS values are not integers.
3. Provide the time point for calculating E_{max}, such as 8 hours, 12 hours, or 24 hours post-dose.
4. [redacted] (b) (4)
5. In the proposed labeling Tables 3 and 5, you use Mean (SE). Clarify why you use SE (Standard Error) instead of SD (Standard Deviation).
6. Provide the percentage reduction formula you used for E_{max} of Drug liking VAS and Drug High VAS.
7. Study 4 (ALO-[redacted] (b) (4)) used a unipolar VAS scale for drug liking, while Studies 1, 2, and 3 used a bipolar VAS scale. In the proposed labeling, Figure 1, you compared all four studies in one plot. Provide a rationale to explain why this is appropriate.

Please confirm receipt.

Many thanks!

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3469198

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/s/

LISA E BASHAM
03/11/2014

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, March 05, 2014 4:13 PM
To: edward.liao@pharma.com
Subject: NDA 205777 3-5-14 Information Request

Hi Ed, please see our review comment and information requests below:

Based on the information provided to date, you have concluded that there are insufficient data to support dosing above 80 mg oxycodone/40 mg of naloxone per day via your drug product. However, you have not provided any data to support that Targiniq ER should not be used at higher daily doses. We note that all currently approved single-entity oxycodone drug products have no maximum daily dose listed in the drug product labeling. Therefore in the absence of data to support the proposed dosing limit, we will use the maximum theoretical daily dose of 1.5 grams of oxycodone (750 mg of naloxone) per day that is applied to extended-release oxycodone products. Therefore, you must address the following concerns as soon as possible:

1) Revise your drug product degradant specifications to NMT (b) (4)% or (b) (4) TDI, whichever is lower, based on the MTDD of 1.5 grams of oxycodone per day. If you cannot meet these specifications, provide adequate safety data to qualify these degradants at the proposed specifications of NMT (b) (4)%. Adequate safety qualification data must include a minimal genetic toxicology screen (one in vitro bacterial mutation assay and one in vitro assay for genetic damage) and a 90-day repeat-dose toxicology study in a single species, unless otherwise justified.

2) Submit safety justification for all excipients when the drug product is consumed up to the MTDD of 1.5 grams of oxycodone. Your toxicological risk assessment should include copies of all cited publications and specifically address any novel excipients as per the FDA guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf.

3) Submit a reasonably aggressive time-line and plan for reducing the specification of (b) (4) (b) (4) to NMT (b) (4) based on the MTDD of this drug product. Alternatively, you may propose to conduct additional weight-of-evidence genetic toxicology studies for this drug substance impurity to qualify this as non-genotoxic.

Regards,

Lisa E. Basham, M.S.
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

Reference ID: 3465688

lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
03/05/2014

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, February 19, 2014 5:07 PM
To: edward.liao@pharma.com
Subject: 2-19-14 Clinical Info Request NDA 205777
Attachments: NDA 205777 Clinical IR - Tables OW and Analgesic Effect (F).pdf

Hi Ed,

Please see the request below from the clinical team for NDA 205777.

1. We note that in your pooled analyses, you have pooled the three studies of special groups and situations (Studies OXN1006, OXN1007 and OXN1017) with the four abuse potential studies as Additional Studies in Group C. Provide pooled safety data for the three special groups and situations studies with Group B (Clinical Pharmacology Phase 1 studies**).** In addition, provide pooled safety data for extension studies OXN3001S and OXN3006S separate from OXN3401S and OXN4502.

2. With regard to your analyses of Opioid Withdrawal, the following information is needed, provided in tables such as the ones attached for Studies ONU3701, ONX3401, OXN3001, OXN3006 and OXN3503.

Please confirm receipt and let me know when we can expect your response. Thank you!

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3456866

Study ONU3701 Open Label Titration Period Table

Previous Opioid	# Subjects	N (%) Subjects Discontinued due to Opioid Withdrawal (OW)	N (%) Subjects Discontinued due to Lack of Effect (LOE)
OxyCR			
Not OxyCR			

Study ONU3701 Randomized Withdrawal Period Table

Treatment Group	N (%) Discontinued due to Opioid Withdrawal (OW)	N (%) Discontinued due to Lack of Effect (LOE)	N (%) with ≥3 Preferred Terms potentially related to OW (DSM IV)
OXN			
Placebo			

Same table as above for the remainder of the Double-blind period for Study ONU3701

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/s/

LISA E BASHAM
02/19/2014

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, January 14, 2014 4:46 PM
To: edward.liao@pharma.com
Subject: 1-14-14 clinical request for NDA 205777

Hi Ed,

Please see the clinical request below for NDA 205777:

1. **Provide your rationale and cite supporting documents for limiting the dose of Oxycodone/Naloxone to 80/40mg daily (40/20mg q 12 hours).**
2. **Identify studies in the NDA in which subjects received dosing >80/40mg per day.**

Please confirm receipt.

Thanks!

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3436509

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/s/

LISA E BASHAM
01/14/2014

Basham, Lisa

From: Basham, Lisa
Sent: Friday, December 13, 2013 4:11 PM
To: edward.liao@pharma.com
Subject: Targiniq ER pediatric studies

Hi Ed,

We cannot grant a full waiver of pediatric studies for Targiniq ER as you requested. Because it is a new combination product, it triggers PREA, and pediatric studies are required. Submit a pediatric plan that includes the following:

1. Request for a waiver for studies in pediatric patients 6 years and younger because the population of patients with chronic pain requiring around the clock opioid treatment in the age group is too small to study.
2. A safety and PK study in patients ages 7 to 17 years
3. A timeline for the safety/PK study that includes the date of final protocol submission, study start, and submission of final study report to the Agency.

Refer to the draft guidance for industry, *How to Comply with the Pediatric Research Equity Act*, located at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079756.pdf,
for additional information on how to request waivers and deferrals.

Regards,

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3422171

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/s/

LISA E BASHAM
12/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205777

INFORMATION REQUEST

Purdue Pharma L.P.
Attention: Edward Liao, Pharm.D.
Director, Regulatory Affairs
One Stamford Forum, 201 Tresser Blvd
Stamford CT 06901-3431

Dear Dr. Liao:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxycodone hydrochloride/ Naloxone hydrochloride Tablets, 10/5, 20/10, and 40/20 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information requests. We request a written response by **Tuesday, December 24, 2013** in order to continue our evaluation of your NDA.

- (b) (4)

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796 4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
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
12/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205777

FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED

Purdue Pharma, L.P.
One Stamford Forum
Stamford, CT 03901-3431

Attention: Edward Liao, PharmD
Director, Regulatory Affairs

Dear Dr. Liao:

Please refer to your New Drug Application (NDA) dated September 22, 2013, received September 23, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride extended-release) Tablets.

We also refer to your amendments dated October 14, 21, 22, 25, 28, 30, and 31 and November 26, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 23, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 26, 2014.

Although you have requested a Priority review classification for this application, this application has been designated a Standard review classification. According to CDERs MANUAL OF POLICIES AND PROCEDURES (MAPP) 6020.3 Rev. 2, Designation Policy: Priority (P) and Standard (S):

- Priority review designation is assigned to applications for drugs that treat serious conditions and provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to available therapies.

- A priority review designation is intended to direct overall attention and resources to the evaluation of applications for drugs that, if approved, provide significant improvements to public health as noted above.

- Standard review designation is assigned to applications for drugs that do not meet the priority review designation criteria.

Upon initial review of this application, we have concluded that it is not possible to determine whether Targiniq ER, if approved, would provide abuse-deterrent features of at least comparable benefit to available therapies based on the information provided. The human abuse liability studies conducted in support of this application have not compared the abuse-deterrent features of Targiniq ER to those of the approved, extended-release oxycodone product, OxyContin. Therefore, while we have determined that you have submitted sufficient information to permit filing of this application, it has been assigned a Standard review classification.

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

> Upon review of your proposed drug substance specification for [redacted] (b) (4), we note that you have proposed a maximum daily dose (MDD) of NMT 40 mg of naloxone via this drug product. A review of your justification for this proposed MDD is necessary before we can concur with your proposal, as the maximum theoretical daily dose for oxycodone of 1500 mg via this drug product would result in a MDD of 750 mg of naloxone. This clearly has an impact on the drug substance (DS) and drug product (DP) specifications. Agreement on the final DS and DP specifications will be based, in part, on review of your clinical justification. Further, we note that you have concluded that, based on current manufacturing capability, a specification of NMT [redacted] (b) (4) [redacted] (b) (4) for [redacted] (b) (4) is the lowest feasible level. This will also require review. If we do not agree with your analysis of the data, we will engage you in further discussions to determine the final specifications, the need to tighten the proposed specification, or the need for post-marketing studies to adequately qualify the genotoxic potential of [redacted] (b) (4).

We are providing the above comment to give you preliminary notice of a <u>potential</u> review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Provide Certificates of Analyses from all suppliers for all batches of drug substances and drug products used in the toxicology and clinical studies. Provide a comparative table indicating which batches of drug substance correspond to which batches of drug product and which batches were used for toxicology, clinical, and stability studies, respectively. Also provide corresponding Purdue batch numbers for each of the Supplier Batch numbers.

2. Update the specifications to include release and stability testing of the drug product for (b) (4) per USP <921>.

3. It appears that for some subjects in Study ONU3701 the actual treatment received in the double-blind period was different from the randomized (planned) treatment. In addition, the study report mentioned that some subjects might have been randomized twice. Provide an explanation or clarification along with any relevant documentation for these randomization issues.

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

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a (b) (4) waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the (b) (4) waiver request is denied and a pediatric drug development plan is required.

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, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BOB A RAPPAPORT
12/06/2013

Rivera, Luz E (CDER)

From: Rivera, Luz E (CDER)
Sent: Tuesday, November 26, 2013 3:47 PM
To: edward.liao@pharma.com
Subject: NDA 205777

Good afternoon Dr. Liao,

We are reviewing your NDA 205777 and request additional information to continue our evaluation.

You propose waiving microbial limits release testing for your drug product. This proposal may be acceptable provided adequate (b) (4) are established and documented. More information on your process is needed. Address the following points.

1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product, including all aspects of the tablet coating process.
2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
3. Describe activities taken when microbiological acceptance criteria are not met at control points.
4. Provide the results of microbial limits testing performed on exhibit or stability batches of the drug product.
5. You should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule and microbial limits specifications for stability to reflect this testing.
6. Commit to performing microbial limits testing annually as part of the post-approval stability protocol

Please submit the information requested by email to me (Luz.E.Rivera@fda.hhs.gov) and officially submit to the application.

Please acknowledge the receipt of this request

Thank you,
Luz E Rivera, Psy.D.
LCDR, US Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ ONDQA
Division of New Drug Quality Assessment III
luz.e.rivera@fda.hhs.gov
301 796 4013

Reference ID: 3413786

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/s/

LUZ E RIVERA
11/26/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 070851
NDA 205777

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Purdue Pharma L.P.
One Stamford Forum
201 Tresser Blvd.
Stanford, CT 06901-3431

ATTENTION: Edward Liao, Pharm.D.
Director, U.S. Regulatory Affairs

Dear Mr. Liao:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act, and your New Drug Application (NDA) dated September 22, 2013, received, September 23, 2013, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxycodone Hydrochloride / Naloxone Hydrochloride Controlled-Release Tablets, 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg.

We also refer to:

- your correspondence to your IND, submitted and received May 2, 2013, requesting review of your proposed proprietary name, Targiniq;

- your amendment to the above referenced May 2, 2013 correspondence, submitted and received on October 16, 2013, in which you amend the proposed proprietary name from Targiniq to Targiniq ER, as recommended; and

- your correspondence to your NDA submitted and received on October 22, 2013, requesting review of your proposed proprietary name, Targiniq ER.

We have completed our review of the proposed proprietary name, Targiniq ER and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your October 22, 2013 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 Vaishali Jarral, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4248. 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}

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

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/s/

CAROL A HOLQUIST
10/28/2013

Basham, Lisa

From: Basham, Lisa
Sent: Friday, October 25, 2013 7:23 PM
To: edward.liao@pharma.com
Subject: 10/25/13 CMC request for NDA 205777

Hi, Ed! Please see the request below from our product quality reviewers for NDA 205777.

1. *Module 3 of your NDA is not complete. Provide a statement referencing the API Manufacturing Process and Process Controls, for each API, to the respective DMFs, in Section 3.S.3 Provide data on the API Container Closure System in section 3.S.4. for each of the APIs. Provide a Statement referencing the stability data for each API, to the respective DMFs in Section 3.S.5.*

2. *Provide a Statement that all Manufacturing and Testing facilities are ready for Inspection.*

Thank you!

Lisa

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3396886

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/s/

LISA E BASHAM
10/25/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205777 **INFORMATION REQUEST**

Purdue Pharma L.P.
Attention: Edward Liao, Pharm.D.
Director, Regulatory Affairs
One Stamford Forum, 201 Tresser Blvd
Stamford CT 06901-3431

Dear Dr. Liao:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxycodone hydrochloride/ Naloxone hydrochloride Tablets, 10/5, 20/10, and 40/20 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information requests. We request a written response by **Wednesday, October 9, 2013** in order to continue our evaluation of your NDA.

- Clarify the exact responsibilities and operations being carried out at both the (b) (4) (b) (4), for both the Drug Substance and Drug Product. Clarify whether these respective responsibilities and operations are for the drug substance, drug product, excipient, or process intermediate.

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796 4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
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
10/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205777

NDA ACKNOWLEDGMENT

Purdue Pharma, L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Edward Liao, Pharm.D.
Director, Regulatory Affairs

Dear Dr. Liao:

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

Name of Drug Product: oxycodone hydrochloride/naloxone hydrochloride controlled-release tablets

Date of Application: September 23, 2013

Date of Receipt: September 23, 2013

Our Reference Number: NDA 205777

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 22, 2013, 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:
http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website
http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 205777** submitted on September 23, 2013, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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, Analgesia, and Addiction 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.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

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, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LISA E BASHAM
10/02/2013

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, October 02, 2013 1:37 PM
To: edward.liao@pharma.com
Subject: 10/2/13 OSI request re: NDA 205777

Hi Ed, See the request below from the Office of Scientific Investigations.

OSI appreciates your submission of the clinsite.xpt data (Site Level Dataset) for use in CDER's Clinical Site Selection Tool. The provided data could not be utilized in the Tool, however, because the TRTEFFR and TRTEFFS variables were reported based on overall study means by arm, rather than individual site by arm. We request that you provide a revised clinsite.xpt dataset that includes:

1. Data for only Studies ONU3701, OXN3001, OXN3006, OXN3401, and OXN3503

2. TRTEFFR and TRTEFFS variables reported by arm, by site

3. Full data for sites identified in the provided Reviewer's Guide, which are noted as having been excluded from the integrated aand individual study analyses (Study ONU3701: Site 2214A, Study OXN3006: Sites 0749A and 1028A, Study OXN3401: Site 0699A, and Study OXN3503: Site 1698A)

Thanks!!

Lisa E. Basham, M.S.
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
lisa.basham@fda.hhs.gov

Reference ID: 3383195

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/s/

LISA E BASHAM
10/02/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 070851

MEETING MINUTES

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Edward Liao, Pharm.D.
Associate Director, Regulatory Affairs

Dear Dr. Liao:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Oxycodone HCL/Naloxone HCl Controlled-Release Tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 13, 2012. The purpose of the meeting was to discuss the requirements for an NDA submission to support an indication of management of [redacted] (b) (4) pain [redacted] (b) (4) around-the-clock [redacted] (b) (4) for Oxycodone Hydrochloride/ Naloxone Hydrochloride Controlled-Release Tablets.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 13, 2012; 2 PM
Meeting Location:	10903 New Hampshire Avenue; Bldg 22; Room 1311; Silver Spring, MD 20993
Application Number:	070851
Product Name:	Oxycodone Hydrochloride/Naloxone Hydrochloride Controlled-Release Tablets
Indication:	Management of (b) (4) pain (b) (4) (b) (4) around-the-clock (b) (4) (b) (4)
Sponsor/Applicant Name:	Purdue Pharma L.P.
Meeting Chair:	Ellen Fields, M.D., M.P.H.
Meeting Recorder:	Lisa Basham

FDA ATTENDEES

Bob Rappaport, M.D.	Division Director
Sharon Hertz, M.D.	Deputy Division Director
Judy Racoosin, M.D., M.P.H.	Deputy Director for Safety
Ellen Fields, M.D., M.P.H.	Clinical Team Leader
Dan Mellon, Ph.D.	Supervisory Pharmacologist
Yun Xu, Ph.D.	Team Leader, Clinical Pharmacology, Division of Clinical Pharmacology 2 (DCP2)
Dionne Price, Ph.D.	Statistic Team Leader
Elizabeth Kilgore, M.D.	Clinical Reviewer
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer, DCP2
Jonathan Norton, Ph.D.	Statistics Reviewer

Reference ID: 3203053

Lubna Merchant, M.S., Pharm.D.	Team Leader, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Vicky Borders-Hemphill, Pharm.D.	Safety Evaluator, DMEPA, OSE
Mark Liberatore, Pharm.D.	Safety Regulatory Project Manager, OSE
Christine Nguyen, M.D.	Deputy Director, Office of Drug Evaluation II
Lisa Basham, M.S.	Senior Regulatory Health Project Manager

SPONSOR ATTENDEES

Gary Stiles, M.D.	Senior Vice-President, R&D
Craig Landau, M.D.	Vice President and Chief Medical Officer
Todd Baumgartner, M.D.	Vice President, Regulatory Affairs
Stephen Harris, M.D.	Executive Medical Director, Clinical Pharmacology
Bruce Berger, M.D.	Senior Medical Director, Medical Research
Catherine Munera, Ph.D.	Director, Biostatistics and Statistical Programming
Margaret Moline, Ph.D.	Director, Clinical Research
George Sylvestre	Director, Project Management
Jerry Green, M.D.	Associate Director, Medical Director
Edward Liao, Pharm.D.	Associate Director, Regulatory Affairs

Reference ID: 3203053

BACKGROUND

The proposed formulation is a controlled-release combination of oxycodone and naloxone (OXN). The formulation is approved in Europe as Targin and is indicated for: "The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation." In the United States, Purdue plans to (b) (4) seek approval for an indication of "management of (b) (4) pain (b) (4) around-the-clock (b) (4) (b) (4)" with the naloxone component intended to impart pharmacologic deterrence to abuse via the intranasal and intravenous routes.

(b) (4)

Purdue requested a type A meeting on April 7, 2011, to discuss their proposed Phase 3 protocol (ONU3701) and statistical analysis plan intended to support the analgesia indication (b) (4). The meeting package was submitted on June 24, 2011. Written responses were provided on August 19, 2011. The written responses conveyed, in summary, that positive results from the proposed Phase 3 study could serve as the basis for establishing analgesic efficacy and that previously conducted European studies may be supportive. Purdue is also conducting in vitro studies to examine the extractability of oxycodone and naloxone from the formulation and in vivo studies evaluating the abuse-deterrent aspects of the formulation. The in vivo studies are as follows:

ONU1003, entitled, "A Single-Center, Randomized, Double-Blind Study in Recreational Opioid Users to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Oxycodone/Naloxone (ONU) Tablets Administered via the Oral, Intranasal and Intravenous Routes,"

ONU 1004, entitled, "A Single-Center, Randomized, Double-Blind Crossover Study to Evaluate the Pharmacodynamics, Pharmacokinetics, and Safety of Oxycodone/Naloxone (ONU) in Opioid Dependent Subjects,"

ONU1007, entitled, "A Single-Center, Randomized, Double-Blind Study in Recreational Opioid Users to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Oxycodone/Naloxone (ONU) Tablets when Chewed or Administered Intact via the Oral Route," and

Reference ID: 3203053

ONU1008, entitled, "A Single-Center, Randomized, Double-Blind Crossover Study to Evaluate the Pharmacodynamics, Pharmacokinetics, and Safety of Intact and Chewed Oxycodone/Naloxone (ONU) Tablets in Opioid Dependent Subjects."

The request for this Pre-NDA meeting was submitted on April 27, 2012, and the meeting was requested for September. The meeting package was submitted on July 23, 2012. Preliminary Responses were sent to Purdue on September 10, 2012, and on September 11, 2012, Purdue informed the Agency via email that they wish to focus discussion on Question 1, specifically the Agency's comment regarding a pre-market trial to asses the risk of cardiovascular events, and the information under Additional Comments pertaining to the requirements for an NDA filed under 505(b)(2) of the Act. They also noted that they have some clarification questions pertaining to our response to Question 3 and the Agency's Additional Comments regarding PREA, and that they will provide the addition information requested under Question 7. Purdue stated that the latter issues (question re: Question 3, PREA, and Question 7) can be responded to in the minutes and that they need not be discussed during the meeting. On September 12, 2012, Purdue emailed the questions and information mentioned above. That information is presented below, following the FDA Responses, in Arial text. Discussion during the meeting is labeled as such and presented in normal text.

MEETING MINUTES

For ease of reference, your questions are reproduced below in italics, followed by our preliminary responses in bold text. Your follow-up questions/comments emailed to the Agency on September 11, 2012, follow in Arial text. Discussion during the meeting is in normal text and labeled as such.

Clinical

Question 1. Does the Agency agree that the studies described in this revised list are adequate to support an approvable NDA for ONU for the indication of "management of (b) (4) (b) (4) *pain* (b) (4) *around-the-clock* (b) (4) (b) (4)*"?*

FDA Response:
You propose to use U.S. Phase 3 Study ONU3701 conducted under this IND as the key efficacy study. As previously advised, it appears that Study ONU3701 is adequately designed to support a finding of efficacy, however, the protocol amendment submitted May 2, 2012, changed the statistical analysis of the primary endpoint. This amendment is still under review, and comments may be forthcoming.

The three Phase 3 European studies may provide supportive analgesic efficacy of OXN if the quality of the trials is acceptable and the study populations are representative of the target patient population in the U.S. for use of this product.

Reference ID: 3203053

You must provide a comparison of the patients enrolled in your studies and the U.S. population, describing any differences and how that may impact the applicability of the data. In particular, any differences in the metabolism of naloxone among ethnic groups must be assessed, including any impact on efficacy.

Study ONU3701, the three Phase 3 European studies with open-label extensions, and post-marketing experience, together with data from Phase 1 and Phase 2 trials, appear sufficient to support a safety database for OXN.

However, as previously conveyed in discussions regarding the pain (b) (4) (b) (4) indication, a sufficient number of subjects must be exposed to the highest proposed doses of OXN in order to adequately assess withdrawal, and the total required safety database depends on the systemic exposure to naloxone at the highest doses for both single and multiple doses. You have not yet submitted this information.

A potential safety signal has been identified in trials of another peripheral mu-opioid antagonist regarding an unexpected number of ischemic cardiovascular events, including myocardial infarction, cerebrovascular accident, and death, in some patients who had documented signs and symptoms consistent with opioid withdrawal. The concern is that the effects of opioid withdrawal on the autonomic nervous system, including changes in hemodynamic parameters, could increase the risk of cardiovascular events. We are now requiring that sponsors for similar products conduct a premarketing, randomized, controlled trial designed and powered to assess the risk of adverse cardiovascular events associated with the use of peripheral mu-opioid antagonists and extended-release opioids.

Purdue Follow-up Question for September 13, 2012:
We note that the Agency is reviewing the ONU3701 protocol amendment that was submitted on May 2, 2012. We appreciate the Agency's review of this protocol amendment. We are planning to unblind ONU3701 in approximately 6-8 weeks and would like to address all of the Agency's concerns prior to unblinding. **Will we be able to get your comments within this timeframe?**

We were surprised to learn of the new requirement for a pre-marketing, randomized, controlled trial designed and powered to assess the risk of adverse cardiovascular events associated with the use of OXN. We are familiar with the publicly available adverse event data for Entereg (alvimopan), a single-entity opioid antagonist, (b) (4) (b) (4) In contradistinction to single entity agents, OXN represents a fixed-ratio combination of oxycodone, a mu-opioid agonist, and naloxone, a mu-opioid antagonist. This combination agent has been extensively studied through the completion of seven randomized controlled trials, and seven open-label trials (Appendix I from the briefing document), together generating over 1500 unique exposures to OXN. Additional safety data has been collected from other completed and ongoing

Reference ID: 3203053

controlled and uncontrolled clinical trials (Appendix II and III from the briefing document). This clinical trial safety data base is supplemented by over (b) (4) (b) (4) patient days generated through patient prescriptions in 20 countries where the product is approved and marketed.

To date, Purdue's evaluation of clinical trial safety data and our ongoing surveillance of international post-marketing adverse event information does not yield evidence of a potential safety signal like that described in your response to our question.

Can FDA provide more information regarding the data and the rationale for this new request? We would also like to discuss your views on possible alternative approaches for evaluating this potential safety signal in the context of this combination product.

DISCUSSION:
The Agency stated that we would provide comments, resources permitting, on the May 2, 2012, protocol amendment within the requested timeframe.

Regarding the Agency's concern about a potential cardiovascular (CV) signal related to concomitant chronic administration of an opioid antagonist and extended-release opioids, Purdue stated that, with the extensive worldwide exposure to OXN (both in studies and in real-world postmarketing use), they have not observed such a signal. They are trying to understand why a signal may be observed with one antagonist and not another.

The Agency stated that there have been products under development for which a safety signal has emerged. One example is Entereg, for which an Advisory Committee discussed cardiac events associated with long-term use. This resulted in the drug receiving an indication limiting its use to the inpatient setting for a maximum of seven days. There is a need for a better understanding of this risk and its potential causes. One possibility is that opioid antagonists cause withdrawal in some patients, and that this may be linked to CV events. We need a better understanding of the timeframe between symptoms of withdrawal and the occurrence of CV events.

Purdue plans to explore these questions by analyzing data from their numerous studies. The study designs vary including different protocols, different comparators, and use of placebo. They plan to conduct a specific analysis of withdrawal symptoms, where an investigator may not have recorded the term withdrawal, but may have described symptoms associated with opioid withdrawal. This will require a thorough review of the case report forms. Although they do not possess double-blinded data over one year duration, they plan to first conduct a purpose-driven analysis using a staged approach because they are not convinced that a clinical trial is the best method to assess the existence of a cardiac signal. They inquired whether the Agency would consider evaluating such a plan if Purdue were to provide more specifics, e.g., types of analyses and display of data. The Agency responded that we would review the proposal but cannot guarantee a review in time for Purdue's planned NDA submission.

Reference ID: 3203053

Purdue asked whether they should be looking for specific CV events, e.g., acute CV events, chronic CV events, myocardial infarction (MI), or the whole set of CV measures, e.g., lipids, or composite endpoints (e.g. both angina and death or MI and death). The Agency responded that Purdue should cast a wide net in order to capture as much information as possible, however the major events of interest are serious acute cardiovascular events including MI, stroke, and sudden death.

Question 2. Does the Agency agree that a dose conversion strategy based on the clinical data from ONU3701 can be included in the OXN package insert as appropriate?

FDA Response:
Your approach to data collection for analyzing opioid conversion appears acceptable and it is possible that your conversion strategy may be included in the label. The extent to which inclusion of opioid conversion data are included in labeling is currently under discussion within the Agency, and the data you submit will be reviewed and considered for inclusion. However, as there appears to be substantial interpatient variability with regard to relative opioid potency, (b) (4)
(b) (4)

DISCUSSION: No discussion required.

Question 3. Does the Agency agree that either a written narrative or CIOMS form can be provided for every SAE, death, discontinuation due to an adverse event, or adverse events of special interest from all completed trials described in the ISS outside of the on-going studies (proposed 30 September 2012 cut-off date) and the post-marketing section of the ISS?

FDA Response:
At this time we cannot agree that a CIOMS form can be a substitute for a written narrative for every SAE, death and discontinuation due to an adverse event, or adverse event of special interest from all completed or ongoing trials described in the ISS. In order to address this issue, we recommend that you provide us with several samples of completed CIOMS forms for SAEs, deaths, and discontinuations due to adverse events for review to determine whether the information required for narratives is included in the forms. CIOMS forms are acceptable for cases described in the post-marketing section of the ISS.

The requirements for narrative summaries of important adverse events (e.g., deaths, events leading to discontinuation, other serious adverse events) as stated in the 2005 Guidance for Industry-Premarketing Risk Assessment are as follows:

Narratives should provide the detail necessary to permit an adequate understanding of the nature of the adverse event experienced by the study subject. (This level of

Reference ID: 3203053

detail may be unnecessary for events expected in the population, e.g., late deaths in a cancer trial. This issue should be discussed with the appropriate review division.) Narrative summaries should not merely provide, in text format, the data that are already presented in the case report tabulation, as this adds little value. A valuable narrative summary would provide a complete synthesis of all available clinical data and an informed discussion of the case, allowing a better understanding of what the patient experienced. The following is a list of components that would be found in a useful narrative summary:

- **Patient age and gender**
- **Signs and symptoms related to the adverse event being discussed**
- **An assessment of the relationship of exposure duration to the development of the adverse event**
- **Pertinent medical history**
- **Concomitant medications with start dates relative to the adverse event**
- **Pertinent physical exam findings**
- **Pertinent test results (e.g., lab data, ECG data, biopsy data)**
- **Discussion of the diagnosis as supported by available clinical data**
- **For events without a definitive diagnosis, a list of the differential diagnoses**
- **Treatment provided**
- **Re-challenge results (if performed)**
- **Outcomes and follow-up information**

We refer you to the above mentioned guidance for additional details: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072002.pdf.

CSS General Comments:

In the NDA, provide the following information and data related to the abuse potential assessment, including drug diversions and overdose:

1. **Descriptions of all reports and details, including narratives of all incidents of abuse, misuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing, or unaccounted for in all clinical studies.**

2. **Case narratives of subjects in clinical studies who are discontinued from studies for lack of compliance to study medication or procedures or who discontinue participation without returning the study medication.**

   Purdue Follow-up Question for September 13, 2012:
   Purdue seeks confirmation that the proposed cut-off date of 30 September 2012 is acceptable and that CIOMS forms are adequate for ongoing studies (Appendix III in the briefing document).

   Does the Agency agree that 30 September 2012 is an acceptable cut-off date for data that will be included in the ISS?

Reference ID: 3203053

DISCUSSION: The Agency stated that September 30, 2012, is an acceptable cut-off date for ISS data, given the planned NDA submission for June 30, 2013. The ISS data lock date would be adjusted if the NDA submission were delayed beyond that time.

Does the Agency agree that CIOMS forms are adequate for ongoing studies?

DISCUSSION:
Purdue stated that the CIOMS forms are being reviewed to determine whether they meet the same standards as narratives. Purdue proposed the following: for pivotal studies, they will submit narratives; for the legacy studies, they will submit narratives and CIOMS forms only if the latter meet the requirements; and for ongoing, unblinded studies, they will submit CIOMS forms only (because narratives are not written until the study is completed). The Agency stated that this appears to be acceptable.

Question 4. Does the Agency agree that Purdue's proposal for presentation of Adverse Reactions in the label is appropriate?

FDA Response:
Your proposal for the presentation of Adverse Reactions (ARs) in the label is generally acceptable. However, the acceptability of your plan to exclude the most common ARs from the long-term extension portion of the European supportive OXN studies will be determined upon review of the data. If there are adverse reactions noted in these studies that may be related to the study drug and have not been observed in the other clinical trials, these events may be included in the label. Similarly, adverse reactions with higher frequencies than in controlled studies may also be included in the labeling.

DISCUSSION: No discussion required.

Biostatistics

Question 5. Does the Agency agree with the proposed plan for presentation of study level data and for the integration of safety and efficacy information in the OXN NDA?

FDA Response:
Your proposal appears to be acceptable. Also see Additional Comments.

DISCUSSION: No discussion required.

Question 6. Does the Agency agree with the approach for documenting meta-data changes and study level data issues, and for presenting corrections to CSR tables?

Reference ID: 3203053

FDA Response:
Your proposed plan seems acceptable. Please note that traceability is an important factor, regardless of whether your data are in legacy or standardized format. Reviewers should be able to navigate from CRFs to tabulation data to analysis data.

DISCUSSION: No discussion required.

Question 7. Does the Agency agree with the proposed approach to explore the relationship between OXN dose and adverse event incidence?

FDA Response:

- **From a clinical perspective, your approach appears generally acceptable except as noted below. Additional analyses may be requested during the review cycle if deemed necessary.**

  You state that for studies ONU3701 and ONU3401 the adverse events will be summarized by "randomized dose." Since these studies use randomized withdrawal designs, clarify what is meant by the randomized dose. You also state that a "treatment-emergent algorithm" will be used. Provide this algorithm.

- **From an eCTD perspective, bring up any serious issues encountered with the review team; all notes/issues should be documented in relevant files. Also submit SAS program files in ASCII format as .txt files. You may name the file "xxx.sas.txt" to indicate to the review team that this specific file is a SAS program.**

Purdue Follow-up Questions for September 13, 2012:

Study ONU3701 consists of 3 phases: an up to 14-day pre-randomization phase; a 12-week double-blind phase, and 1 week follow-up phase following the completion of double-blind treatment. During the open-label titration period of the pre-randomization phase, subjects will be converted from their prior opioid to OXN and titrated to a tolerable and effective dose (protocol section 9.1.2). Subjects who qualify for continuation into the double-blind phase will be randomized to placebo or OXN at the same dose that provided adequate pain control during the open-label titration period. This dose is referred to as the "randomized dose" in the background to Question 7 included in the Briefing Package to the pre-NDA meeting dated July 23, 2012. A similar design was followed in study OXN3401 except that subjects received Oxy IR in theopen-label titration period and were then randomized to placebo, Oxy CR, and OXN. The tolerable and effective dose of Oxy IR achieved in the titration period was used to convert subjects to Oxy CR and OXN and is referred to as the "randomized dose" in our correspondence with the Agency.

Reference ID: 3203053

The analysis of AEs in the ISS will be analyzed using a treatment emergent algorithm as defined in Section 9.7.1.9.1 of the ONU3701 protocol and reproduced below:

Data for adverse events will be analyzed using the treatment-emergent signs and symptoms (TESS) philosophy. TESS are defined as adverse events that:

- **emerge during treatment, having been absent at pretreatment (baseline) or**
- **reemerge during treatment, having been present at baseline but stopped prior to treatment or**
- **worsen in severity during treatment relative to the pretreatment state, when the adverse event is continuous.**

Only treatment-emergent adverse events will be included in summary tables. However, all adverse events will be included in a by-subject adverse event listing. Adverse events that occur up to seven days following the subject's last dose of double-blind study drug are included as treatment-emergent events.

In the definition above, "treatment" can be either the study drug received during the open-label titration or the study drug received during the double-blind phase. In the first case, the algorithm would be used to summarize AEs that are emergent during the open-label titration phase, and in the second case the algorithm would be used to summarize AEs occurring during double-blind treatment.

A similar definition will be used to evaluate the relationship between OXN dose and adverse events. For these analyses, "treatment" will be taken to be either the dose at AE onset, or the "randomized dose" depending on whether summaries focus on adverse events occurring during the open-label titration phase, the double-blind phase of the pool of Oxy CR-controlled studies, or the double-blind phase of the pool of placebo-controlled studies.

DISCUSSION:
The Agency stated that Purdue's clarification of the definition of randomized dose is acceptable and inquired whether Purdue planned to pool the data from the OXN group and the oxycodone IR group. Purdue clarified that they will analyze data from the two groups separately.

The Agency has asked that we provide SAS programs in ASCII format as .txt files. We assume that the SAS programs required at the time of submission are the ones needed to create the analysis datasets and the summary tables for the Phase 3 CSRs, the ISS and the ISE. Could the Agency confirm this is an accurate assumption?

DISCUSSION:
The Agency confirmed that the SAS programs requested at the time of submission are the ones needed to create the analysis datasets and the summary tables for the Phase 3 CSRs, the ISS, and the ISE.

Reference ID: 3203053

Risk Management

Question 8. Does the Agency agree that the class REMS for long-acting opioids will apply to OXN?

FDA Response:
On July 9, 2012, the class-wide extended-release/long acting (ER/LA) Opioid Analgesic REMS was approved. The Agency agrees that the ER/LA Opioid Analgesic REMS will apply to OXN. However, a full clinical review of OXN after submission of the NDA will be necessary to determine if any additional risk mitigation strategies are needed, since additional information regarding risks and safe product use may emerge during the review of the NDA.

DISCUSSION: No discussion required.

NDA/Regulatory

Question 9. Does the Agency agree that the OXN NDA may be considered for priority review?

FDA Response:
Yes, as a potentially abuse-deterrent formulation, the NDA may be considered for priority review. A final decision will be made at the time of filing of the application.

DISCUSSION: No discussion required.

Question 10. Does the Agency agree that Purdue will not have to provide financial disclosure forms for the Phase 3 OXN studies conducted in Europe?

FDA Response:
Yes. As the European studies are not covered studies as defined by 21 CFR 54.2(e) financial disclosure will not be required.

DISCUSSION: No discussion required.

Question 11. Does the Agency agree with Purdue's proposed plan to comply with 21 CFR 312.120 for the foreign clinical studies that will be included in its NDA submission?

FDA Response:
Yes, your proposal is acceptable. Upon review of your supporting documentation, we will evaluate your compliance with 21 CFR 312.120 for those studies from which data are included in the ISE and ISS.

Reference ID: 3203053

DISCUSSION: No discussion required.

Abuse Liability

Question 12. Does the Agency agree with the types of In Vitro Tamper Deterrence Studies underway and the associated study design principles, and are there any critical modalities of testing absent from Purdue's in vitro investigational plan?

FDA Response:

CSS comments:
Detailed protocols were not provided for review and comment. Based on the overview provided of the experimental approach, the in vitro manipulation and physiochemical chemical extraction studies appear to be appropriate. All in vitro studies must be conducted on the to-be-marketed formulation.

Premarketing Assessment of Abuse-Deterrent Formulations

We remind you that there are three areas of testing that must be conducted premarketing on potential abuse deterrent formulations. All studies must be conducted on the to-be-marketed product and be scientifically rigorous, blinded, and have an appropriate positive control as a comparator drug. Depending on the results of these studies, information may be suitable to be included in labeling. The three levels of studies fall into the following categories.

1. **In vitro studies**

   Data from studies designed to evaluate the product's resistance to attempts to defeat the controlled-release properties that are conducted – These studies should explore use of extraction experiments with a variety of solvents with a wide range of polarities and conditions, including (b) (4) **and various methods of physical manipulation.**

2. **Pharmacokinetic studies**

   Data from studies that evaluate the effects on the pharmacokinetic profile of different methods of physical manipulation identified in the in vitro studies – These studies can enroll normal volunteers who are naltrexone blocked for safety. Experimental data should demonstrate an association between the rate of rise of Tmax for the active pharmaceutical ingredient as an indicator of abuse potential.

3. **Clinical studies**

Reference ID: 3203053

Data from clinical studies to evaluate the abuse liability, including drug liking and euphorigenic effects of manipulated and intact product and comparison with non-abuse-deterrent forms

DISCUSSION: No discussion required

ADDITIONAL COMMENTS

Nonclinical:

1. **We note that you have changed your regulatory strategy discussed in previous meetings to the 505(b)(1) pathway. A 505(b)(1) application, or "stand-alone NDA," describes an application that contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use. Accordingly, all nonclinical studies, including basic pharmacology, ADME, and carcinogenicity, are required for a 505(b)(1) application. We remind you that carcinogenicity studies do not exist for oxycodone and carcinogenicity studies in two species are necessary to support a 505(b)(1) application for this new drug product. Because of the long history of use for oxycodone, the studies may be conducted postmarketing as long as they are initiated by the time of NDA filing, unless otherwise justified.**

2. **If you elect to pursue filing your NDA via the 505(b)(1) pathway, you must submit studies which characterize the basic pharmacology as well as the absorption, distribution, metabolism, and excretion (ADME) of oxycodone and naloxone in order to support labeling of your product. In the absence of actual studies, reliance on "general knowledge" may address the NDA requirements as a 505(b)(1); however, we caution you that it is very difficult to show that data are "general knowledge" and such claims are carefully scrutinized by the Agency. If reference to literature is necessary to fulfill the requirements of an NDA application, and the Agency does not agree that the information is deemed "general knowledge," your application may be deemed a 505(b)(2) application. Should you elect to rely upon "general knowledge," clearly justify why the data are considered to be "general knowledge." Reference to information in common textbooks does not necessarily equate to "general knowledge." An application that relies on literature that names an approved drug product is considered a (b)(2) application and requires patent certification and notification to the relied upon drug.**

3. **As previously discussed in the context of your original plan to submit a 505(b)(2) application, carcinogenicity studies for oxycodone would not be required, as this drug product would not result in a change in the risk to patients taking the drug compared to other approved chronically-used oxycodone drug products.**

4. **Upon preliminary review, it appears that the levels of several excipients in your**

Reference ID: 3203053

formulation exceed levels in approved drugs when your product is consumed at the maximum theoretical daily dose (MTDD) of oxycodone (1.5 g/day). These excipients would be considered novel and must be adequately qualified for safety with appropriate studies or literature-based justification. Any studies conducted must be submitted to the IND as per the following guidance Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf)**. As noted in the document, ". . . 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).**

5. **For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2) and ICH Q3B(R2), or be demonstrated to be within the specifications of the listed drug relied upon for approval through the 505(b)(2) pathway. Unless otherwise justified, adequate qualification must include:**

   a. **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.**

   b. **Repeat-dose toxicology study of appropriate duration to support the proposed indication.**

   c. **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 ICH Q3A(R2) and ICH Q3B(R2) 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 refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity that exceeds the ICH qualification thresholds.**

6. **Potentially genotoxic impurities or degradation products pose an additional risk; therefore, a specification that provides for a maximal daily intake of NMT** (b) (4) (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**

Reference ID: 3203053

structural alert for mutagenicity must be provided with the NDA submission and must include an 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 such that the maximal daily intake of the impurity is NMT (b) (4) (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.

7. **NOTE: We may 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)**

8. **Phenanthrene-derivative opioid drug products may contain impurities containing an (b) (4) moiety, which is a structural alert for mutagenicity. Therefore, the specification for these impurities in the drug substance must be reduced to reflect a maximal daily intake of NMT (b) (4) (b) (4) or adequate safety qualification must be provided. We recommend 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.**

DISCUSSION: See Purdue's general 505(b)(2) question under **ADDITIONAL COMMENTS; Clinical Pharmacology**.

Clinical:

Analysis of opioid withdrawal in the OXN clinical development program:

The protocol for Study ONU3701 states that a subject will be considered to have evidence of opioid withdrawal if they meet any of the following criteria: 1) COWS ≥ 13 during the double-blind period on or before Visit 5 that represents an increase in the COWS score recorded at Visit 2; 2) Subject has an adverse event of opioid withdrawal based on the judgment of the investigator and recorded in the CRF pages occurring before or at the time of discontinuation; or 3) Subject is considered to have discontinued with evidence of opioid withdrawal based on review by the adjudication committee. The adverse events must occur during treatment or within minutes to several days following opioid dose reduction or cessation.

1. **Opioid withdrawal is a potentially important adverse event that may be observed with OXN. In study ONU3701, you propose an approach for identifying cases of opioid withdrawal in patients discontinuing from the study. This issue needs to be evaluated in all patients, not just those discontinuing from the trial. Additionally, assess opioid withdrawal not just in patients with dose reduction or treatment cessation, but also in patients who remain on their**

Reference ID: 3203053

randomized dose. The case finding approach as described above with the noted modifications is reasonable to use.

2. **For the Phase 3 studies that have been completed, provide an analysis of the occurrence of withdrawal symptoms both in subjects remaining in the trials and those discontinuing due to withdrawal symptoms. Use the approach outlined above. You may pool the analyses as appropriate based on study design and population.**

3. **For all studies, provide narrative summaries for any SAEs or discontinuations due to opioid withdrawal.**

4. **Based on the counts of cases identified in each treatment group in the controlled studies, provide rates (number of patients with events per 100 person years) in separate tables for discontinuations and serious AEs due to opioid withdrawal.**

DISCUSSION: No discussion required.

Electronic Submission:

You have indicated that you plan to submit the NDA as an eCTD and that you will include CDISC-compliant electronic datasets.

In regard to the eCTD format, refer to the guidance *Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf.

Our recommendations for implementation of the CDISC standards can be found in the CDER Common Data Standards Issues Document, available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM254113.pdf.

We also refer you to the following resources which are intended to assist submitters in the preparation and submission of standardized study data to CDER: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

DISCUSSION: No discussion required.

Reference ID: 3203053

Clinical Pharmacology:

1. **If you plan to submit the NDA under the 505(b)(1) route, then clinical pharmacology information in the planned product label must be supported by data from studies conducted by or for you or for which you have a right of reference or use. This includes absorption, distribution, metabolism, elimination (ADME) information; special population information; drug interactions (alcohol, metabolism, transporter, etc); and QT-prolongation risk of the product. We note that several studies address some of the indicated comments. However, a comprehensive discussion of all clinical pharmacology aspects and source of information is required when an NDA is submitted as a 505(b)(1) application.**

2. **If you plan to submit the NDA under the 505(b)(2) route, to fulfill the 505(b)(2) regulatory requirements, a PK bridge with an NDA product approved in U.S. is needed for each component in your drug product. Usually such "bridge" is established via a relative bioavailability study. This requirement will be a fileability issue for a 505(b)(2) type NDA. Note the 505(b)(2) requirement-related comments previously provided in the PIND meeting minutes in 2009. Address all clinical pharmacology aspects of your product label using in house data or the information from the listed drug's label or published literature, including absorption, distribution, metabolism, elimination (ADME) information, special population information, drug interactions (alcohol, metabolism, etc), QT-prolongation risk of the combination.**

Purdue Follow-up Question for September 13, 2012:
Thank you for your comments on the regulatory strategy.
If we elect to file this NDA as a 505(b)(2), we understand "a PK bridge with an NDA product approved in the U.S. is needed for each component" of the drug product and that "usually such a bridge is established via a relative bioavailability study".

For the oxycodone component, we would propose a relative bioavailability study to OxyContin.
Is this acceptable to support this requirement of the 505(b)(2) pathway?

For the naloxone component, options include a comparison to:
- Watson's generic Talwin NX (pentazocine and naloxone hydrochlorides, USP), containing 0.5 mg base naloxone hydrochloride;
- Generic Narcan (naloxone hydrochloride, 0.4 mg/ml or 1 mg/ml) injection
- Suboxone sublingual tablets or sublingual film, buprenorphine hydrochloride and naloxone hydrochloride), including up to 2 mg base naloxone hydrochloride

Reference ID: 3203053

Given these formulation choices, we would propose conducting the relative bioavailability study with the oral formulation, Talwin NX. However, we note that Talwin NX has been discontinued and that Watson's pentazocine and naloxone hydrochloride (an ANDA product) now is the reference listed drug (RLD).

Given Talwin NX no longer is commercially available, would a relative bioavailability study with the RLD (Watson product) be acceptable? If not, what naloxone-containing comparator would be acceptable?

DISCUSSION:
Purdue went over the history of their planned regulatory filing approaches. They had originally planned to submit the NDA as a 505(b)(2) application but, because they are conducting animal carcinogenicity studies of naloxone, considered the possibility of submitting a 505(b)(1) application. For a 505(b)(1) application, however, they would also be required to conduct carcinogenicity studies on oxycodone. Therefore, they are once again pursuing the 505(b)(2) pathway. They inquired whether they may reference OxyContin for the oxycodone component and suggested that the possible references for naloxone would be Talwin, Narcan, or Suboxone. They proposed Talwin, but it is no longer available, so they inquired as to whether the Watson generic would be acceptable as a reference for the naloxone component.

The Agency responded that Purdue may reference OxyContin for the oxycodone component and clarified that they would not be relying on the Agency's previous findings of safety and efficacy for OxyContin because it belongs to Purdue, but would be cross-referencing OxyContin in support of their NDA for OXN. For a 505(b)(1), the Agency continued, Purdue would need to submit everything that would be required as if this were a New Molecular Entity (NME), including ADME, carcinogenicity for all components, and a thorough QT study. The Agency did clarify, however, that the carcinogenicity study could be conducted as a postmarketing requirement in this particular case.

For a 505(b)(2) application, Purdue has a choice of applications to rely upon for the naloxone component as long as the drug is an approved listed drug, i.e., it has not been removed for reasons of safety. Since Talwin is no longer marketed, if Purdue chooses to rely on Talwin, they would reference Talwin in the NDA for patent certification and notification purposes, but would use the ANDA generic designated as the Reference Listed Drug (RLD) as the comparator in the relative bioavailability (BA) study.

The Agency suggested that Purdue conduct the following exercise as they are considering what they need to reference for a 505(b)(2) application: write a draft label and then see what is missing. Purdue may reference more than one drug as long as they do relative bioavailability studies with each of them. If needed, Purdue could rely on some information from one drug and other information from another. Purdue asked whether the Agency would accept a 3-way cross-over relative BA study. The Agency stated that this would be acceptable.

The possibility of using Suboxone as the listed drug for naloxone was also discussed. The Agency stated that exposure to naloxone using Suboxone will be very low, and that would not

Reference ID: 3203053

support the safety of OXN if the naloxone exposure from OXN was higher. The Agency suggested that Purdue conduct the BA study and then, depending on the data, provide justification as to why the data support the OXN application.

POST MEETING NOTE: Purdue followed up with an email inquiry as to whether a comparative BA study would also be required with OxyContin.

Response: You should conduct a relative BA study between your proposed product and OxyContin to compare the oxycodone systemic exposure between them. Then you may use the findings from OxyContin to support the oxycodone component for the proposed product.

ADDITIONAL POST-MEETING COMMENTS: A 505(b)(2) application is an application that contains "full reports of investigations" of safety and effectiveness where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. Therefore, you would be referencing the OxyContin NDA, not relying upon it. Relying upon another NDA for which you do not have right of reference or use would make your application a (b)(2). Use of OxyContin as a referenced application and as reference in a relative BA study may be acceptable. In the NDA submission, you must establish that reliance on OxyContin (or any other NDA product you plan to rely on) is scientifically appropriate and submit data necessary to support any aspects of your proposed drug product. You may also rely on the information from literature. If you intend to rely on literature where a different oxycodone formulation may have been used, discuss how the observations may be applied to your product. If literature is used, copies of the articles must be included and any proprietary names in those reports identified. If a product is identified by proprietary name and the information in the literature article is required for approval, including for the labeling, then that product must be included in the list of products relied upon for approval and the required patent notification and certification procedures followed.

When relying on FDA's finding of safety and/or effectiveness for a discontinued listed drug and supporting the scientific appropriateness of reliance through a comparative bioavailability study, the ANDA product designated as the RLD in the Orange Book should be used as the comparator in a comparative clinical trial to establish a bridge between the proposed drug product and the specified listed drug. Note also that reliance on FDA's finding of safety and/or effectiveness for a discontinued listed drug is contingent on FDA's finding that the drug was not discontinued for reasons of safety or effectiveness.

<u>Biopharmaceutics:</u>

1. **Dissolution Test: Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:**

    a. **Solubility data for the drug substance covering the pH range**

Reference ID: 3203053

b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product – If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least (b)(4)% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least 12 samples per testing variable

c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim)

d. Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

2. Dissolution Acceptance Criteria: For the selection of the dissolution acceptance criteria of your product, the following points should be considered:

a. The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).

b. Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).

c. A minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the release profile. The last time point should be the time point where at least (b)(4)% of drug has release. If the maximum amount release is less than (b)(4)%, the last time point should be the time when the plateau of the release profile has been reached.

Note that the final determination on the acceptability of the dissolution method is a review issue that will be determined during the IND or NDA review. However, the acceptability of the proposed dissolution criteria for your product will be made during the NDA review process based on the totality of the dissolution data that are submitted.

Reference ID: 3203053

3. **When evaluating for the potential for alcohol-dose dumping, conduct in vitro drug release testing initially using the highest strength. Follow-up with an in vivo study may be required, depending on the result of the in vitro testing. We recommend that you discuss the result of your in vitro study with us prior to the NDA submission.**

   a. **The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.**

   b. **Generally a range of alcohol concentrations in 0.1 N HCl and the QC dissolution medium is recommended. If the optimal dissolution medium has not been identified, then dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.**

   c. **Report f2 values to assess the similarity (or lack thereof) in the dissolution profiles.**

      1) **Compare the shape of the dissolution profile to see if the modified release characteristics are maintained, especially in the first 2 hours.**

      2) **The report should include the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study.**

4. **Note that the submission of bioequivalence (BE) and/or bioavailability (BA) information for lower strength (s) of your proposed product may be waived if the following CFR requirements are met:**

   a. **Inclusion of the biowaiver request as part of the NDA submission**

   b. **The lower strength(s) and higher strength product have the same dosage form**

   c. **There are BA/BE data for the highest strength**

   d. **The lower strength(s) product is proportionally similar in its active and inactive ingredients to the highest strength product**

   e. **The lower and highest strength products have the same drug release mechanism**

   f. **Dissolution profile comparisons between the highest and lower strengths in three different media meet the f2 similarity requirements**

DISCUSSION: No discussion required.

Reference ID: 3203053

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

Purdue Follow-up Question for September 13, 2012:
In the meeting minutes for the End-of-Phase 2 meeting (dated December 17, 2010), the Agency made the following comment (in italics):

A pediatric plan must be submitted with the NDA. Include requests for waivers and deferrals, the types of studies planned, and a timeline for the studies that includes the date of final protocol submission to the Agency, the date of study completion, and the date of final study report submission to the Agency.

As discussed at the End-of-Phase 2 meeting, the Division stated that the pediatrics plan should be submitted with the NDA. This continues to be Purdue's plan. Does the Agency agree?

DISCUSSION: The Agency is still discussing this issue and will follow up when more information becomes available.

PRESCRIBING INFORMATION

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

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

DISCUSSION: No discussion required.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for

Reference ID: 3203053

their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance *Assessment of Abuse Potential of Drugs* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

DISCUSSION: No discussion required.

MANUFACTURING FACILITIES

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

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

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

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

Reference ID: 3203053

Corresponding names and titles of onsite contact:

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

DISCUSSION: No discussion required.

ISSUES REQUIRING FURTHER DISCUSSION
The Agency will follow up with Purdue about the timing of the Pediatric Plan submission as more information becomes available.

Key Discussion Points:

1. The Agency will provide comments on the May 2, 2012, protocol amendment within the sponsor's desired timeframe as resources allow.

2. Purdue will submit a proposal describing their approach to evaluating existing data for a signal of CV risk.

3. Purdue plans to file a 505(b)(2) application. They will reference their OxyContin NDA for the oxycodone component and rely on either Talwin NX or Suboxone or both for the naloxone component. If they reference Talwin NX, they will conduct the relative BA study with the ANDA designated as the RLD.

4. Given the anticipated NDA submission by June 30, 2013, it is acceptable that the safety data cut off date for inclusion in the ISS is September 30, 2012.

5. CIOMS forms may be acceptable for the SAEs, deaths, and discontinuations due to adverse events in legacy studies, but narratives are preferred. For the ongoing studies, CIOMS forms will be submitted. Purdue will submit examples of CIOMS forms.

Reference ID: 3203053

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
10/12/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 070851

EOP2 MEETING MINUTES

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Edward Liao, Pharm.D.
Associate Director, Regulatory Affairs

Dear Dr. Liao:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Oxycodone HCl/Naloxone HCl Controlled-Release Tablets.

We also refer to the meeting between representatives of your firm and the FDA on November 18, 2010. The purpose of the meeting is to discuss your proposed Phase 3 program.

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: November 18, 2010 (10:30-11:30 AM)
LOCATION: 10903 New Hampshire Ave., Silver Spring, MD; Bldg 22; Room 1315
APPLICATON: **IND 070851**/Oxycodone HCl/Naloxone Controlled-Release HCl Tablets
INDICATION: For the management of (b) (4) pair (b) (4) (b) (4), around-the-clock (b) (4) (b) (4) (b) (4)
STATUS OF APPLICATION: Active
SPONSOR: Purdue Pharma L.P.
TYPE OF MEETING: Type B/End-Of-Phase 2
MEETING CHAIR: Sharon Hertz, MD; Deputy Director, Division of Anesthesia and Analgesia Products (DAAP)
MEETING RECORDER: Lisa Basham, Senior Regulatory Health Project Manager

FDA Attendees	Title
Bob Rappaport, MD	Division Director, DAAP
Sharon Hertz, MD	Deputy Division Director, DAAP
Thomas Permutt, PhD	Division Director, Division of Biometrics II
Ellen Fields, MD, MPH	Clinical Team Leader, DAAP
Robert P. Fiorentino, MD, MPH	Acting Clinical Team Leader, Division of Gastroenterology Products (DGP)
Dionne Price, PhD	Statistics Team Leader for DAAP
Silvia Calderon, PhD	Team Leader, CSS
Elizabeth Kilgore, MD	Clinical Reviewer, DAAP
Zana Handy Marks, MD, MPH	Clinical Reviewer, DGP
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer for DAAP
Jonathan Norton, PhD	Statistics Reviewer for DAAP
Behrang Vali, MS	Mathematical Statistician for DGP
James Tolliver, PhD	Reviewer, CSS
Lisa Basham, MS	Senior Regulatory Health Project Manager, DAAP

Sponsor Attendees	Title
Gary Stiles, MD	Sr. VP, Research & Development
Craig Landau, MD	VP & Chief Medical Officer
Todd Baumgartner, MD	VP, Regulatory Affairs
Margaretta Nyilas, MD	Executive Medical Director
Stephen Harris, MD	Executive Medical Director, Clinical Pharmacology
Catherine Munera, PhD	Director, Biostatistics and Statistical Programming
George Sylvestre, Jr., MBA	Director, Project Management
Jerry A. Green, MD	Associate Medical Director, Medical Research
Edward Liao, PharmD	Associate Director, Regulatory Affairs
(b) (4)	Consultant

BACKGROUND:

The proposed formulation is a controlled-release combination of oxycodone and naloxone (OXN). The combination product is being developed for (b) (4) indication of chronic pain (b) (4) (b) (4) (b) (4). The naloxone component is concluded to (b) (4) possibly deter abuse. A Pre-IND meeting was held on May 26, 2005. Since that meeting, the product has been marketed in Germany as Targin Tablets and the European development program has been completed. With this data available, a second PIND meeting was held on February 24, 2009. Several communications were issued to the sponsor following this meeting, (b) (4) (b) (4)

MEETING MINUTES:

NOTE: Your questions are shown below in italicized font, followed by our responses, provided to you on November 15, 2010, in bold font. Your follow-up comments, provided on November 17, 2010, are shown in boxed font. Discussion during the meeting is shown in normal font.

Clinical:

1. *Based on the October 27, 2010, conference call with FDA, Purdue has revised its ONU Phase 3 program to conduct 2 studies (described below) and believes that the study design of these 2 studies will be adequate and sufficient to support the following proposed indications for OXN at doses up to 80/40 mg daily:*

   - *Oxycodone HCl/naloxone HCl controlled-release tablets (OXN) are indicated for the management of* (b) (4) *pain* (b) (4)*, around-the-clock* (b) (4)

(b) (4)

Does the Agency agree?

FDA Response: No.

- **You have proposed (b) (4) indications for OXN. However, your product is a combination of two active drugs, and patients who receive this combination must require both components of the drug. Therefore, a (b) (4) indication that includes the management of (b) (4) (b) (4)**
- **You must provide replicated evidence of efficacy for OXN as an analgesic (b) (4) (b) (4). Two successful studies are required, (b) (4) assessing pain (b) (4).**

Purdue Follow-up Questions for November 18, 2010:

We appreciate FDA's view (b) (4) (b) (4) Based on FDA's suggestion we have revised the indication:

> **Oxycodone HCl / Naloxone HCl controlled-release tablets (OXN) are indicated for the management of (b) (4) pain (b) (4) around-the-clock (b) (4) (b) (4)**

As proposed by the Agency, Purdue plans to conduct two randomized, placebo and active-controlled, trials of Oxycodone / Naloxone Controlled-release Tablets (OXN) to assess the analgesic efficacy (compared to placebo) (b) (4) (b) (4)

Each study includes a 12-week double-blind period with (b) (4) primary endpoints. The proposed primary analgesic efficacy outcome in each study is the "average pain over the last 24 hours" at week 12 of the double-blind period comparing OXN to placebo. (b) (4) (b) (4)

(b) (4) study will be considered successful if we achieve a statistically significant result ($p<0.05$) in favor of OXN versus placebo for the assessment of analgesic efficacy, (b) (4) (b) (4)

Does the Agency agree that the revised indication is appropriate for OXN?

Does the Agency agree that the Phase 3 study program outlined above will support approval of this indication?

DISCUSSION: The Agency stated that the proposed indication appears appropriate; however, specific language will be determined during review. The outlined proposed Phase 3 program also appears appropriate to evaluate the efficacy of the drug for the proposed indication. (b) (4) (b) (4)

2. *Study 1 is a multi-center, double-blind, parallel-group study that will randomize patients with chronic low back pain and opioid-induced constipation to placebo, OXY, and OXN in a 1:1:1 ratio.* (b) (4) *"a single Phase 3 adequate and well-controlled study in the proposed population would be acceptable to demonstrate the analgesic efficacy of OXN", Purdue believes that if analgesic efficacy is demonstrated in Study 1, there is adequate evidence to support the following indication:*

   - *Oxycodone HCl/naloxone HCl controlled-release tablets (OXN) are indicated for the management of* (b) (4) *pain* (b) (4) *around-the-clock* (b) (4)

   Does the Agency agree?

   FDA Response: No, we do not agree.

   - (b) (4)

- (b) (4)

- (b) (4)

DISCUSSION: No discussion necessary.

3. *Does the Agency agree that Study 1 and Study 2, along with the Phase 3 European studies and safety database from post-marketing exposure to OXN ex-US are adequate to evaluate the safety of OXN with respect to opioid withdrawal?*

FDA Response:

- **A 12-week duration appears adequate from a clinical standpoint to determine the occurrence of signs and symptoms of opioid withdrawal through the use of COWS and SOWS. The final determination regarding the adequacy of data is a review issue.**

- **You must have adequate exposure to the highest doses during the 12-week studies to adequately assess the likelihood of withdrawal symptoms occurring in patients who take these higher doses.**

- **The Phase 3 European studies may provide supportive safety information related to withdrawal, however, the quality and reliability of postmarketing reports are not adequate to serve as a primary source of safety data.**

DISCUSSION: The sponsor stated that they expect to have approximately 100 subjects exposed to the highest dose (about 20%). The Agency stated that the adequacy of the number of patients exposed will depend on the systemic exposure to naloxone at the highest doses for both single- and multiple-doses. If there is no exposure, then the concern about withdrawal will be minimized. The Sponsor asked whether a pharmacokinetic study in healthy subjects would provide the necessary exposure data and they added that a study of that type would also allow them to measure metabolite levels. The Agency stated that this would be acceptable and suggested also collecting blood samples, especially from patients with withdrawal symptoms, to evaluate naloxone exposure.

Pediatrics:

4. *Upon review of the deferral request for the pediatric assessment required for Pediatric Research Equity Act (PREA), will the Agency grant a deferral?*

   FDA Response:

   The Division does not make the determination regarding waivers and deferrals. This determination is made by the Pediatric Review Committee (PeRC) during the review cycle. However, it appears appropriate to defer studies in pediatric patients until the safety and efficacy of OXN has been assessed in adults.

   A pediatric plan must be submitted with the NDA. Include requests for waivers and deferrals, the types of studies planned, and a timeline for the studies that includes the date of final protocol submission to the Agency, the date of study completion, and the date of final study report submission to the Agency.

DISCUSSION: No discussion necessary.

5. *Upon review, does the Agency agree that the proposed pediatric development plan for ONU is satisfactory to comply with PREA?*

   FDA Response: No.

   - **Pediatric Research Equity Act (PREA) Requirements are based on the drug product and the indication. Therefore, your studies must be conducted in the appropriate patient population (i.e. patients requiring ATC opioids for chronic pain** (b) (4)**.**

   - **In order to fulfill PREA requirements, you must conduct studies to assess efficacy, safety and PK in children ages 7-17 years who require ATC treatment with opioids for chronic pain** (b) (4)**.**

   - **Although analgesic efficacy for single entity oxycodone can be extrapolated from findings in adults, the efficacy of OXN for the proposed indication in pediatric patients requires an adequate and well-controlled clinical efficacy trial.**

DISCUSSION: No discussion necessary.

Biostatistics:

Presentation of Data

6. *Does the Agency agree with the proposed plan for presentation of the study level clinical data?*

FDA Response: Yes, but note the following additional requests.

- **You propose to map pre-STDM "legacy" datasets to SDTM, without submitting the original CRF data files. While it is helpful to have all data in SDTM format, also submit the original data files. This provides a level of traceability that is helpful in the review process.**

- **You propose to provide DEFINE.XML files for newer datasets. While this is consistent with the CDISC standard, also provide these files in PDF format. Submit the data definition files (DEFINE.XML and DEFINE.PDF copy) for both the clinical and analysis datasets while also providing an annotated case report form (aCRF).**

- **Submit the software programs used for all efficacy analyses. Our preference is that these programs are sufficient to reproduce the results in the submission.**

- **See responses to Questions 1-3 for comments on the suitability of your proposed Phase 3 studies.**

DISCUSSION: No discussion necessary.

Structure of Integrated Summary of Efficacy (ISE):

7. *Does the Agency agree with the proposed format of the ISE?*

FDA Response:

- **Your proposal to present the results of the Phase 3 studies individually, rather than conduct an integrated analysis, is acceptable. We note, however, that the scope of the ISE is not limited to Phase 3 studies, but includes all studies with data relevant to efficacy. See "Guidance for Industry – Integrated Summary of Effectiveness" for details.**

- **In contrast, you also propose that the disposition, exposure, and demographic characteristics of the Phase 3 studies be presented in the aggregate. This is only appropriate if these characteristics are fairly homogeneous across studies. Otherwise, report them separately for each study.**

- (b) (4)

- **See responses to Questions 1-3 for comments on the suitability of your proposed Phase 3 studies.**

DISCUSSION: No discussion necessary.

Clarification of the Response to Question 6 from the Pre-IND Meeting:

8. *Does the Agency agree that the data from the German post-marketing study and the ex-US post-marketing experience will not be pooled with the other Phase 1 - 3 studies included in the NDA and will be presented separately in the ISS?*

   FDA Response: Yes, we agree.

DISCUSSION: No discussion necessary.

Discussion of ONU3701 (b) (4) Response:

9. *During the End of Phase 2 meeting, we would like to engage the Agency's biostatisticians in a discussion of the implications of the NAS recommendations for the handling of missing data in clinical trials. We would like to gain a better understanding of the Agency's interpretations of the NAS report. At this meeting, can the Agency provide its interpretation of the NAS report and thoughts on implementing the NAS recommendations in the ONU Phase 3 studies?*

   FDA Response: Yes, we can discuss the NAS recommendations.

Purdue Follow-up Questions for November 18, 2010:

1. The NAS report stresses the need to define explicitly the parameter or causal estimand on which we will base our inference (Chapter 2). We propose that the estimand for the assessment of analgesic efficacy be the difference in pain scores at Week 12 for all randomized subjects based solely on their randomized treatment, and not on the treatment they received. This approach is consistent with the ITT principle.

   Does the Agency agree with this choice of estimand?

2. A certain amount of missing data is unavoidable in a 12 week study even if attempts are made to collect data after a patient d/c treatment. However, in the context of a study where the collection of data across all double-blind visits is planned for all randomized subjects, missing retrieved drop-out data can be assumed to be missing at random. Therefore, we would assume that the post-discontinuation pain scores for patients who fail to come back for a study visit are similar to the pain scores for patients who discontinue and come back for every study visit.

   Does this Agency agree that missing retrieved drop-out data can be considered missing at random?

3. In the proposed ONU pivotal studies we have defined "responder analyses" that are consistent with the FDA guidance we received thus far. In these analyses, subjects who discontinue study drug early are categorized as failures or are considered non-responders. In the case of responder analyses for analgesic efficacy, this is equivalent to using BOCF, a single imputation method, to estimate the Week 12 pain scores for patients who discontinue early.

   What are the implications of the NAS report for responder analyses?

4. Based on current Agency feedback, we are planning to conduct two 3-arm studies (placebo, extended release oxycodone, OXN) with (b) (4) co-primary variables to assess (b) (4) the analgesic efficacy (b) (4) of OXN. Our strategy for handling missing data may be different for the (b) (4) co-primaries. For example, to assess analgesic efficacy we would follow a strategy consistent with our previous questions regarding the analysis of pain scores; (b) (4)

   Does the Agency agree that the strategy for handling missing data may be different for the (b) (4) co-primaries?

DISCUSSION:
The Sponsor began the discussion by noting that it may take a while to come to an agreement on how to implement the NAS recommendations and that this program and several other studies across multiple projects could be delayed because of this missing data imputation issue. (b) (4)

In response to the Sponsor's follow-up questions above, the Agency noted that our response would require discussion between the clinical and statistical teams, and we have not yet had the opportunity to have that discussion. In general, however, our understanding of the Academy's report is in agreement with the Sponsor's. The Agency will need to discuss, however, whether the proposed estimand is appropriate for the Sponsor's proposed trials.

The data will not be missing at random, but treating them as though they were may be the least bad approach. Much depends on success in following patients who discontinue treatment. If most are successfully retrieved, the approach has merit. If only a few are successfully retrieved, it is problematic.

The Agency agrees with your observation that a responder analysis can be mathematically similar or even identical to BOCF and agrees with the Academy's criticism of BOCF and other single-imputation methods if they are viewed as ways of estimating the intent-to-treat estimand. The Agency still thinks the responder analysis is useful in analgesic trials. The outcome is then correctly understood as a composite of successful completion with acceptable pain scores.

The Agency agrees that the strategy for handling missing data may be different for the (b) (4) co-primaries.

The Agency would still like to see a continuous responder analysis, even if it is not chosen as the primary efficacy variable.

(b) (4)

POST MEETING NOTE: The Division is engaging in ongoing discussions regarding implementation of the NAS recommendations. We will provide additional feedback following the internal discussions.

Abuse Liability:

10. *Does the Agency agree that the ONU abuse liability program, consisting of several in vitro studies and the 3 human abuse liability studies (ONU1003, ONU1004, and ONU9001), is adequate and sufficient to evaluate the abuse liability of OXN?*

FDA Response:

- **Detailed protocols were not provided for review and comment. As such, our responses are limited to the brief description of the high points and goals of their studies and should not be interpreted as support and acceptance of the study protocols.**

- **Detailed protocols were not provided regarding the in vitro manipulation and chemical extraction studies or for the studies designated ONU1003, ONU1004 or ONU9001.**

- **Note that naloxone and oxycodone have not been approved for intranasal administration and oxycodone has not been approved for intravenous injection. The safety of the proposed clinical abuse liability studies must be adequately justified for these routes of administration. A toxicology study in a single species that includes both acute and delayed observations should be completed for each novel route of administration, unless otherwise justified. Clinical studies must not employ crushed drug product due to the presence of talc and other potentially harmful excipients.**

- **Based on the limited information that was provided, the in vitro manipulation and chemical extraction studies appear to be appropriate. As a reminder, all in vitro studies need to be conducted on the to-be-marketed formulation. With regard to alcohol drug interaction, we note your plan to conduct an in vitro study. We recommend that you follow it up with an in vivo drug interaction study based on the in vitro study results.**

- **Overall, based on the limited information provided, the design of clinical abuse liability study ONU1003 seems appropriate. With regard to abuse liability study # 1003, we note that you intend to use immediate-release oxycodone solution as a comparator for PK and drug liking measures. From experience, we have noted that such comparison could result in misleading conclusions where any misuse/manipulated treatment might appear better compared to immediate release solution/treatment. In order to understand if the tampered product is retaining extended-release characteristics, comparison should be made with intact product consumed orally. Hence, an additional treatment arm of intact OXN is required to be added to the oral administration (Group 1) segment of ONU1003. We realize that inclusion of such an arm will require an additional dummy/placebo treatment for oral consumption intact.**

- **With regard to ONU1004, appropriate justification for the selected population and dosage strength selected to study needs to be provided. Include detailed information about the conditions of the study and safety evaluation of the patients in the full protocol. In addition, oral administration of the intact OXN tablet should be evaluated.**

- **Regarding study ONU9001, justification and validation should be provided in the NDA.**

Purdue Follow-up Question for November 18, 2010:
In your recommendation that intact OXN be included in the oral portion of ONU1003 and ONU1004, we note that your rationale cites the possibility that tampered OXN may retain extended-release characteristics. In vitro data indicate that OXN's controlled release formulation does not provide meaningful mechanical tamper resistance and that simple crushing converts an OXN tablet into an immediate-release presentation of both the oxycodone and the naloxone content.

Given this, can you expand upon the utility of inclusion of intact OXN tablets in the evaluation of the abuse liability of OXN administered orally?

DISCUSSION:
The Agency stated that the use of intact OXN tablet is recommended because it will serve as an important reference arm, in addition to the IR treatment and placebo. In terms of study results, one outcome would be that the crushed product has similar drug liking compared to placebo. A more likely alternative result would show that the crushed product has less drug liking (~X%) compared to IR product that is not similar to placebo. This will lead to an important additional question, "What is the meaning of the observed ~X% of lower drug liking compared to IR treatment?" In such a situation, it will be beneficial to understand the relationship of the crushed product's drug liking characteristics compared to intact OXN.

The Agency noted that the primary route of abuse is swallowing the intact tablet, therefore it would be valuable to know the drug liking of the intact tablet. If the tablet is crushed, it will be important to see if the naloxone mitigates drug liking at all. A complete picture is needed to fully understand the drug product.

11. *Assuming the 3 human abuse liability studies (ONU1003, ONU1004, and ONU9001) show that naloxone demonstrates abuse deterrence to intravenous and intranasal abuse of oxycodone in OXN, does the Agency agree that these results are sufficient to justify the inclusion of naloxone in OXN, (b) (4)?*

FDA Response:

If an opioid formulation is shown to have clinically relevant abuse deterrent physiochemical properties based on a full premarketing abuse liability evaluation, that product can be considered for approval. It is possible that the inclusion of naloxone in OXN may result in the combination having some abuse deterrent properties, and therefore, the inclusion of naloxone would be justified. Refer to the response to Question 10 regarding the adequacy of the proposed abuse liability program.

DISCUSSION: The Sponsor asked if OXN would be approvable as an analgesic with abuse deterrent attributes, (b) (4) provided 1) it was demonstrated to be safe and well tolerated in the intended patient population; and 2) abuse liability studies demonstrated the abuse-deterrent properties of naloxone. The Agency responded that, if the abuse liability studies demonstrate an apparent reduction in likeability, then approvability as a formulation with abuse-deterrent attributes may be considered. (b) (4) (b) (4) (b) (4) The sponsor responded that it is not clear which product (reformulated OxyContin and OXN) may prove superior in deterring abuse and that each formulation may target a different abuse behavior. The Agency suggested adding an OxyContin arm to the abuse liability studies to allow for comparison of the (b) (4) formulations in terms of abuse via different routes.

Clinical Pharmacology:

12. *Assuming the Phase 3 studies do not show a QTc safety signal, does the Agency agree that because the safety profiles of oxycodone and naloxone are well-characterized, and there is extensive clinical trial and post-marketing experience with the combination product in Europe, a thorough QT [ICH E14] study of OXN will not be required for approval of an ONU NDA?*

    FDA Response:

    The ICH E14 Guidance pertains primarily "to novel agents and approved drugs when a new dose or route of administration is being developed that results in significantly higher exposure." The currently proposed Oxycodone/Naloxone (OXN) does not meet the requirements noted above and, as such, a thorough QT Study would not be required, pending review of QTc safety data from the proposed Phase 3 studies.

DISCUSSION: No discussion necessary.

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/s/

LISA E BASHAM
12/17/2010