

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
207621Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207621

SUPPL #

HFD # 170

Trade Name Troxyca ER

Generic Name Oxycodone hydrochloride and naltrexone hydrochloride

Applicant Name Pfizer, Inc

Approval Date, If Known August 19, 2016

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)

b) 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:

c) Did the applicant request exclusivity?

YES NO

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

3 Years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

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# 021011

Roxicodone® (oxycodone HCl)

NDA# 018932

Revia® (naltrexone HCl)

NDA# ***

Refer to the Orange Book for additional applications for oxycodone and naltrexone.

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

#1 ALO-02-10-3001(also known as B4531001)

A multicenter, 12-month, open-label, single-arm, safety study of oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules in subjects with moderate to severe chronic noncancer pain (CNCP)

#2 B4531002

A multicenter, 12-week, double-blind, placebo-controlled, randomized withdrawal study to determine the efficacy and safety of ALO-02 (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules in subjects with moderate to severe chronic low back pain (CLBP)

#3 B4531008

A randomized, double-blind, double-dummy, placebo-controlled, single-dose, 6-way crossover study to determine the relative abuse potential of ALO-02 (oxycodone HCl and naltrexone HCl extended-release capsules) compared to oxycodone immediate-release and placebo when administered orally to non-dependent, recreational opioid users

#4 B4531009

A randomized, double-blind, placebo-controlled, single-dose, 4-way crossover study to determine the relative abuse potential of ALO-02 (oxycodone HCl and naltrexone HCl ER capsules) compared to oxycodone IR and placebo when administered intranasally to non-dependent, recreational opioid users.

#5 B4981002

A randomized, single-dose, placebo-controlled, double-blind, 3-way crossover study to determine the relative abuse potential of intravenous oxycodone hydrochloride alone or in combination with intravenous naltrexone hydrochloride in opioid experienced non-dependent subjects

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #5	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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

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

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #5	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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"):

Same 5 investigations as listed in 2(c)

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 # 107037 YES NO
Explain:

Alpharma Pharmaceuticals LLC, a division of Pfizer, is the sponsor named in the Form FDA-1571 for INDs **107037** (b) (4) under which the new clinical investigations that are essential to approval of this NDA were conducted.

Investigation #2

IND # 107037 YES NO
Explain:

Investigation #3

IND # 107037 YES NO
Explain:

Investigation #4

IND # 107037 YES NO
Explain:

Investigation #5

IND # (b) (4) YES NO
Explain:

Alpharma Pharmaceuticals LLC, a division of Pfizer, is the sponsor named in the Form FDA-1571 for INDs **107037** (b) (4) under which the new clinical investigations that are essential to approval of this NDA were conducted.

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

Investigation #1

YES
Explain:

NO
Explain:

Investigation #2

YES
Explain:

NO
Explain:

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

YES NO

If yes, explain:

Name of person completing form: Diana L. Walker, PhD
Title: RPM, DAAAP
Date: August 19, 2016

Name of Office/Division Director signing form: Sharon Hertz, MD
Title: Director, DAAAP

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

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

/s/

DIANA L WALKER
08/19/2016

SHARON H HERTZ
08/19/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207621 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Troxyca ER Established/Proper Name: oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules Dosage Form: oral capsules		Applicant: Pfizer, Inc. Agent for Applicant (if applicable):
RPM: Diana Walker		Division: DAAAP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: _____</p> <p><i>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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is _____ 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ 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, 505(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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 4 – New Combination
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: Information Advisory
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> 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)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action and date: Approval; August 19, 2016
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	March 11, 2015 March 9, 2015
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: February 11, 2015 DMEPA: April 29, 2015 DMPP/PLT: April 27, 2016 September 14, 2015 OPDP: December 15, 2015 September 15, 2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: Maternal Health Team: September 29, 2015
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	February 11, 2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) September 17, 2015
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>August 19, 2015</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i>)	included
❖ 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)	included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg March 18, 2014
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg November 8, 2010
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	

❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date of Meeting	June 8, 2016
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 19, 2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None August 19, 2016
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	Final: September 14, 2015 Filing: February 17, 2015
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See clinical reviews.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None Drug Utilization: August 8, 2016
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> N/A CSS-Stats – September 22, 2015 CCS-final – September 16, 2015 Filing – February 11, 2015
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	June 6, 2016
• REMS Memo (<i>indicate date</i>)	<input type="checkbox"/> None - August 18, 2016
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	July 8, 2016 January 15, 2016 December 18, 2015 December 4, 2015
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested December 21, 2015 October 1, 2015 (2) September 11, 2015
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Final: September 11, 2015 Filing: February 19, 2015

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Final: September 14, 2015 Filing: February 6, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None Final: December 1, 2015 Filing: February 6, 2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None #3 – December 4, 2015 #2 – December 2, 2015 #1- September 14, 2015 Filing review – February 11, 2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See Product Quality Review September 14, 2015
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change))</i>	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

DIANA L WALKER
08/23/2016

From: [Walker, Diana](#)
To: [Thinnes, Lynley K](#)
Cc: [Pritchard, Lynn \(Regulatory\)](#)
Subject: NDA 207621 Troxyca ER Label revisions 06jul16
Date: Wednesday, July 06, 2016 2:52:28 PM
Attachments: [USPI-Troxyca ER-capsule to Pfizer_06July2016.doc](#)

Dear Lynley,

Please find attached the package insert label in track changes.

Please review this document, and:

1. Accept the changes with which you agree.
2. Make revisions and add a rationale comment for any language with which you do not agree.
3. Please check for the accuracy of the cross references, figure and table numbers (including in-text references to those figures and tables), etc..
4. Please check for any formatting or typographical errors and make those corrections.

Please return the label containing your revisions in track changes to me via email only. There is no need to submit formally to your NDA at this time, as there may be additional negotiation before the action date.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
07/11/2016

From: [Walker, Diana](#)
To: [Thinnes, Lynley K \(Lynley.K.Thinnes@pfizer.com\)](#)
Cc: [Pritchard, Lynn \(Regulatory\) \(Margaret.Pritchard@pfizer.com\)](#)
Subject: NDA 207621 REMS Revisions 02Jun16
Date: Thursday, June 02, 2016 2:14:54 PM
Attachments: [risk-evaluation-and-mitigation-strategy 4.26.2016 clean.doc](#)
Importance: High

Dear Lynley,

I have received feedback on the REMS submission and requested revisions. Please revise and submit the following requested documents as soon as possible through the Gateway:

The following documents from your REMS submission on May 25, 2016 are not correct.

1. Risk Management REMS and Materials Tracked Changes (Word): [rems-and-materials-tracked-changes.doc](#)
2. Risk Management REMS and Materials Clean (Word): [rems-and-materials-clean.doc](#)
3. Risk Management REMS and Materials Clean 1 (PDF): [rems-and-materials-clean-1.pdf](#)

First, the ER/LA REMS Blueprint in these 3 document does not include Xtampza product-specific information, which was approved by the Agency in the ER/LA REMS on April 26, 2016. Second, the Troxyca product-specific information language in the ER/LA REMS Blueprint you submitted is different from the agreed-upon language from December 2015. The following information is what was agreed upon in December 2015 and is not impacted by the changes to the Troxyca Package Insert since that time.

Troxyca ER	Oxycodone Hydrochloride/Naltrexone Hydrochloride Extended-Release Capsules, 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, 80 mg/9.6 mg
Dosing Interval	<ul style="list-style-type: none">▪ Every 12 hours
Key Instructions	<ul style="list-style-type: none">▪ Opioid-naïve and opioid non-tolerant patients: 10 mg/1.2 mg, every 12 hours▪ Total daily dose may be adjusted by 20 mg/2.4 mg every 2 to 3 days as needed▪ Swallow capsule whole (do not chew, crush, or dissolve).▪ Crushing, chewing, or dissolving will release oxycodone, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms.▪ For patients that have difficulty swallowing, Troxyca ER, can also be taken by sprinkling the capsule contents (pellets) on applesauce and swallowing immediately without chewing.▪ Do not administer Troxyca ER pellets through a nasogastric or gastric tube
Specific Drug Interactions	<ul style="list-style-type: none">▪ CYP3A4 inhibitors may increase oxycodone exposure.▪ CYP3A4 inducers may decrease oxycodone exposure.

Use in Opioid-Tolerant Patients	Single doses of greater than 40 mg/4.8 mg, or a total daily dose greater than 80 mg/9.6 mg are only for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	<ul style="list-style-type: none"> ▪ See individual product information for conversion recommendations from prior opioid.

The attached Word document is the most recently FDA-approved ER/LA REMS document and appended materials from April 26, 2016, which includes Xtampza information but does not include proposed Troxyca product-specific information. Insert the above language for Troxyca's product specific information into the Blueprint within the attached document.

You must submit an amendment to your application through the Gateway with the following 13 documents prior to the action date (**please submit as soon as possible**):

Revised documents:

1. Risk Management REMS and Materials Tracked Changes (Word) A **tracked, Word** document containing the ER/LA REMS document and all appended materials (i.e. the attached Word document, tracked with the above Troxyca product specific information inserted)
2. Risk Management REMS and Materials Clean (Word) A **clean, Word** document containing the ER/LA REMS document and all appended materials (i.e. the attached Word document, clean, with the above Troxyca product specific information inserted)
3. Risk Management REMS and Materials Clean 1 (PDF) A **clean, PDF** document containing the ER/LA REMS document and all appended materials (i.e. the attached Word document, clean, with the above Troxyca product specific information inserted)

Documents which were acceptable in your May 25, 2016 submission but must also be submitted in the amendment to your application:

4. ER/LA Opioid Analgesic REMS Website Clean
5. Patient Counseling Document Clean
6. Prescriber Letter 1 Clean
7. Prescriber Letter 2 Clean
8. Prescriber Letter 3 Clean
9. Professional Organization Licensing Board Letter 1 Clean
10. Professional Organization Licensing Board Letter 1 Clean
11. REMS Supporting Document Clean 1 (PDF)
12. REMS Supporting Document Clean (Word)
13. REMS Supporting Document Tracked Changes (Word)

If you prefer the Agency confirm the revised documents are correct prior to you submitting them through the gateway, submit revised materials via email by COB June 3, 2016.

Kindly acknowledge receipt of this email, and whether you have any clarifying questions.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
06/08/2016

From: [Walker, Diana](#)
To: [Thinnes, Lynley K \(Lynley.K.Thinnes@pfizer.com\)](#)
Subject: NDA 207621 Request for Updated REMS 18may16
Date: Wednesday, May 18, 2016 1:28:50 PM
Importance: High

Dear Lynley,

Pfizer has previously submitted REMS documents for NDA 207621. Given the recent approval of another opioid that is part of the ER/LA REMS, you must resubmit the most up-to-date ER/LA REMS, which includes you Troxyca product-specific information added into the Blueprint. The RPC is the industry source for the latest versions of the ER/LA REMS document, appended materials, and supporting document for distribution to NDAs seeking application approval. We request that you submit the REMS document, appended materials, and supporting document in Word format with your changes redlined. The REMS document and appended materials should be submitted in 1 consolidated document and as separate files for each document. The ER/LA website can be submitted as a PDF.

Please submit the requested updated REMS materials to your NDA (through the Gateway) by May 24, 2016.

If you have any questions, please don't hesitate to contact me.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
06/08/2016

From: [Walker, Diana](#)
To: [Thinnes, Lynley K \(Lynley.K.Thinnes@pfizer.com\)](mailto:Thinnes.Lynley.K@pfizer.com)
Subject: NDA 207621 PMR information 17may16
Date: Tuesday, May 17, 2016 12:41:22 PM
Importance: High

Dear Lynley,

I have two PMR related topics to send to you for the Troxyca NDA.

First, PMR 2965-2 (please see email string below from December 2015) has been replaced by two PMRs (PMR 2965-2 and 2965-3) based on the Agency's current thinking regarding PMRs for abuse deterrent products. The timeframes for the milestone dates in yellow are set, based on approval date. Please send me your concurrence and/or comments.

Additionally, FDA has determined that you are also required to conduct the following individual postmarketing studies of TROXYCA ER (oxycodone and naltrexone) Capsules: 2965-2 In order to provide the baseline data to support the hypothesis-testing studies required under PMR 2965-3, conduct a descriptive study that analyzes data on the following:

- (1) utilization of TROXYCA ER (oxycodone and naltrexone) and selected comparators. Reports should include nationally-projected quarterly retail dispensing, overall and by age group and census region; AND
- (2) abuse of TROXYCA ER (oxycodone and naltrexone) and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and patterns of abuse for TROXYCA ER (oxycodone and naltrexone) as well as mutually agreed-upon, selected comparators to provide context.
 - Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.
 - Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.
 - Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g. 95% confidence intervals for quarterly estimates) and calculate utilization-adjusted outcome estimates where possible.

This study will be conducted according to the following schedule:

Final Protocol Submission: XX/XXXX (6 months after approval)

Study Completion: XX/XXXX (18 months after approval)

Final Report Submission: XX/XXXX (2 years after approval)

2965-3 Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of TROXYCA ER (oxycodone and naltrexone) actually result in a meaningful decrease in misuse and abuse, and their (b) (4) addiction, overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of TROXYCA ER (oxycodone and naltrexone) and should incorporate recommendations contained in *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry* (April 2015). Assessing the impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA’s *Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*.

This study will be conducted according to the following schedule:

Final Protocol Submission: XX/XXXX (2.5 years after approval)

Study Completion: XX/XXXX (4.5 years after approval)

Final Report Submission: XX/XXXX (5 years after approval)

Study protocols, proposed statistical analysis plans (SAPs), and the milestones for each study conducted under PMR 2965-3 must be mutually agreed upon with FDA, and informed by results from PMR 2965-2. Protocols and SAPs should be submitted to FDA prior to initiating these formal studies, in sufficient time for the Agency to review and provide comments, and concur with the protocols. The protocols and SAPs should incorporate formal hypothesis testing in addition to descriptive analyses and should include power calculations based on actual data.

Second, for PMR 2965-1 and PMRs 2965- 4, -5 , -6, Pfizer originally proposed/confirmed the dates below in yellow, prior to the delays caused by the AC meeting. I know you have already submitted your pediatric protocol.

For the other dates in yellow below for the PREA and nonclinical PMRs, please either confirm these milestone dates, or propose revised dates, assuming an Action date sometime after the AC meeting.

You could also list the dates similar to those above, i.e., 2 years after approval, etc.

Your deferred pediatric study required by Section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and Section 505B(a)(3)(B) of the FDCA. This required study is

listed below.

- 2965-1. Conduct a pharmacokinetic and safety study of an age-appropriate formulation of Troxyca ER (oxycodone and naltrexone) in patients seven to less than 17 years of age with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Final Protocol Submission: 04/2015
Study Completion: 01/2019
Final Report Submission: 07/2019

- 2965-4. Conduct an in vivo comet assay for (b) (4).

The timetable you submitted on December 10, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2016
Study Completion: 11/2016
Final Report Submission: 02/2017

- 2965-5. Conduct an in vivo comet assay for (b) (4).

The timetable you submitted on December 10, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2016
Study Completion: 11/2016
Final Report Submission: 02/2017

- 2965-6. Conduct a pre- and post-natal development study in the rat model to assess the potential impact of dibutyl sebacate on development.

The timetable you submitted on December 10, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2016
Study Completion: 03/2017
Final Report Submission: 11/2017

Please respond via email and follow this with a correspondence amendment to your NDA 207621.

Warm regards,

Diana

From: Walker, Diana
Sent: Monday, December 07, 2015 1:59 PM
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 PMR information 07dec15

Dear Kate,

Please see below an additional PMR that will be required for Troxyca. Please include this in your NDA submission with the other PMRs that I sent in my Friday, December 4, 2015, email.

2965- 2.

(b) (4)



Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP

Tel: 301-796-4029

Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
06/08/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FDA INTERNAL MEMO

APPLICATION/DRUG: NDA 207621, Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride)

This memorandum documents certain facts concerning an application that relates to Kleinfeld Kaplan & Becker, LLP's citizen petition on behalf of Purdue Pharma L.P., dated December 22, 2015 (FDA-2015-P-5108).

As of May 16, 2016, the 505(b)(2) application for NDA 207621, Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride) is pending and under review. This application was submitted by Pfizer, Inc., on December 19, 2014. Pfizer submitted a Major Amendment to the NDA on October 5, 2015, and submitted new studies to the NDA. An Advisory Committee meeting to discuss this application is scheduled for June 8, 2016, and review of the application will not be completed when the petition response is due under 505(q) of the Federal Food, Drug, and Cosmetic Act.

Diana Walker
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/

DIANA L WALKER
05/16/2016

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Cc: [Walker, Diana](#)
Subject: NDA 207621 Package Insert Label revisions 25Jan16
Date: Monday, January 25, 2016 12:50:23 PM
Attachments: [USPI-Troxyca ER-oxycodone hydrochloride, naltrexone hydrochloride-capsule FDA revisions 25Jan2016.doc](#)

Dear Kate,

Please find attached the package insert label for Troxyca with the Agency's comments in track changes. Please review this label and please send me back a revised label following the requests below:

1. Accept those changes with which you agree.
2. Respond to the comments from the review team by making any requested edits in track changes, or if you agree and have no additional comments, simply accept the changes and delete the comment.
3. For the language with which you do not agree, please make revisions in track changes, and also include a comment containing your rationale/support for your alternative proposed language.
4. Please check for any editorial or formatting errors and make corrections.

Please send me your revised label via email. There is no need to submit to your NDA, as we will continue negotiating the labeling language via email.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

Diana L. Walker, Ph.D.
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DIANA L WALKER
02/04/2016

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Cc: [Jani, Parinda](#)
Subject: NDA 207621 Package Insert labeling comments 15dec15
Date: Tuesday, December 15, 2015 4:18:25 PM
Attachments: [Draft pkg-insert-track 15Dec15 - sent to Pfizer.doc](#)
Importance: High

Dear Kate,

Please find attached the package insert label for Troxyca with the Agency's comments in track changes. Please review this label and please send me back a revised label following the requests below:

1. Accept those changes with which you agree.
2. Respond to the comments and requests from the review team by making the requested edits in track changes.
3. For the language with which you do not agree, please make revisions in track changes, and also include a comment containing your rationale/support for your alternative proposed language.
4. Please check for any editorial or formatting errors and make corrections.

Please send me your revised label as soon as possible via email. There is no need to submit to your NDA, as we will negotiate the labeling language via email.

I will be out of the office next week, but please send the label back as soon as possible. I am copying my supervisor, Parinda Jani, who can also forward this on to the team for review in my absence, so please copy her when you send back the label.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
01/13/2016

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Cc: [Jani, Parinda](#)
Subject: NDA 207621 Abuse Liability Information request 18dec15
Date: Friday, December 18, 2015 1:36:27 PM
Importance: High

Dear Kate,

I have received the following information request. Please respond as soon as possible with a submission to your pending NDA 207621 for Troxyca of your response and reanalysis. Note that the request for revisions to the proposed labeling does not need to be submitted to the NDA; those changes should be added to the draft label that you are currently working on in track changes, and sent to me directly via email.

Provide the results for Drug Liking, High, and Take Drug Again for the oral human abuse liability study (1008) and the intranasal human abuse liability study (1009), excluding subjects 1052 (oral study) and 1092 (intranasal study) from ALL treatment periods for ALL of these analyses, as these subjects had a pre-dose response for high of 50, indicating a potentially systematic issue with these subjects. Additionally, for Drug Liking and Take Drug Again only, provide the results for Drug Liking and Take Drug Again in the respective tables in the proposed labeling.

Please let me know if you have any questions. I will be out of the office 12/20 – 12/25, so if you have questions during that week, please contact my supervisor, Parinda Jani, copied on this email. I will be back in the office on 12/28.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
01/13/2016

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 Abuse Liability Study Information Request 10dec15
Date: Thursday, December 10, 2015 2:08:21 PM
Importance: High

Dear Kate,

I have received an information request from our review team. Please provide the requested information as soon as possible, or by Monday, December 14, 2015. Please send this information via email, followed by a submission to your NDA. Note that for #1a, you can provide these materials separately from the label, just as tables.

Please respond to the following:

In reference to the oral human abuse liability study (B4531008), the median Emax of high for intact Troxyca ER 60 mg/7.2 mg was reported to be 4 on a 0 to 100 point unipolar visual analog scale (VAS) with a range of -46 to 100. We note that one subject had a negative score (i.e., -46) and that the pre-dose and post-dose scores were 50 and 4, respectively, to derive a -46 for this subject.

1. Provide a detailed explanation for how a subject could have a negative result for Emax of high on a 0 to 100 unipolar VAS. Further, describe why a subject who had a score of 50 at pre-dose was allowed to continue if that subject was evidently already experiencing a substantial high. Describe the workup that was undertaken for this subject before continuing them in the study (e.g., clinical evaluation, urine drug screen, etc.) and provide justification for continuing that subject in the study based on the workup.

a. Repopulate the table in the proposed label reporting the results for the oral human abuse liability study (i.e., Table 4. Summary of Abuse Potential Measures of Drug Liking and High with Oral Administration of Intact and Crushed TROXYCA ER Compared to Crushed IR Oxycodone HCl), excluding this subject from all of the analyses (i.e., all treatment arms). Provide a side-by-side comparison of these results with and without the subject in question.

2. A median Emax of high of 4 is unusual for an opioid. Provide a detailed explanation for this result.

a. Describe the duration of the observation period for Emax and describe when Emax occurred relative to Tmax.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
01/13/2016

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 REMS Information Request 06dec15
Date: Sunday, December 06, 2015 2:10:09 PM
Attachments: [ERLA Opioid REMS Complete_TC_Dec 2015.doc](#)

Dear Kate,

I have received the following information request from our DRISK review team concerning your REMS for NDA 207621, Troxyca. Please respond to the following comments, and the attached document, with an official submission to your NDA as requested below.

The Office of Surveillance and Epidemiology (OSE), DRISK has completed the review of the ER/LA Opioid Analgesic REMS document and appended materials submitted on July 24, 2015. DRISK has the following comments, below, in response to the your proposal, including the redlined/highlighted changes to the ER/LA Opioid Analgesic REMS document and appended materials. Please respond to these comments by December 10, 2015 to facilitate further review for this submission.

- 1. Please note the additional track changes and comments in the attached *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics*.**
- 2. NOTE: OxyContin (approved on August 13, 2015), Morphabond (approved on October 2, 2015), and Belbuca (approved on October 23, 2015) were approved by the Agency with a revised ER/LA Opioid REMS. The attached ER/LA Opioid REMS materials includes OxyContin, Morphabond, and Belbuca's product-specific information in the Blueprint, Patient Counseling Document, Prescriber Letters and Website where noted. If approved, Troxyca ER's REMS must include the OxyContin, Morphabond, and Belbuca product specific information.**
- 3. The "Most Recent Modification" date on the REMS document must be changed to "XX/XXXX" as indicated in the redlined, attached REMS document when resubmitted to the Agency. If this product is approved, this date will be updated by the Agency to reflect the approval date.**
- 4. Resubmission and Format Instructions:**
 - a. Submit the following materials, and any other materials with additional proposed revisions not listed here, as both a redlined Word document and as a clean, final, formatted PDF document:**
 - i. Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics**
 - ii. FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics**
 - iii. Prescriber Letters**
 - iv. ER/LA Opioid Analgesic REMS website**
 - b. Submit the following materials (which were not revised) as clean, final, formatted Word and PDF documents**
 - i. ER/LA Opioid REMS Document**
 - ii. Professional Organization/Licensing Board Letters**

Please contact me with any questions or if you have any problems opening/viewing this email or attached document.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
01/13/2016

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 PMR information 07dec15
Date: Monday, December 07, 2015 1:59:12 PM

Dear Kate,

Please see below an additional PMR that will be required for Troxyca. Please include this in your NDA submission with the other PMRs that I sent in my Friday, December 4, 2015, email.

2965- 2.

Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of TROXYCA ER actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of TROXYCA ER. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance, Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013) and proposed comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.

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

Final Protocol Submission:	12/2016
Study Completion:	12/2020
Final Report Submission:	06/2021

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
01/13/2016

Walker, Diana

From: Walker, Diana
Sent: Friday, December 04, 2015 9:40 AM
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 PMR Information Request 04Dec2015

Dear Kate,

Please see below for four PMRs that the Division has determined are necessary for your product, NDA 207621, Troxyca. Please submit your proposed milestone dates requested for the three PMRs below as soon as possible.

Note that, as Troxyca will be part of the ERLA REMS, the PMRs as part of that program will also be required, but are not listed in this email. If you have questions concerning those PMRs, please let me know and I will send those in a second email.

Note that, for PMR 2965-1, which is your PREA PMR, the milestone dates have already been populated per the dates you proposed in your NDA submission, and also reflect the date of your protocol submission in April.

2965-1. Conduct a pharmacokinetic and safety study of an age-appropriate formulation of Troxyca ER in patients 7 to less than 17 years of age with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Final Protocol Submission: 04/2015
Study/Trial Completion: 01/2019
Final Report Submission: 07/2019

Please submit proposed milestone dates for the three PMRs listed below:

2965-3. Conduct an in vivo comet assay for (b) (4)

Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

2965-4. Conduct an in vivo comet assay for (b) (4)

Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

2965-5. Conduct a pre- and post-natal development study in the rat model to assess the potential impact of dibutyl sebacate on development.

Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

If you have any questions, feel free to contact me.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
01/13/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FDA INTERNAL MEMO

APPLICATION/DRUG: NDA 207621, Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride)

This memorandum documents certain facts concerning an application that relates to Kleinfeld Kaplan & Becker, LLP's citizen petition on behalf of Purdue Pharma L.P., dated June 9, 2015 (FDA-2015-P-2120).

As of November 2, 2015, the 505(b)(2) application for NDA 207621, Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride) is pending and under review. This application was submitted by Pfizer, Inc., on December 19, 2014. Pfizer submitted a Major Amendment to the NDA on October 5, 2015, and submitted new studies to the NDA. Review of these studies is not complete. The PDUFA date for this application is January 19, 2016, and review of the application will not be completed when the petition response is due under 505(q) of the Federal Food, Drug, and Cosmetic Act.¹

Diana Walker
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

¹ FDA's regulation at 21 CFR 314.430(b) provides that "FDA will not publicly disclose the existence of an application or an abbreviated application before an approval letter is sent to the applicant under § 314.105 or tentative approval letter is sent to the applicant under § 314.107, unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged."

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/s/

DIANA L WALKER
11/04/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 7, 2015

TO: File

THROUGH: n/a

FROM: Diana Walker, RPM, DAAAP

SUBJECT: **Memo of Teleconference on October 2, 2015**

APPLICATION/DRUG: NDA 207621 Troxyca ER

The following were on the call from the FDA:

Sharon Hertz, Director, DAAAP
Joshua Lloyd, Clinical Team Leader
Daniel Mellon, Supervisor, Pharmacology-Toxicology
Elizabeth Bolan, Nonclinical Reviewer
Diana Walker, RPM

The following were on the call from the Applicant, Pfizer:

Ross Bell (Nonclinical)
Joseph Brady (Nonclinical)
Susanna Tse (Nonclinical)
Alan Litwack (Asset Team Lead)
Sean Donevan (Medical)
Gernot Wolfram (Clinical)
Bimal Malhotra (Clinical Pharmacology)
Therese Debiak-Krook (CMC)
Donald Guzek (Pharmaceutical Sciences)
Saima Khan (Regulatory)
Kate Collins (Regulatory)

During the teleconference on October 2, 2015, the Division informed the Applicant that the support provided by the Applicant for the qualification of dibutyl sebacate has been found to be inadequate, and additional support for the safety of this excipient will be required for approval of this NDA. The Division also noted that we are aware of the nonclinical studies submitted by the applicant to their IND; however, these studies cannot be reviewed unless they are submitted to

the NDA. When asked by the Applicant for clarification on what is missing from the current support provided in the NDA, the Division stated that the single paper submitted in support is inadequate. What is required are the studies that the Division had requested at the meetings during the IND stages of the product, before the NDA was submitted. The Division suggested that most of the required information would likely be contained in the study reports submitted to the IND, and wondered why these were not submitted as support in the NDA. The Applicant stated that they had believed that the material they submitted with the NDA was already adequate, and that they would not need additional study data. The Applicant asked whether the Agency would consider requesting this additional information as a PMR. The Division stated that a PMR for this information will not be considered, since it is our policy not to issue a PMR for completed studies. The Applicant asked whether, if they were to submit the required studies by Monday, October 5, the Division would consider not extending the clock, but completing the review of the materials within the current PDUFA date. The Division stated that the review team will not be able to review the studies that quickly, and that, while the Division may be able to complete the reviews sooner, an official clock-extension will be for 3-months.

The Applicant agreed to submit the studies as soon as possible

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/s/

DIANA L WALKER
10/08/2015



NDA 207621

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Attention: Kathleen Collins
Director, Worldwide Safety and Regulatory

Dear Ms. Collins:

Please refer to your New Drug Application (NDA) dated and received December 19, 2014, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Oxycodone hydrochloride and naltrexone hydrochloride, 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, 80 mg/9.6 mg Extended-Release Capsules.

On October 5, 2015, we received your major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 19, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 30, 2015.

If you have any questions, call Diana L. Walker, PhD, Senior Regulatory Health Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, 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/

SHARON H HERTZ
10/07/2015

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 Statistical Comments 22sep15
Date: Tuesday, September 22, 2015 10:40:26 AM
Attachments: [image001.png](#)
[image006.png](#)
[image007.png](#)

Dear Kate,

I am sending you additional comments from the statistical reviewer. These comments are informational only, no additional submission is required.

We have reviewed Pfizer's response to Question 2 in the Statistical Information Request dated August 31, 2015, and are providing the comments below:

1. The fact that skewness of the distribution has greater effect on the distribution of a t-type random variable than the kurtosis does and the positive skewness in the parent distribution results in the sampling distribution of t-type random variables being negatively skewed. The short right tail in the sampling distribution of t leads to a loss of power for upper-tailed tests of the population means. Johnson's t1 test is an upper-tailed test for the mean of the distributions as asymmetric as an exponential distribution.

2. The reviewer re-examined the data from Studies 1009 and 1002, and found:

(1) Both distributions of $ALO30c - (1 - \delta^*)O_{xy30c}$ and $ALO20IV - (1 - \delta^*)O_{xy20IV}$ are positively skewed.

(2) Both tests in studies 1009 and 1002 for the primary comparison between the test drug and the positive control are lower-tailed tests.

Therefore, the Johnson's t1 test is not proper for the primary comparison in both Studies 1009 and 1002.

3. You may simply use the t test for the primary comparison in both Studies 1009 and 1002.

Please feel free to contact me if you have any questions.

Warm regards,

Diana

From: Walker, Diana
Sent: Wednesday, September 09, 2015 2:37 PM
To: 'Collins -Novikov, Kathleen'
Subject: RE: NDA 207621 Statistical Information request 31aug15

Dear Kate,

I am sending you follow up on your responses to Question #3. You are not required to resubmit your re-analysis if you choose to do a re-analysis, this is for informational purposes so that, if any of the numbers from these analyses are used in labeling you will understand the rationale.

Our statistics reviewer has examined your results for the secondary analysis again for study 1009. The results may differ between Pfizer and FDA in the secondary analysis because there are two placebos in the study, and Pfizer used the placebo matched weight of ALO-02 in the calculation for the percent reduction. Attached is a copy of a poster presented at the 2015 CPDD annual meeting. Our reviewer highlighted the sentence related to choice of placebo in the calculation of percent reduction on the poster, and requested that I pass it on to you. The PDF is attached.

Warm regards,

Diana

From: Collins -Novikov, Kathleen [<mailto:Kathleen.Collins-Novikov@pfizer.com>]
Sent: Tuesday, September 08, 2015 5:49 PM
To: Walker, Diana
Cc: Collins -Novikov, Kathleen
Subject: RE: NDA 207621 Statistical Information request 31aug15

Dear Diana,

The response to questions 1 and 3 should be dispatched shortly via the Gateway. We plan to submit the response to question 2 by the 14th of September 2015.

Thanks

Kate

From: Walker, Diana [<mailto:Diana.Walker@fda.hhs.gov>]
Sent: Monday, August 31, 2015 2:31 PM
To: Collins -Novikov, Kathleen
Subject: NDA 207621 Statistical Information request 31aug15

Dear Kate,

I have received an information request/comments from our statistics reviewer. Please submit a response to the following request to your NDA as soon as possible.

We have reviewed your response dated August 13, 2015, to our second request on the statistical analyses. Our comments are listed below:

- 1. For study 1008, you did not adjust the heteroscedasticity in your primary analysis. You should add the command “repeated/group=trtname sub=subjid R;” in your model**

statements. In addition, your statement “random subjid(drggroup)/subject=subjid(drggroup);” can be simplified to “random subjid;” . Both statements will get you the same results, but the latter will save your program running time.

2. The normality assumption of the mixed-effects model is not satisfied for Studies 1009 and 1002. However, you still use the mixed-effects model for your analyses. Note that because the skewness of the distribution of interest (For example, the distribution of $(E_{\text{max, ALO30}} - (1 - \delta^*)E_{\text{max, Oxy30}} - \delta^* x)$ is less than 2 (the skewness of an exponential variate), the Johnson’s t test should be used. Johnson’s article is attached.
3. The result from your secondary analysis for High VAS in Study 1009 does not match our result. We found that you used n=27 instead of n=28 in your calculation (See your supporting table 3.2).

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
09/22/2015

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 Clinical Pharmacology Information request 14sep15
Date: Monday, September 14, 2015 8:40:48 AM
Importance: High

Dear Kate,

I have received an additional information request from our clinical pharmacology reviewer. Please submit a response to the following request to your NDA as soon as possible.

Please provide the requested information by COB, 9/15/2015.

- 1. The B4531001 study report (Section 9.5.3.2.) indicates that the plasma samples for naltrexone were analyzed within 577 days from sample collection. Based on the response to Question 1 (provided in your September 11, 2015, submission to NDA 207621), the long-term storage stability for naltrexone supports only up to 415 days. Hence for study B4531001, provide two separate .xpt files of naltrexone concentrations for subjects 1) analyzed within stability period (\leq 415 days) and 2) analyzed outside stability period (\geq 415 days). Include in the .xpt files, the variable name 'number of days' between sample collection and sample analysis along with all variable names currently listed in ADPC dataset.**
- 2. Provide in tabular format, the naltrexone concentrations analyzed within the stability period (\leq 415 days) for the subjects who experienced opioid withdrawal events (OWD) in both studies (B4531001 and B4531002). Include the date of OWD event and the date of sample collection.**

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
09/22/2015

From: [Walker, Diana](#)
To: [Collins -Novikov, Kathleen](#)
Subject: NDA 207621 Administrative Information Request 15sep15
Date: Tuesday, September 15, 2015 12:19:00 PM
Importance: High

Dear Kate,

I have received a follow-up request regarding your previous submission. We acknowledge that you submitted a copy of a submission provided previously to the Embeda NDA. Our 505(b)(2) Committee is requesting that you provide a formal submission to the Troxyca NDA 207621 of an original document, and not a copy of a previous document sent to a different NDA.

Provide a formal letter to NDA 207621, which explains the corporate relationship between Pfizer and Alpharma.

Due to the short review timelines, please provide this information as soon as possible so that we will be able to meet the PDUFA timelines for your application.

Warm regards,

Diana

From: Collins -Novikov, Kathleen [<mailto:Kathleen.Collins-Novikov@pfizer.com>]
Sent: Wednesday, September 02, 2015 7:00 PM
To: Walker, Diana
Cc: Collins -Novikov, Kathleen
Subject: RE: NDA 207621 Administrative Information Request 01sep15

Dear Diana,

Just want to let you know that the responses to the Administrative Information Request and the Nonclinical Information Request were submitted today via the Gateway. The Labeling Information Request is scheduled for dispatch tomorrow.

Thanks

Kate

From: Walker, Diana [<mailto:Diana.Walker@fda.hhs.gov>]
Sent: Tuesday, September 1, 2015 8:48 AM
To: Collins -Novikov, Kathleen
Subject: NDA 207621 Administrative Information Request 01sep15

Dear Kate,

Our 505(b)(2) committee is reviewing your application and has an information request. Please submit the requested document to your NDA as soon as possible.

Pfizer is cross-referencing the Embeda NDA 22321 (morphine sulfate/naltrexone

hydrochloride extended release capsule). We note however that the Orange Book shows that Embeda is owned by Alharma Pharms. Please provide a correspondence that describes your corporate relationship with Alharma Pharms so that we can confirm that you have the ability to cross-reference that application.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
09/22/2015

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 Administrative Information Request 10sep15
Date: Thursday, September 10, 2015 2:39:24 PM
Importance: High

Dear Kate,

Our clinical review team has the following information request. Please submit the requested information to me via email by tomorrow, September 11, 2015, followed by an official submission to your NDA as soon as possible next week.

On your Financial Disclosure Form 3455, (b) (6) is listed for Study B4531002, Site (b) (6). However, in the CSR for Study (b) (6) is listed as the principal investigator for that site. Clarify who the principal investigator is for Site (b) (6). If the principal investigator is not (b) (6) clarify why you submitted financial disclosure information (b) (6) for Study (b) (6).

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
09/22/2015

From: [Walker, Diana](#)
To: [Collins -Novikov, Kathleen](#)
Subject: NDA 207621 Clinical Pharmacology Information request 09sep15
Date: Wednesday, September 09, 2015 9:41:51 AM
Importance: High

Dear Kate,

I have received an information request/comments from our clinical pharmacology reviewer. Please submit a response to the following request to your NDA as soon as possible.

Please provide below information by COB, 9/11/2015.

- 1. You indicated that "Additional stability will be evaluated for naltrexone and reported under (b) (4) study 8253977 (Pfizer Validation No. B4539002)". Provide the extended long-term stability evaluation for naltrexone. If already provided in a submission to your NDA, direct us to the location within the NDA.**
- 2. In the study 4531001, the number of treated subjects was 395. However, the concentration data for naltrexone and 6-beta- naltrexol, was provided only for 375 and 385 subjects, respectively. Provide clarification on the missing subjects' concentration data. Provide concentration data for missing subjects for all analytes.**
- 3. In the study 4531002, N=410 subjects entered the OL Titration, of which N=134 were randomized to Placebo and N=147 randomized to ALO-02. However you provided concentration data only for 350 subjects for all analytes. Provide clarification on the missing subjects' concentration data. Provide concentration data for the missing subjects for all analytes.**
- 4. In the study report 4531002, you indicated that "three study samples, collected during the Open-Label Titration Period, were outside of the naltrexone established frozen matrix stability at the time of analysis for Subjects 10011002, 10041006, and 10601010 who were early terminated and were not randomized to the Double-Blind Treatment Period". In concentration datasets for the subject 10011002, a value of 0 pg/mL was shown for all analytes (oxycodone, noroxycodone, naltrexone and 6-beta naltrexol). For the Subjects 10041006 and 10601010, the oxycodone and noroxycodone concentration values were reported; however a value of 0 pg/mL was reported for naltrexone and 6-beta naltrexol concentrations. Provide details about the analyte concentrations for these 3 subjects and clarify how 0 pg/mL for naltrexone and 6-beta naltrexol was determined for these subjects.**

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
09/09/2015

PeRC Meeting Minutes
August 19, 2015

PeRC Members Attending:

Lynne Yao
Linda Lewis
Gettie Audain
Meshaun Payne
Robert "Skip" Nelson
Gregory Reaman
Andrew Mulber
Kevin Krudys
Thomas Smith
Dionna Green
Ruthie Davi- (Taladafil review only)
Yeruk Mulugeta
Belinda Hayes
Daiva Shetty
Kristiana Brugger

ALO-02 (oxycodone HCL and naltrexone HCL) Partial Waiver/Deferral/Plan

- Proposed Indication: Management of pain severe enough to require daily, around -the-clock, long term Opioid treatment and for which alternative treatment options are inadequate
- The division reminded the PeRC that this formulation of opioid includes an abuse deterrent component that releases naltrexone if the product is tampered with in any way. This formulation would not be of substantial health benefit to pediatric patients less than 7 years of age because in order to develop an age appropriate formulation, the abuse deterrent properties would be lost. However, the PeRC noted that for other abuse deterrent formulations, or other longer-acting opioids, studies should be conducted in patients less than 6 years of age because there is a clear need to develop longer-acting pain relief products for younger patients who have pain severe enough to require daily, around-the-clock treatment when other options are inadequate.
- *PeRC recommendations:*
 - The PeRC agrees the pediatric plan as described in the Agreed iPSP (i.e., waiver in children < 7 years of age, and deferred studies in patients 7-17 years of age).
 - The PeRC also acknowledges a mistake as identified by DPARP in the current draft iPSP guidance: The iPSP template should include both study initiation and study completion dates. The current iPSP only requires study initiation date. However, for tracking purposes, when the PREA requirement is issued, the study completion date must be included in the approval letter. Therefore, the iPSP draft guidance should be modified to include both study initiation and study completion dates.

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/s/

GETTIE AUDAIN
09/01/2015

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 Administrative Information Request 01sep15
Date: Tuesday, September 01, 2015 8:48:25 AM

Dear Kate,

Our 505(b)(2) committee is reviewing your application and has an information request. Please submit the requested document to your NDA as soon as possible.

Pfizer is cross-referencing the Embeda NDA 22321 (morphine sulfate/naltrexone hydrochloride extended release capsule). We note however that the Orange Book shows that Embeda is owned by Alpharma Pharms. Please provide a correspondence that describes your corporate relationship with Alpharma Pharms so that we can confirm that you have the ability to cross-reference that application.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
09/01/2015

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 Statistical Information request 31aug15
Date: Monday, August 31, 2015 2:31:25 PM
Attachments: [PDF article by Johnson 1978.pdf](#)
[image003.png](#)

Dear Kate,

I have received an information request/comments from our statistics reviewer. Please submit a response to the following request to your NDA as soon as possible.

We have reviewed your response dated August 13, 2015, to our second request on the statistical analyses. Our comments are listed below:

- 1. For study 1008, you did not adjust the heteroscedasticity in your primary analysis. You should add the command “repeated/group=trtname sub=subjid R;” in your model statements. In addition, your statement “random subjid(drggroup)/subject=subjid(drggroup);” can be simplified to “random subjid;” . Both statements will get you the same results, but the latter will save your program running time.**
- 2. The normality assumption of the mixed-effects model is not satisfied for Studies 1009 and 1002. However, you still use the mixed-effects model for your analyses. Note that because the skewness of the distribution of interest (For example, the distribution of ($E_{\max, ALO30} - (1 - \delta^*)E_{\max, OQ30} - \delta^* x$) is less than 2 (the skewness of an exponential variate), the Johnson’s t test should be used. Johnson’s article is attached.**
- 3. The result from your secondary analysis for High VAS in Study 1009 does not match our result. We found that you used n=27 instead of n=28 in your calculation (See your supporting table 3.2).**

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
08/31/2015

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 Pediatric Information Request 20aug15
Date: Thursday, August 20, 2015 10:57:50 AM

Dear Kate,

I received the following information request regarding your pediatric study proposal timeline. Please update your NDA with an amendment addressing this information request as soon as possible.

You have provided the following proposed timeline with your pediatric study plan, however, additionally please provide a date for **Study Completion**:

Protocol Submission: March 2015 (submitted April 7, 2015)

Study Initiation: November 2015

Study Completion:

Study Submission: July 2019

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
08/20/2015

From: [Walker, Diana](#)
To: [Collins -Novikov, Kathleen](#)
Subject: NDA 207621 Statistical Information Request #2 - 05Aug15
Date: Wednesday, August 05, 2015 10:04:05 AM
Attachments: [image012.wmz](#)
[image013.png](#)
[image014.wmz](#)
[image015.png](#)
[image016.wmz](#)
[image017.png](#)
[image018.wmz](#)
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[image026.wmz](#)
[image027.png](#)
[image028.wmz](#)
[image029.png](#)
[oledata.mso](#)

Dear Kate,

We have reviewed the response to our information request below, which was submitted to your NDA Friday, July 31, 2015. We have the following comments and additional requests. Please submit this information to your NDA as soon as possible.

1. The statistical method used for the primary comparison between the test drug and the positive control is incorrect.

For example, for Drug Liking Emax in Table 2 . Note that is an estimate of . Therefore, the hypothesis

vs.

is **NOT** equivalent to

vs. .

You should test

vs.

where $x=50$ and 0 for Drug Liking VAS and High VAS, respectively.

2. The normality assumption of the mixed-effects model is satisfied for both Drug Liking VAS and High VAS in Study B4531008. Explain the reason for using non-parametric tests (Friedman's test for Drug Liking VAS and Wilcoxon signed rank test for High VAS) for comparisons between intact ALO-02 60 mg and placebo.
3. The comparison between intact ALO-20 60 mg and IR oxycodone HCl 60 mg is not appropriate given the difference in performance of extended-release and immediate-release products, and is not suitable for inclusion in labeling.
4. Provide SAS programs for your analyses.

Warm regards,

Diana

From: Walker, Diana [<mailto:Diana.Walker@fda.hhs.gov>]
Sent: Monday, July 13, 2015 9:25 AM
To: Collins -Novikov, Kathleen
Subject: NDA 207621 Statistical Information Request 13Jul15

Dear Kate,

I have received the following information request/comments from our statistical review team regarding studies b4531008, b4531009 and b4981002.

We note that your analyses of the data from Studies b4531008, b4531009 and b4981002 differ from those recommended in the 2015 FDA Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling for the primary analysis and the responder analysis. To understand how we will review this data, we recommend that you conduct analyses using the statistical methodologies recommended in the guidance. The following are some specific comments:

The hypothesis for the primary analysis for bipolar Drug Liking VAS can be easily extended to the unipolar High VAS.

For the primary analysis you may test:

$$H_0: \mu_C - \mu_T \leq \delta_1 \text{ vs. } H_a: \mu_C - \mu_T > \delta_1$$

where μ_C and μ_T denote means of test drug and positive control, respectively;

$\delta_1 = \delta^*(\mu_C - x)$, $0 < \delta^* < 1$, and $x=50$ and 0 for Drug Liking VAS and High VAS, respectively.

You may use δ^* in the order of smallest number to largest number with 0.05 increment to test the null hypothesis until an insignificant result is obtained. Note that multiplicity adjustments for the closed testing procedure are not required.

In addition, you should use the Chen-Bonson's equivalence test

(b) (4)

that is, test

$$H_0: \mu_T - \mu_P \geq \delta \text{ vs. } H_a: \mu_T - \mu_P < \delta$$

where $\delta = 11$ and 22 for Drug Liking VAS and High VAS, respectively.

For the responder analysis, your description for the percentage of subjects who had at least 30% or 50% reduction in Emax for crushed TROXYCA ER compared to crushed IR

oxycodone HCl does not take any variability into account. We suggest you perform the responder analysis using cut off points in the order of smallest percent to largest percent with 5% increment to define a responder, and then testing the null hypothesis: the majority of subjects were not responders, until an insignificant result is obtained. Similar to the suggested method for the primary analysis, multiplicity adjustments are not required.

You should use the following formula to calculate % reductions for all studies:

$$\% \text{ reduction} = \begin{cases} \frac{E_{\max, \text{ref}} - E_{\max, \text{test}}}{E_{\max, \text{ref}} - X} \times \left(1 - \frac{E_{\max, P} - X}{Y} \right) \times 100\%, & \text{if } E_{\max, P} > Z; \\ \frac{E_{\max, \text{ref}} - E_{\max, \text{test}}}{E_{\max, \text{ref}} - X} \times 100\%, & \text{if } E_{\max, P} \leq Z. \end{cases}$$

where $X=50$, $Y=50$, and $Z=55$ for Drug Liking VAS, and $X=0$, $Y=100$ and $Z=10$ for High VAS.

If it looks like there are any formatting problems with this email, let me know and I can send you the information as a Word document.

Warm regards,

Diana

Diana L. Walker, Ph.D.
 Sr. Regulatory Health Project Manager
 FDA/CDER/ODE II/DAAAP
 Tel: 301-796-4029
 Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
08/20/2015

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 REMS Information Request 20Jul15
Date: Monday, July 20, 2015 10:36:07 AM
Importance: High

Dear Kate,

There was a new REMS recently approved, June 2015, for the Extended-Release, Long-Acting (ERLA) Opioid class REMS. Please submit the following requested information:

Please submit a complete, updated REMS document by COB July 24, 2015. This includes a proposed REMS document, REMS materials, REMS supporting document, and Medication Guide.

It should be based on the most recently approved ERLA REMS document (6/2015).

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER
08/20/2015

Walker, Diana

From: Walker, Diana
Sent: Monday, July 13, 2015 4:16 PM
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 Clinical Information Request 13Jul15

Dear Kate,

I have received the following information request/comments from our clinical review team. Please submit the following requested information to your NDA as soon as possible.

In the Full Protocol Report for Protocol B4531002, Section 16.1.1 (Appendices Protocol and Protocol Amendments), you provide a table (pages 3-6) of the Document History with the Protocol Amendments and Summary of Changes (excerpt below). However, you do not provide the actual protocol versions for Protocol Amendments 1 and 2 so it is not possible to compare the first two protocol versions with the last (Protocol Amendment 3).

1. Provide:
 - a. A table which delineates the actual changes between the protocol versions
 - b. Track change versions of the protocols showing the amendments, or explain where in the submission **this** information may be found.
2. Provide the number of subjects enrolled/randomized for each protocol amendment.

Document History

Document	Version Date	Summary of Changes
Original Protocol	12 January 2012	N/A
Protocol Amendment 1	16 March 2012	<ol style="list-style-type: none"> 1. Description of the electronic methods of capturing Patient Reported Outcomes (ePRO). 2. Clarification of the rationale and implementation of the double-blind gradual or dummy taper during specific study periods. 3. Revision of the Treatment Response Criteria and Subject Withdrawal Criteria for Positive Urine Drug Tests.
Protocol Amendment 2	11 April 2012	<ol style="list-style-type: none"> 1. Clarification of the plan for transition of end of study care to post-study care. 2. Revision of Exclusion Criteria #3 (Section 4.2). 3. Clarification of the available daily dose levels during the Open-Label Conversion and Titration Period (Section 5.3.3.2). 4. Revision of the positive urine drug test description resulting in subject withdrawal (Section 6.2). 5. Clarification of the Urine Drug Test assessment (Section 7.2.8).
Protocol Amendment 3	29 October 2012	<ol style="list-style-type: none"> 1. Minor clarifications (Protocol Summary). 2. Deletion of a sentence in the Background section and minor clarifications (Section 1.2).

Warm regards,

Diana

Diana L. Walker, Ph.D.
 Sr. Regulatory Health Project Manager
 FDA/CDER/ODE II/DAAAP
 Tel: 301-796-4029
 Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
07/13/2015

Walker, Diana

From: Walker, Diana
Sent: Monday, July 13, 2015 9:25 AM
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 Statistical Information Request 13Jul15

Dear Kate,

I have received the following information request/comments from our statistical review team regarding studies b4531008, b4531009 and b4981002.

We note that your analyses of the data from Studies b4531008, b4531009 and b4981002 differ from those recommended in the 2015 FDA Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling for the primary analysis and the responder analysis. To understand how we will review this data, we recommend that you conduct analyses using the statistical methodologies recommended in the guidance. The following are some specific comments:

1. The hypothesis for the primary analysis for bipolar Drug Liking VAS can be easily extended to the unipolar High VAS.

For the primary analysis you may test:

$$H_0: \mu_C - \mu_T \leq \delta_1 \text{ vs. } H_a: \mu_C - \mu_T > \delta_1$$

where μ_C and μ_T denote means of test drug and positive control, respectively; $\delta_1 = \delta^*(\mu_C - x)$, $0 < \delta^* < 1$, and $x=50$ and 0 for Drug Liking VAS and High VAS, respectively.

You may use δ^* in the order of smallest number to largest number with 0.05 increment to test the null hypothesis until an insignificant result is obtained. Note that multiplicity adjustments for the closed testing procedure are not required.

In addition, you should use the Chen-Bonson's equivalence test (b) (4)
[REDACTED] that is, test

$$H_0: \mu_T - \mu_P \geq \delta \text{ vs. } H_a: \mu_T - \mu_P < \delta$$

where $\delta = 11$ and 22 for Drug Liking VAS and High VAS, respectively.

2. For the responder analysis, your description for the percentage of subjects who had at least 30% or 50% reduction in Emax for crushed TROXYCA ER compared to crushed IR oxycodone HCl does not take any variability into account. We suggest you perform the responder analysis using cut off points in the order of smallest percent to largest percent with 5% increment to define a responder, and then testing the null hypothesis: the majority of subjects were not responders, until an insignificant result is obtained. Similar to the suggested method for the primary analysis, multiplicity adjustments are not required.

You should use the following formula to calculate % reductions for all studies:

$$\% \text{ reduction} = \left\{ \begin{array}{l} \frac{E_{\max,ref} - E_{\max,test}}{E_{\max,ref} - X} \times \left(1 - \frac{E_{\max,P} - X}{Y} \right) \times 100\%, \text{ if } E_{\max,P} > Z; \\ \frac{E_{\max,ref} - E_{\max,test}}{E_{\max,ref} - X} \times 100\%, \text{ if } E_{\max,P} \leq Z. \end{array} \right\}$$

where $X=50$, $Y=50$, and $Z=55$ for Drug Liking VAS, and $X=0$, $Y=100$ and $Z=10$ for High VAS.

If it looks like there are any formatting problems with this email, let me know and I can send you the information as a Word document.

Warm regards,

Diana

Diana L. Walker, Ph.D.
 Sr. Regulatory Health Project Manager
 FDA/CDER/ODE II/DAAAP
 Tel: 301-796-4029
 Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
07/13/2015

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 CMC Information Request 29May15
Date: Friday, May 29, 2015 11:27:39 AM

Dear Kate,

I have received the following information request for NDA 207621 from our Office of Product Quality (OPQ) Staff (CMC issues). Please submit the following requested information to your NDA as soon as possible.

We have reviewed the Pharmaceutical Development Report submitted to support your Pediatric Study Plan and have the following comments. Provide information or rationale regarding the following:

1. **Investigate the feasibility** [REDACTED] (b) (4)
2. **Investigate the possibility** [REDACTED] (b) (4)
3. **Investigate the feasibility** [REDACTED] (b) (4)
4. **If 1 to 3 above, fail, then investigate all possibilities** [REDACTED] (b) (4)

Kindly acknowledge receipt of this email.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
05/29/2015

Walker, Diana

From: Walker, Diana
Sent: Thursday, May 14, 2015 3:44 PM
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 Clinical Information Request 14May15

Dear Kate,

I have received the following clinical information request for NDA 207621. Please submit the following requested information to your NDA as soon as possible:

For the disposition of subjects in Study B4531002 (as shown in Table 7 below), provide a definition for the criteria used for the following categories for both the Open-Label Titration period and the Double-Blind period:

- No longer willing to participate in study
- Other

Table 7. Subject Disposition – Double-Blind Treatment Period

	Placebo N=134 n (%)	ALO-02 N=147 n (%)	Overall N=281 n (%)
Number of Subjects Randomized	134 (100.0)	147 (100.0)	281 (100.0)
Randomized but not treated ^a	0 (0.0)	1 (0.7)	1 (0.4)
Number of Subjects who Finished the Double-Blind Treatment Period	81 (60.4)	107 (72.8)	188 (66.9)
Number of Subjects Discontinued from the Double-Blind Treatment Period	53 (39.6)	40 (27.2)	93 (33.1)
Reasons for Discontinuation			
Insufficient clinical response	16 (11.9)	4 (2.7)	20 (7.1)
Adverse events	9 (6.7)	14 (9.5)	23 (8.2)
Subject died	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	8 (6.0)	9 (6.1)	17 (6.0)
Lost to follow-up	3 (2.2)	6 (4.1)	9 (3.2)
No longer willing to participate in study	11 (8.2)	6 (4.1)	17 (6.0)
Other	6 (4.5)	1 (0.7)	7 (2.5)

Source: [Table 14.1.1.1.2](#)

Kindly acknowledge receipt of this email.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
05/14/2015

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 DRISK/REMS Information Request 19Mar15
Date: Thursday, March 19, 2015 11:12:50 AM

Dear Kate,

I have received an information request from our DRISK/REMS review team. Please submit the requested information to your NDA as soon as possible.

Please respond to the following request for information:

The ERLA REMS submitted with your application is outdated and does not include Troxyca product-specific information. The most recent ERLA REMS was approved in December 2014. Submit the most recently approved ERLA REMS document, appended materials and supporting document with your proposed revisions to the ERLA REMS Blueprint to incorporate Troxyca product-specific information.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
03/19/2015

Walker, Diana

From: Walker, Diana
Sent: Wednesday, March 18, 2015 10:23 AM
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 Clinical Information Request 18Mar15

Dear Kate,

I have received an information request from our clinical review team. Please submit the requested information to your NDA as soon as possible.

Please respond to the following requests for information:

Provide more detailed narratives for subjects who experienced opioid withdrawal in Studies B4531002 and B4531001 to include at least the following:

- Identify incoming opioid or non-opioid analgesic during the Screening Period prior to entering the Open-Label Conversion and Titration Period.
- Identify types and doses of opioid or non-opioid analgesics that the subjects were taking during the Screening Period to determine the Dose Calculation Worksheet conversion.
- Provide a description of the types of symptoms (including timing of onset) that subjects experienced that led the Investigator to determine that they were experiencing opioid withdrawal (OW). Specifically, it is not informative for the narrative to state that the subject experienced OW without describing the associated symptoms that formed the basis of the determination.
- Include COWS and SOWS scores at the time of the OW onset.
- Provide the outcome of the OW AE, including disposition (i.e., discontinued from study; discontinued from study drug but continued in the study).
- Provide a description of the Investigator's justification for causality determination of the OW event (i.e., of non-compliance, tapering, other). It is not sufficient for the Investigator to determine that the OW was due to noncompliance, tapering or other without supporting documentation in the narrative.

In addition to the full narratives, this information should be summarized in a table similar to the one below for all subjects who experienced opioid withdrawal in Studies B4531002 and B4531001.

Sample Opioid Withdrawal Table

Subject ID	Incoming opioid or non-opioid analgesic (include dose)	Date/Starting dose study drug (Conversion)	Date/Dose/Treatment Period Onset Opioid Withdrawal (OW) AE	OW Preferred Terms (symptoms) Including Timing	COWS and SOWS scores at time of OW onset	Outcome/Disposition

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
03/18/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207621

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

ATTENTION: Kathleen Collins
Director, Worldwide Regulatory Strategy

Dear Ms. Collins:

Please refer to your New Drug Application (NDA), dated and received December 19, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxycodone Hydrochloride and Naltrexone Hydrochloride, Extended-release Capsules, 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, 80 mg/9.6 mg.

We also refer to your correspondence, dated and received December 22, 2014, requesting review of your proposed proprietary name, Troxyca ER.

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

If any of the proposed product characteristics as stated in your December 22, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Diana L. Walker, Regulatory Project Manager in the Office of New Drugs, at (301)796-4029.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
03/11/2015



NDA 207621

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Attention: Kathleen Collins
Director, Worldwide Safety and Regulatory

Dear Ms. Collins:

Please refer to your New Drug Application (NDA) dated and received December 19, 2014, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Oxycodone hydrochloride and naltrexone hydrochloride, 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, 80 mg/9.6 mg Extended-Release Capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 19, 2015.

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 September 21, 2015.

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

Pharmacology-Toxicology

1. Phenanthrene-derivative opioid drug products may contain impurities [REDACTED] (b) (4) [REDACTED] which is a structural alert for mutagenicity. Therefore, the [REDACTED]

specification for these impurities in the drug substance must be reduced to reflect a maximal daily intake of NMT 1.5 mcg/day or adequate safety qualification must be provided. Upon preliminary review, [REDACTED] (b) (4) appear to contain structural alerts and these impurities will require further evaluation to determine the appropriate specification. 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.

Statistics

2. Submit the SAS programs for generating the analysis datasets, efficacy tables, and figures for Study B4531002.

Product Quality

3. You have only provided the batch formula [REDACTED] (b) (4) used to manufacture the capsules. Additionally, provide the batch formula [REDACTED] (b) (4) for each of the capsule strengths.

4. You state [REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] (b) (4)
Therefore, provide justification [REDACTED] (b) (4)
In addition, demonstrate [REDACTED] (b) (4)
[REDACTED] (b) (4)
for each capsule.

5. Establish control limits [REDACTED] (b) (4)
[REDACTED] (b) (4)

6. Provide particle size distribution (PSD) data [REDACTED] (b) (4)
[REDACTED] (b) (4) for all of the pilot, clinical, and registration batches.

7. For the control of the oxycodone HCl [REDACTED] (b) (4)
[REDACTED] (b) (4)

Controlled Substances Staff

8. Module 1.14.4 should have a link to a table of contents containing links to all nonclinical and clinical studies related to evaluating abuse potential. Establish links to the in vitro abuse-deterrent (Category 1) studies and to the Integrated Summary of Safety sections documenting abuse, diversion, and withdrawal in the clinical study program.
9. Provide the "Dosage and Administration Instructions (DAI)" and "Pharmacy Manual" for each of the human abuse potential studies (i.e., B4531008, B4531009, and B4531002), or provide their location within the NDA submission.

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). 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), Medication Guide, and patient PI (as applicable), 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 partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Diana L. Walker, PhD, Senior Regulatory Health Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Acting Director
Division of Anesthesia, Analgesia, and
Addiction products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SHARON H HERTZ
02/23/2015

From: [Walker, Diana](#)
To: Kathleen.Collins-Novikov@pfizer.com
Subject: NDA 207621 Request for Information 02Feb15
Date: Monday, February 02, 2015 9:40:52 AM
Importance: High

Dear Kate,

I have received the following information request from our review team. Please submit the following information to your new NDA for Troxyca ER, NDA 207621:

The Pregnancy and Lactation Labeling Rule (PLLR) published December 4, 2014 (79 FR 72063). The PLLR requires a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. The PLLR implementation date is June 30, 2015; however, we will be providing labeling edits and revisions consistent with PLLR for your current submission. See Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format

(
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>
).

Provide a review of the available published literature regarding the use of oxycodone and naltrexone during pregnancy and lactation, as well as a literature review on the drugs' potential effects on fertility, that may be used to support recommendations in labeling.

If you have any questions concerning this information request, feel free to contact me.

Warm regards,

Diana

Diana L. Walker, Ph.D.
Sr. Regulatory Health Project Manager
FDA/CDER/ODE II/DAAAP
Tel: 301-796-4029
Email: Diana.Walker@fda.hhs.gov

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/s/

DIANA L WALKER
02/02/2015



NDA 207621

NDA ACKNOWLEDGMENT

Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Attention: Kathleen Collins
Director, Worldwide Safety and Regulatory

Dear Ms. Collins:

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 Product: Oxycodone hydrochloride and naltrexone hydrochloride, 10mg, 20mg, 30mg, 40mg, 60mg, 80mg Extended-Release Capsules

Date of Application: December 19, 2014

Date of Receipt: December 19, 2014

Our Reference Number: NDA 207621

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17, 2015, 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).

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) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, PhD
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

DIANA L WALKER
12/30/2014



IND 107037

MEETING MINUTES

Alpharma Pharmaceuticals, LLC
c/o Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

Attention: Kathleen Collins
Director, Worldwide Safety and Regulatory

Dear Ms. Collins:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Oxycodone hydrochloride and Naltrexone hydrochloride Extended-Release Capsules (ALO-02).

We also refer to the meeting between representatives of your firm and the FDA on March 18, 2014. The purpose of the meeting was to discuss the available data for the development program for ALO-02 and the content and format of the planned NDA.

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) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, PhD
Sr. 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: March 18, 2014, 10:00 – 11:00 a.m. (Eastern)
Meeting Location: 10903 New Hampshire Avenue
 White Oak Building 22, Conference Room: 1309
 Silver Spring, Maryland 20903

Application Number: IND 107037
Product Name: Oxycodone hydrochloride and Naltrexone hydrochloride
 Extended-Release Capsules (ALO-02)
Indication: Moderate to severe pain
Sponsor/Applicant Name: Alpharma Pharmaceuticals, LLC, c/o Pfizer, Inc.

Meeting Chair: Sharon Hertz, MD, Deputy Director, DAAAP
Meeting Recorder: Diana Walker, PhD, Sr. Regulatory Project Manager, DAAAP

Industry Representatives	Title
Kenneth Sommerville, MD	Vice President, Global Clinical Lead - Opioids
Gernot Wolfram, MD	Senior Director, Global Clinical Lead ALO-02
Glenn C. Pixton, MS	Director, Statistics Lead
Mary Catherine W (Kathleen) Collins, MS	Director, Regulatory Lead
Gary G. Wilson, PhD	Senior Director, Safety Risk Lead
Timothy Donald Holt, BS	Associate Director, Development Operation
Sean Donevan, PhD	Senior Director, Medical Affairs Product Lead
Bimal K. Malhotra, PhD	Senior Director, Clinical Pharmacology Lead
Rosonald R Bell, MS, PhD, DABT	Associate Research Fellow, Nonclinical Drug Safety Research & Development
Robert J. Mauthe, PhD	Senior Director, Drug Safety Research and Development
Donald Guzek, BS, MBA	Associate Research Fellow, Pharmaceutical Sciences Team Leader
Beth Kendersky, MS	Senior Director, Global CMC, Pharmaceutical Sciences
Therese Debiak-Krook, MS	Associate Director, Global CMC, Pharmaceutical Sciences
Melissa Hanna-Brown, PhD	Associate Research Fellow, Analytical R&D, Pharmaceutical Sciences
Saima Khan, PhD	Senior Director, Global Regulatory
Jacquelyn G Wilson, MSc, Pharm.D.	Director, Clinical Research
Kyle Matschke, MAS	Associate Director, Clinical Pharmacology Statistics

FDA	Title
Bob A. Rappaport, MD	Division Director, DAAAP
Sharon Hertz, MD	Deputy Director, DAAAP
John Feeney, MD	Clinical Team Leader, DAAAP
Robert Levin, MD	Medical Officer, DAAAP
Daniel Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Elizabeth Bolan, PhD	Pharmacology/Toxicology Reviewer, DAAAP
Julia Pinto, PhD	CMC Lead, ONDQA
Tapash Ghosh, PhD	Biopharmaceutics Team Leader, ONDQA
Yun Xu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology
Suresh Naraharisetti, PhD	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Silvia Calderon, PhD	Controlled Substances Staff (CSS) Team Leader
Katherine Bonson, PhD	CSS Reviewer
Diana Walker, PhD	Sr. Regulatory Project Manager, DAAAP

1.0 BACKGROUND

ALO-02 (PF-06412527) is an extended-release (ER) formulation of oxycodone hydrochloride with a sequestered core of naltrexone hydrochloride intended to be taken orally twice-a-day (b) (4)

Pellet filled capsules (referred to as ALO-02) contain an ER formulation of oxycodone HCl (an opioid agonist) with sequestered naltrexone HCl (an opioid antagonist) designed to manage pain when administered orally as an intact formulation and to reduce the drug liking and euphoric potential of oxycodone if the formulation is disrupted.

The objective of the meeting is to obtain feedback on the current available data and guidance on the planned submission of the ALO-02 NDA. This 505(b)(2) NDA plans to reference NDA 18932 Revia® (naltrexone HCl) Tablets and NDA 21011 Roxicodone (oxycodone HCl) Tablets.

The preliminary responses to the meeting questions were sent via email on March 10, 2014. The Sponsor sent discussion points for the meeting, which are included in the meeting minutes below.

2.0 DISCUSSION

For ease of reference, the Sponsor's original questions are incorporated below in *italics* followed by the FDA Response in **bold** font. Discussion that took place during the meeting is captured following the question to which it pertains in normal text.

Question 1:

In accordance with the Agency's recommendation from the End of Phase 2 meeting, the Sponsor has revised the dissolution method acceptance criteria. A summary of the dissolution method history is provided in this briefing package.

Does the Agency have any comments on the dissolution method and the proposed acceptance criteria for oxycodone release as outlined in Section 8.4.2.5?

Division Response:

We have the following comments related to your proposal:

1. **Your proposal outlined in Section 8.4.2.5 appears acceptable. The Agency will conduct a thorough review of your full dissolution development and validation report and the proposed dissolution method and acceptance criteria for your proposed drug product upon NDA submission.**
2. **Biowaiver:** (b) (4)
 - a. **A PK study or studies may be needed** (b) (4)

- b. A biowaiver request with justification, and supporting comparative dissolution profile data (plus f2 calculation) should also be submitted

(b) (4)

Additional Biopharmaceutics/Nonclinical Comments:

Provide in vitro profile data to demonstrate the extent of release of naltrexone and naltrexone-related drug product degradants from the formulation. These data are necessary if you intend to justify the specifications of any naltrexone-related degradants in the drug product based on the maximum amount of naltrexone delivered daily from this drug product, when used according to the product labeling, rather than the maximum amount actually present in the drug product.

This may be achieved through selection of an in-vitro dissolution method that is sensitive and specific for both oxycodone and naltrexone.

Pfizer Response: Pfizer acknowledges FDA's comment # 1 and no further discussion is required at the meeting.

Pfizer proposes to combine a discussion of FDA's comment 2a and 2b with question #4 related to the clinical pharmacology program.

In response to FDA's additional comment around selection of an in-vitro method that is sensitive for both oxycodone and naltrexone, Pfizer proposes that a dissolution method developed specifically for naltrexone and naltrexone-related degradants would be appropriate. Pfizer will perform this dissolution experiment to justify the specifications only.

Does the Agency concur?

Discussion:

The Sponsor stated their intent to develop two dissolution methods, one for oxycodone, and one specifically for naltrexone and naltrexone-related degradants to show there is not preferential release of the naltrexone degradants. The Agency agreed that this proposal is acceptable, and recommended that the Sponsor submit the dissolution method for review. The Sponsor agreed that they will submit the dissolution method.

Question 2:

In accordance with the Agency's recommendation from the End of Phase 2 meeting and follow-up correspondence, the Sponsor completed a literature based safety assessment for the ALO-02 excipients that exceeded precedented levels based on a maximum theoretical daily dose (MTDD) of (b) (4) g oxycodone. This assessment is introduced in Section 8.4.3 and provided in Appendix 2.

Does the Agency agree that the safety assessment as provided in the briefing package supports the safety qualification of the excipients?

Division Response:

Based on the information provided in Appendix 2, our preliminary response is that we do not concur that you have provided adequate safety justification for the proposed drug product formulation excipients up to the MTDD of this drug product. However, a final determination

of the adequacy of the safety assessment based on a detailed review of all of the data will be made during the NDA review cycle.

In order to complete this assessment during the NDA review, provide copies of all of the articles cited in the safety assessment. In addition, reference to tertiary review articles containing only summary data are generally unacceptable as the primary data are not available for review. If review articles are used, provide copies of the original source material (i.e. primary references). In addition, describe how the data in the literature reports meet the standardized regulatory requirements of GLP toxicology studies.

Based on preliminary review of the summary information provided in the meeting package, we are providing the following comments which may suggest deficiencies in your safety justification for the novel excipients in your drug product formulation when consumed at the MTDD. As the information in the meeting package is only summary data, additional concerns may arise once the original publications are reviewed.

Talc

We note that you cite references suggesting that talc is not absorbed from the gastrointestinal (GI) tract. These studies require review to determine if they are definitive enough to allow us to waive the missing fertility and early embryonic development and pre- and post-natal developmental toxicology studies. Further, if it is not absorbed, talc would still be in contact with the GI tract. Therefore, adequate histopathologic assessment of the GI tract in the cited repeat-dose toxicology studies is essential to determine if chronic oral toxicology studies or carcinogenicity studies are necessary for drug approval.

Finally, we note that in our previous communications with you, we recommended an intranasal toxicology study prior to clinical studies to assess intranasal abuse liability of crushed drug products. As per our current Division policy, we have allowed human intranasal studies with crushed opioid pills to proceed without the animal toxicology studies if the study only enrolls subjects with a prior history of crushing and abusing opioid pills via the intranasal route of administration and with an appropriate informed consent, which included language to inform the subject of the risks of crushing and snorting pills, particularly since many pills, including your drug product, contain talc, which, if it gets into the lungs, can result in lung granulomas.

(b) (4)

We may consider extrapolation of data

(b) (4)

If you intend to extrapolate data (b) (4) to

support the MTDD of this excipient in your product, your NDA must include a discussion of all of the differences between these products and include justification why these differences do not raise safety concerns.

We note that there are currently no reproductive and developmental toxicology data or carcinogenicity data (b) (4). The review of your NDA will have to take into consideration the adequacy of the absorption data and the chronic toxicology GI histopathology data to determine if it is appropriate to waive these studies.

Dibutyl Sebacate

Based on the summary of the data in the meeting package, there appear to be limited data on dibutyl sebacate for chronic toxicology, reproductive and developmental toxicology, and carcinogenicity. Although this excipient is permitted as a flavoring agent in foods, it is not clear what the typical daily intake of this compound is via food consumption. Your NDA submission must include adequate justification why the standard reproductive and developmental toxicology studies and carcinogenicity studies for new excipients are not necessary to support your proposed novel dose of this excipient via this formulation.

Sodium Lauryl Sulfate (SLS)

It is not clear from the meeting package how much SLS was actually consumed in the referenced repeat-dose toxicology studies that employed dietary administration of SLS. If food consumption data were collected in this study, you must provide these data in the NDA to support your conclusion that these studies provide adequate coverage for the MTDD of SLS via this drug product. Based on the limited information in the reproductive toxicity summary provided, it is not clear how these studies compare to the standard reproductive and developmental toxicology battery. Provide the original reference material if possible. If not available, your NDA must justify why you believe additional studies are not required or the studies should be completed.

Your NDA should include a detailed discussion of all of the excipients in the drug product formulation up to the MTDD via this drug product. When data are not available, you must provide adequate justification why the missing data are not essential to support approval of your drug product. In the absence of adequate justification, additional studies may be required.

Pfizer Response: Pfizer will provide copies of all cited literature including as much of the primary literature as is available. In some cases, the primary reports are unavailable, but has been submitted to international groups (e.g. International Agency for Research on Cancer of the World Health Organization (IARC), Joint FAO/WHO Expert Committee on Food Additives (JECFA), Cosmetic Ingredient Review (CIR), National Industrial Chemicals Notification and Assessment Scheme (NICNAS) for review. Pfizer believes that this peer-reviewed literature typically provides a sufficient review of the quality and suitability of the data. In some cases, the studies may not have been conducted in GLP compliant facilities and assessment of the adherence to standardized GLP Toxicology studies may not be possible since many of the studies were conducted prior to the FDA's finalization of GLP regulations (1979); however the studies are scientifically sound and provide information that can be used in the overall assessment of safety. Using this approach, Pfizer believes that the Safety Assessment conducted provides sufficient safety information for each of the excipients, appropriately supplements the extensive human use of each of the excipients, and is consistent with the responsible use of laboratory animals.

For Talc, Pfizer has reviewed the pharmacokinetic studies utilizing radioactive tracer which shows the lack of gastrointestinal absorption in several species as well as the oral carcinogenicity studies in which no changes were observed microscopically in the gastrointestinal tract. The primary and reviewed literature sources provide clear evidence of both a lack of oral bioavailability and lack of gastrointestinal changes.

- **Does the FDA agree with the approach with using peer-reviewed literature to support the qualification of talc?**

- **Does the agency agree that in the absence of oral absorption and gastrointestinal effects, no additional chronic toxicology, developmental and reproductive toxicology or carcinogenicity studies are warranted?**

(b) (4) Pfizer will provide the requested information (b) (4)

In addition, repeat dose toxicology studies provide assurance that they are safe to high doses in excess of what humans would be exposed to even at a MTDD of (b) (4) g/day with no changes observed in the gastrointestinal tract.

- **Does the FDA agree with the approach with using data generated by the manufacturer to support the qualification (b) (4)?**
- **Does the agency agree that in the absence of oral absorption and gastrointestinal effects, no carcinogenicity or reproductive and developmental toxicology studies are warranted?**

For dibutyl sebacate, in addition to utilization of the JECFA review, Pfizer has reviewed the primary literature for this excipient. Review of the available data indicate very low toxicity for this compound (NOEL of 6.25% or approximately 6250 mg/kg for 2-year study in male rats, and no effect on fertility at 6.25%) and a large margin (1350-fold) over the human exposure at (b) (4) g/day MTDD. The literature source provides clear evidence that dibutyl sebacate is not carcinogenic and did not affect male or female rat fertility, litter size or survival of offspring. Pfizer will also investigate the typical daily intake for this compound as a food additive and include the assessment in the NDA.

- **Does the FDA agree that carcinogenicity, reproductive and developmental toxicology studies are not warranted for dibutyl sebacate?**

For sodium lauryl sulfate (SLS), Pfizer has reviewed the output of the Cosmetic Ingredient Review (CIR) and National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as well as the available primary literature. Because additional data was made available to CIR and NICNAS groups, their independent reviews provide a thorough safety assessment of SLS and provide suitable information on the general, reproductive and developmental toxicology as well as the carcinogenic potential of SLS and support the safety for the levels present at the MTDD of (b) (4) g/day of ALO-02. The referenced studies do not provide details on the amount of food consumed but Pfizer will utilize conservative weight (food consumption and body weight) conversions to support coverage for the MTDD of SLS. As possible, Pfizer will provide the primary literature used for these reviews.

- **Does the FDA agree with the approach with using the international review agencies such as CIR and NICNAS to support the qualification of SLS?**

Discussion:

The Sponsor stated that they will make sure that relevant endpoints were assessed in any literature reports used to support the safety of the excipients, and further agreed to follow the excipient guidance. The Sponsor also noted that they would balance the supportive literature with additional studies as required.

The Division stated that tertiary reviews containing summary data from other agencies to support excipient qualification may be acceptable depending on the source of the information and the level of detail included in the tertiary review. However, the Division encouraged the Sponsor to locate the

original literature reports or data and identify any missing information. The decisions made by the Division are based on data, and summaries are not acceptable. Any gaps in the literature-based justification must be filled with actual data.

The Sponsor asked whether if during the review the need for additional studies is identified would those studies be able to be conducted post-marketing. The Division stated that the decision would be made on a case-by-case basis during the review.

The Sponsor asked the Division for further guidance on the most critical excipients on which to focus. The Division stated that our responses in the preliminary comments identified potential deficiencies for specific excipients that may be of concern.

The Division noted that, as per the excipient guidance, developmental and reproductive toxicology studies may be waived if it can be shown that systemic exposure of the compound does not occur. The Division also noted that the excipient guidance outlines several criteria for waiving carcinogenicity assessments. However, chronic toxicology data to assess the GI effects would still be needed.

Additionally, the Division stated that morphine-containing products, such as Embeda, are a Pregnancy Category C whereas oxycodone-containing products are a Pregnancy Category B. The Division will look a closer at the developmental and reproductive toxicology data for any excipients in this formulation since it will probably receive a Pregnancy Category B designation based on the drug substance.

Question 3:

Nonclinical studies including pharmacology, PK, and toxicology studies have not been performed by the Sponsor with ALO-02 ER capsules. This application will be filed as a 505(b)(2) and will rely on FDA's findings of safety for the reference drugs (Revia[®] NDA 19-932 and Roxicodone[®] NDA 21-011). In addition, the publically available literature on nonclinical studies of oxycodone and naltrexone safety and PK in animals will be reviewed and summarized in the Nonclinical Overview section of the Common Technical Document (CTD), which will be provided with the NDA submission. The overall goal of the literature review is to determine if there are any nonclinical data not currently reflected in the reference drug labels and are relevant for the safety evaluation of ALO-02 (see Section 8.2).

Does the Agency agree that no nonclinical studies are required to support the review of the NDA?

Division Response:

We agree with your proposal not to conduct any new studies for oxycodone or naltrexone in support your 505(b)(2) application, and with your plan to review the literature published since the time of approval of the referenced product to support the safety of the drug product.

Pfizer Response: We agree and no further discussion is required at the meeting.

Discussion:

There was no further discussion of this question.

Question 4:

The Sponsor followed the Agency's comments from the End of Phase 2 meeting, and completed studies and analyses in the clinical pharmacology program per the Agency's suggestions to:

- *confirm the selection of naltrexone ratio in the ALO-02 formulation,*
- *estimate the relative bioavailability (BA) of oxycodone and naltrexone to their respective reference products,*
- *estimate the effects of administration with high-fat meal or sprinkling on applesauce on PK/BA of ALO-02,*
- *estimate the effects of administration with alcohol on PK/BA of ALO-02,*
- *determine the single- and multiple-dose PK of ALO-02,*
- *perform a covariate analysis of oxycodone PK data across Phase 1 and Phase 3 studies*
- *assess sequestration of naltrexone in the ALO-02 formulation after single-dose administration in healthy subjects and chronic dosing in patients*

Does the Agency agree that these studies and analyses are adequate to support the NDA review?

Division Response:

No, we do not agree. We have the following comments:

- 1. You must evaluate the PK dose proportionality for all proposed strengths for both oxycodone and naltrexone of your product. Also refer to the EOP2 minutes concerning the dose proportionality discussion.**

On Page 21 of the meeting package you state that the relative BA of naltrexone from crushed ALO-02 relative to IR Naltrexone (ALO-02-07-101 and ALO-02-09-2001) will be estimated by a cross-study comparison. In these studies (ALO-02-07-101 and ALO-0209-2001), the reference drug naltrexone was administered as a solution made from Revia, not as the intact tablet. The Agency's findings of safety and/or efficacy of the listed drug are established under the approved dosing regimens for the listed drug as described in the product labeling. Therefore, the proposed approach is inadequate to establish a bridge between naltrexone from ALO-02 relative to the listed drug. Also refer to our 505(b)(2) comments.

- 2. In the alcohol interaction study (B4531004), you used ALO-02 20 mg/2.4 mg, not the highest strength of your product. Additionally, we note that this study was conducted in healthy subjects with naltrexone blockade. As a result, the effect of alcohol on the pharmacokinetic profile of naltrexone was not evaluated. Provide your rationale for conducting the study using a dose other than the highest strength, and with naltrexone blockade that precluded an evaluation of the potential effect of alcohol on the pharmacokinetic profile of naltrexone.**
- 3. The final to-be-marketed formulation must be used in the PK studies and clinical efficacy studies. Otherwise, you must provide adequate bridging information or justification why the study results apply to your final to-be-marketed product.**

Pfizer Response: We wish to discuss this topic further with the Division during our meeting. In advance of the meeting, we want to highlight the following responses to your comments:

1a. Justification for Request for Waiver

(b) (4)

Based on the following considerations, we seek a waiver

(b) (4)

(b) (4)

1b. Justification for Relative BA Analysis for Naltrexone from Crushed ALO-02 vs. Revia in Solution

As pointed out by the Agency, Revia 50 mg tablets were crushed and dissolved for administration in studies ALO-02-07-201 and ALO-02-09-2001. These studies evaluated PK and PD effects across a range of naltrexone doses between 2.4-14.4 mg, and the 7.2 mg dose was included in both studies. Based on the considerations highlighted below, Pfizer believes that the analysis of a single crushed ALO-02 60 mg/7.2 mg capsule (B4531008) vs. 7.2 mg dose of naltrexone from crushed tablet in solution (studies ALO-02-07-201 and ALO-02-09-2001) was the most appropriate and feasible approach to estimate naltrexone relative BA.

- Revia is available in the 50 mg tablet strength only. A relative BA estimation of naltrexone from crushed ALO-02 at the same dose as that of Revia 50 mg would have required dosing ALO-02 at a very high dose (seven crushed ALO-02 60 mg/7.2 mg capsules, totaling 420 mg oxycodone immediate release and 51 mg naltrexone), which would not be safe or ethical in healthy volunteers.
- Alternatively, a comparison of Revia 50 mg tablet to a single ALO-02 60 mg/7.2 mg crushed capsule would have required dose normalization across a 7-fold dose range, which cannot be supported due to the lack of data on dose proportionality of naltrexone in the 10-50 mg dose range (dose proportionality is established for naltrexone over 50-200 mg dose range only).
- Therefore, Pfizer considers the comparison of a single crushed ALO-02 60 mg/7.2 mg capsule from study B4531008 vs. 7.2 mg dose of NLT from a crushed Revia tablet in solution from studies ALO-02-07-201 and ALO-02-09-2001 as valid, and does not compromise subject safety or invoke the assumption of PK linearity due to the concerns highlighted above.

2. Justification for Dose and Naltrexone Block in Alcohol Interaction Study

- The alcohol interaction study B4531004 with the final ALO-02 formulation was not performed at the highest strength of 80 mg/9.6 mg due to the potential of increased oxycodone exposures in the presence of alcohol. A lower dose of ALO-02 20 mg /2.4 mg was administered under naltrexone block in this study, in consideration of subject safety and retention in the 4-way crossover study in healthy volunteers.

(b) (4)

- This is also supported by the results of a previous alcohol interaction study ALO-02-08-103 with a prototype ALO-02 formulation that was conducted without naltrexone block at the 40 mg dose. The ALO-02-08-103 study results showed a similar increase of oxycodone C_{max} at

40% alcohol, with no naltrexone exposures across the 4-40% alcohol strengths tested. Thus, the results from the study with ALO-02 20 mg under naltrexone block may complement those from the study with ALO-02 40 mg without naltrexone block.

3. All the pivotal clinical pharmacology and Phase 3 studies were performed with the final to-be-marketed common pellet formulation.

The two phase 3 studies included all proposed strengths of ALO-02 (containing 10, 20, 30, 40, 60 and 80 mg oxycodone HCl).

- Study B4531001 (long term open label safety study) used the proposed commercial capsule sizes and colors.
- Study B4531002 (safety and efficacy) was a double blind study which used a (b) (4) capsule for all strengths. To bridge these clinical image capsules to the commercial capsules (which vary in size and color depending on the strength), Pfizer intends to conduct comparative dissolution studies using the proposed commercial dissolution method for oxycodone release and demonstrate f_2 similarity.

(b) (4)

Does the Agency agree?

Discussion:

The Sponsor restated their argument that they should receive a waiver for a dose proportionality study, and asked whether the Agency agrees.

The Agency stated that there are two reasons why the Sponsor's proposal to not conduct a bioequivalence study and request for a biowaiver (b) (4) cannot be justified. (b) (4)

The Agency emphasized that if there are portions of the NDA application that deviate from the norm such as this cross-study comparison with gaps in the PK data, it will be investigated during the review. It may or may not be found adequate at that time, and could result in a Complete Response action. Therefore, it was strongly recommended that the application be complete upon submission, as there would be no commitment to review any late PK, in vitro or animal data submitted during the NDA review cycle. It was also noted that there is evidence that the naltrexone is not fully sequestered and there were detectable plasma levels in the Phase 3 study. It was strongly recommended that the Sponsor conduct a complete PK study prior to NDA submission.

The Sponsor asked whether they could submit a biowaiver request package for review prior to submission of the NDA. The Agency agreed, but could not promise a specific timeline for a response.

The Sponsor requested comments from the Agency on their proposal for conducting a relative BA analysis for naltrexone from crushed ALO-02 versus Revia in solution. The Agency stated that, for a relative BA study conducted for a 505(b)(2) application, the highest strength must be used under label-recommended use conditions, and must be compared to Revia 50 mg oral under the label-recommended use conditions since the previous safety and efficacy findings of Revia were established under the label-recommended use conditions. If the systemic exposure for ALO-02 is comparable or

lower than Revia, then it is acceptable to rely on the systemic safety findings of Revia to support the systemic safety of ALO-02.

The Sponsor described their alcohol interaction studies, and stated that, due to concerns for subject safety, they conducted studies with the 20 mg dose under naltrexone block instead of the highest 80 mg strength. The Agency did not agree that evaluation of the 20 mg dose was adequate, and stated that, as the greater risk is with the safety of the highest strength of oxycodone, there has to be some other justification besides the risk of respiratory depress for not using the highest strength, as naltrexone would ensure the safety of the subjects with the highest strength as well.

The Sponsor stated that they have conducted an in vitro alcohol study using from 5 to 40% alcohol, and did not see significant release until the 2-hour time point, at which point there was 46% release. In terms of the kinetics, there is faster release in alcohol than water, but they are still collecting data. The Agency asked the Sponsor to submit the release profiles and in vitro data results and that this will be reviewed and comments would be provided on the need for further alcohol interaction studies. If time permits, comments may be added as a postmeeting note to the meeting minutes, or alternatively sent as an advice letter after review of the material.

The Agency agreed that studies used to support the label must use the to-be-marketed strength, and that the varying color will not be a concern provided the Sponsor submits adequate dissolution data to support it.

In a correspondence received March 26, 2014, Pfizer included the following Post-meeting note, with a request for concurrence on the key study features:

Pfizer Post-Meeting Note (26 March 2014)

Pfizer agreed to consider including a dose-proportionality study as suggested, although in light of the EOP2 guidance it remains unclear if the main interest is to assess naltrexone exposures at the highest dose level (b) (4)

and the question should be focused on the assessment of naltrexone exposures at the highest dose level.

Agency Post-Meeting Response:

The Division’s main interest is the naltrexone systemic exposure since the exposure to naltrexone will raise concern for opioid withdrawal in patients. As indicted in the EOP2 meeting minutes, if the Sponsor has data showing that at the highest dose level, there are no naltrexone levels, then a dose-proportionality study is not needed for this product. As the Sponsor indicated that naltrexone is detectable in the Phase 3 study based on sparse PK sampling. Therefore, information on dose proportionality is still needed.

We agree the proposed study will address (1) dose proportionality for ALO-02, and (2) establish the scientific “bridge” between ALO-02 and Revia for 505(b)(2) pathway. As naltrexone levels from ALO-02 must be accurately measured, naltrexone block may not be used in the proposed study. The study must be designed with a patient population that can tolerate the 80 mg oxycodone arm.

In lieu of conducting a human PK study to address dose proportionality, you may submit a biowaiver request.

Upon further discussion internally, the Sponsor’s request for biowaiver (b) (4) can be granted as long as the following conditions are met:

You may submit the biowaiver request to the Agency for review under this IND. While we will try to review the submission in a timely manner, we cannot promise any specific timeframe.

Post-meeting comment on the use of AOL-02 in special populations:

In your meeting package, it was mentioned that naltrexone is not fully sequestered and was detected in patients in the Phase 3 study. Oxycodone is extensively metabolized in the liver, so its pharmacokinetics will change in patients with liver impairment. Naltrexone and its primary metabolite are excreted primarily in the urine so renal disease may alter its pharmacokinetics. In addition, the Revia label states that an increase in naltrexone AUC of approximately 5- and 10-fold is reported in patients with liver cirrhosis, and these data also suggest that alterations in naltrexone bioavailability are related to liver disease severity. Therefore, the pharmacokinetics of ALO-02 will change in renal-impaired patients and hepatic-impaired patients. If the magnitude of the

increase in systemic exposure of naltrexone is greater than that of oxycodone in these patients, it will raise a concern for opioid withdrawal. In your NDA submission, provide adequate information and propose recommendations in the label on the use of AOL-02 in special populations (elderly, etc.), especially in renal-impaired patients and hepatic-impaired patients.

Question 5:

As discussed in Section 8.1.3, Study B4531002, a multicenter, 12-week, double-blind, placebo-controlled, randomized withdrawal study to determine the efficacy and safety of ALO-02 in subjects with moderate-to-severe CLBP is intended to form the primary basis of an efficacy claim in the NDA. The protocol has been reviewed by the Agency under Special Protocol Assessment (SPA) (FDA letters, dated 21 July and 02 December 2011).

Does the Agency agree that the analysis of the efficacy data from Study B4531002 is adequate and would support review of the NDA?

Division Response:

It appears that the analysis of the efficacy data from Study B4531002 will support review of the NDA. We may request additional analyses as needed during the review process.

Pfizer Response: No further discussion is required at the meeting.

Discussion:

There was no further discussion of this question.

Question 6:

The clinical program comprises 2 Phase 3 studies one of which evaluates efficacy as a primary endpoint (Study B4531002). The second study (B4531001), is a long-term, open-label safety study with assessments of analgesic effects as secondary endpoints. Therefore, data from Study B4531001 is considered to be supportive of the efficacy data from Study B4531002. The efficacy data for the 2 Phase 3 studies are intended to be presented separately because of the fundamental differences in study design, treatment duration, and efficacy endpoints (see Section 8.1.3).

As only one primary efficacy study (B4531002) will be provided in the NDA, with supportive information from the long-term safety study (B4531001), does the Agency agree that the requirement for an Integrated Summary of Efficacy (ISE) can be waived for this submission?

Division Response:

No. As a 505(b)(2) application, the ISE should include a discussion of how the findings from the single efficacy study, reliance on the Agency's findings for the listed drugs, and any cited literature references support a finding of efficacy for this product.

Pfizer Response: We agree and no further discussion is required at the meeting.

Discussion:

There was no further discussion of this question.

Question 7:

The clinical program encompasses clinical studies including 2 Phase 3 efficacy and safety studies, 5 PD studies of abuse potential and naltrexone dose ratio, and 7 Phase 1 PK studies (see Section 8, Table 3). Safety results will be provided individually from each of the 14 studies included in the NDA. Key safety results will be pooled from the 2 Phase 3 studies (B4531001 and B4531002) for similar study periods as indicated in Table 1.

Table 1. Pooling for Phase 3 Data (Studies B4531001 and B4531002)

	Pooled Analysis	
	Titration	Maintenance
B4531001	Weeks 1 – 6	Weeks 7-18
B4531002	Weeks 1 – 4, 5, or 6	Double-Blind Weeks 1-12 ALO-02

Is the pooling strategy for the Summary of Clinical Safety (SCS) and the Integrated Summary of Safety (ISS) acceptable to the Agency?

Division Response:

We agree with pooling safety data from Studies B4531001 and B4531002 but note that in “Table1. Pooling for Phase 3 Data”, data is not included after Week 18 for Study B4531001. Safety data for the entire study duration should be included in the safety analyses.

Pfizer Response: We agree and no further discussion is required.

Discussion:

There was no further discussion of this question.

Question 8:

The Sponsor is providing shells for the Summary of Clinical Efficacy (SCE) (Appendix 1.2), the SCS (Appendix 1.3), and the ISS (Appendix 1.4) in this briefing document. Will the data presentations as outlined in these shells be acceptable?

Division Response: Yes, we agree.

Pfizer Response: No further discussion is required.

Discussion:

There was no further discussion of this question.

Question 9:

As indicated in the SCS and ISS shells (Appendix 1), subgroup analysis of the Phase 3 study data will be provided for adverse events (AEs) (pooled) and laboratory results of potential clinical significance (by study) by age, gender, race, and prior opioid experience (naïve or experienced). As all Phase 3 studies were conducted in a single region (United States [US]), subgroup analysis by region cannot be undertaken. Does the Agency agree?

Division Response: Yes, we agree.

Pfizer Response: No further discussion is required at the meeting.

Discussion:

There was no further discussion of this question.

Question 10:

The Sponsor intends to provide both standard safety narratives and narratives of special interest to support the NDA.

Standard safety narratives will be provided in the SCS and ISS shells for the patients with serious adverse events (SAEs), patients who died during the studies, and those who discontinued due to AEs. The narratives of special interest are proposed to include both narration and summary tables of events related to misuse, abuse and aberrant behaviours across the clinical trial program for ALO-02, as described in detail in Section 8.1.6. Full narratives are proposed for both phase 3 studies and will include narration of events related to abuse, misuse, drug diversion, aberrant behaviour (defined below), overdose (intentional and unintentional), and drug withdrawal. These narratives will not include Phase 1 studies, since these studies were all conducted in non-dependent volunteers who received single doses, in a controlled setting. Summary tables listing events of aberrant behaviors (urine drug testing [UDT], concomitant use of non-study opioids, Clinical Opiate Misuse Measure [COMM] scores indicative of aberrant behavior) will be summarized as applicable for the two phase 3 studies. In addition, summary tables listing all AEs related to abuse (Controlled Substance Staff [CSS] and Standard Medical Dictionary for Regulatory Activities (MedDRA) Query [SMQ] terms) across all clinical studies (both phase 1 and 3) will be included. These narratives and summary tables will be presented in separate sections of the SCS and the ISS.

10a. Does the Agency agree with the proposal for standard (safety) narratives?

Division Response:

No, we do not agree. These should be full narratives, not adverse event report forms. Summary tables should also be provided. However, your proposal that the standard safety narratives will be provided in the SCS and ISS shells for the patients with serious adverse events, patients who died during the studies, and those who discontinued due to adverse events (AEs) is acceptable.

AEs related to abuse potential should be monitored in all clinical studies as a means of evaluating the safety of the drug product. It is unclear how reports of abuse-related AEs can provide support of an abuse-deterrent claim in the absence of an appropriate active comparator and endpoints that measure abuse potential.

10b. Does the Agency agree with the proposal for narratives of special interest?

Division Response:

No, we do not agree. Full narratives related to abuse, misuse, drug diversion, aberrant behavior, overdose, and drug withdrawal should be provided for all studies conducted in any phase, not just those collected during Phase 3 studies. Of particular interest are the Phase 1 human abuse potential studies, since they were designed to evaluate a range of doses of ALO-02, as well as tampered doses, both of which reflect abuse-related concerns and abuse-deterrent claims. As noted for the standard safety narrative, the narratives of special interest should be full narratives, in addition to adverse event report forms.

The proposed assessments of clinical opioid withdrawal, abuse potential, drug accountability, and compliance with medication, as provided in the Adverse Events of Special Interest (section 2.8.4.2.3 of the SCS), are also acceptable.

Your proposal that narratives of special interest include both narration and summary tables of events related to misuse, abuse and aberrant behaviors for ALO-02 is acceptable. The definitions provided for these terms are acceptable.

10c. Does the Agency agree with the use of the CSS/SMQ terms of AEs related to abuse provided in Section 8.1.6?

Division Response: No, we do not agree.

The list of abuse-related terms should be consistent with those described in the FDA guidance for industry: *Assessment of Abuse Potential of Drugs*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf> (see Addendum below for complete list).

The Phase 3 studies, as well as the Phase 1 human abuse studies and the alcohol interaction study, should be monitored using these AE terms.

Pfizer Response: We agree and no further discussion is required at the meeting regarding questions 10(a) and 10 (b).

Regarding question 10c, upon review of possible adverse event terms referenced in the FDA guidance for industry: *Assessment of Abuse Potential of Drugs*, the following abuse-related MedDRA PTs are proposed:

Guidance Terms	Proposed MedDRA Version 16.1 Preferred Terms, Based on Guidance Terms
Mood elevation, Elevated mood	Elevated mood
Sedation	Sedation Altered state of consciousness Depressed level of consciousness Lethargy Loss of consciousness Somnolence Stupor
Psychotomimetic events	Schizophrenia and other psychotic disorders (All PTs within HLG T) Delusional symptoms (All PTs within HLT) Delirium
Euphoria, Euphoric mood	Euphoric mood

Mood alteration	Mood altered
Feeling drunk	Feeling drunk
Hallucination (visual and auditory)	Perception disturbances (All PTs within HLT)
Feeling abnormal	Feeling abnormal
Inappropriate affect, Elation inappropriate, Exhilaration inappropriate, Feeling happy inappropriately, Inappropriate elation, Inappropriate laughter, Inappropriate mood elevation	Inappropriate affect

Pfizer proposes to include summary tabulations of the MedDRA AE terms listed in the table above, in addition to AE terms included in the drug abuse, dependence, and withdrawal SMQ. This proposal replaces Table 10 (section 8.1.6) in the briefing document. **Does the Agency agree with this approach?**

Discussion:

The Sponsor asked whether their proposed abuse-related MedDRA Preferred Terms are acceptable. The Controlled Substances Staff agreed, and clarified that the goal in assessing these events is primarily to identify whether there are any euphoria signals. Since ALO-02 contains oxycodone, a Schedule II drug with known abuse potential, it is likely that euphoria responses will be reported.

Question 11:

The Sponsor proposes to submit case report forms (CRFs) for deaths, SAEs and discontinuations from treatment due to AEs for all clinical studies included in the submission.

The Sponsor requests a waiver for the requirement to provide patient profiles according to 21CFR314.50(f)(1), as this would be redundant to the CRF information.

Is this acceptable to the Agency?

Division Response:

Patient profiles are not a required portion of any application; therefore, a waiver is not necessary. Patient profiles are considered optional and are sometimes requested at the discretion of some review divisions to facilitate review. We are not requesting patient profiles at this time.

Since some of the deaths, SAEs and discontinuations may reflect abuse-related responses to oxycodone, full narratives should be provided, in addition to the CRFs.

Pfizer Response: No further discussion is required at the meeting.

Discussion:

There was no further discussion of this question.

Question 12:

The table below indicates the datasets that are planned to be provided with the NDA submission. The Sponsor will provide Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) datasets and analysis datasets for each individual study in the clinical program, as indicated. The Sponsor will also provide analysis datasets for the pooled safety data.

Table 2. Datasets to be Provided for Clinical Studies Included in the ALO-02 Development Program

Study Number	Datasets to be Provided in NDA
---------------------	---------------------------------------

Phase 1 Clinical Pharmacology and Pharmacokinetics in Healthy Volunteers

ALO-02-07-102	No datasets will be provided, prototype formulations evaluated in this pilot study
ALO-02-08-103	No datasets will be provided, prototype formulations evaluated in this pilot study
ALO-02-09-1001	raw
B4531003	raw, analysis
B4531004	raw, analysis
B4531006	raw, analysis
B4531007	raw, analysis

Pharmacodynamic Studies of the Dose Ratio of Naltrexone and Abuse Potential in Non-Dependent Recreational Drug Users

ALO-02-07-201 (also known as AP104, ALO-02-101)	raw
ALO-02-09-2001	raw, analysis
B4531008	raw, analysis
B4531009	raw, analysis
B4981002	raw, analysis

Phase 3 Efficacy and Safety Studies in the Target Population of Patients with Chronic Pain

ALO-02-10-3001 (also known as B4531001)	raw, analysis
B4531002	raw, analysis
Pooled studies	
Integrated Safety Summary	analysis

Does the Agency agree with this proposal for the planned datasets?

Division Response:

Yes, we agree with the proposed datasets as long as they comply with the appropriate regulations (see Attachment 1).

For your clinical pharmacology studies, the datasets of concentrations and the non-compartmental PK analysis in SAS transport files (.xpt) must include (but are not limited to) the information of treatment, dose, subject number, nominal time, actual time, sequence, and period.

Pfizer Response: We agree and no further discussion is required at the meeting.

Discussion:

There was no further discussion of this question.

Question 13:

Different versions of MedDRA coding were applied to the AE data for each individual study report, based on when the individual studies were conducted. The Sponsor plans to utilize the original MedDRA version used for each study report, when results from individual study reports are referenced or presented in the SCS and ISS. The Sponsor plans to utilize MedDRA Version 16.1 for pooled clinical data presentations in the SCS, ISS, and the Clinical Overview. The Sponsor plans to provide individual study datasets coded to the MedDRA Version used in the original study reports, and integrated AE datasets coded to MedDRA Version 16.1. Is this approach acceptable?

Division Response: Yes, we agree.

Pfizer Response: No further discussion is required at the meeting.

Discussion:

There was no further discussion of this question.

Question 14:

Given that inappropriate use of opioids is a major public health concern in the US, and that prevention of opioid abuse is an important initiative for US Department of Health & Human Services, would the Agency grant priority review to the NDA for ALO-02?

Division Response:

No. Oxycodone is currently already available in a formulation with inactive ingredients intended to make it more difficult to manipulate for misuse and abuse.

Pfizer Response: FDA has stated publically that opioids with Abuse Deterrent Formulation (ADF) are a priority for FDA in addressing the epidemic of prescription drug abuse.

Pfizer would like to understand FDA's position for not considering priority review for ALO-02 based on existence of another approved abuse deterrent formulation of oxycodone regardless of the incremental benefit offered by subsequent product(s).

- Pfizer believes that ALO-02 will provide evidence of abuse deterrence from category 1, 2 and 3 studies across multiple routes (oral, intranasal, intravenous) which has not been shown with currently approved products. We believe ALO-02 addresses an unmet medical and public health need and will provide an incremental benefit to support the FDA's efforts in reducing the epidemic of prescription opioid abuse.
- In addition to the abuse deterrent technology, the PK profile (2/3rd reduction in C_{max} and considerably delayed T_{max} compared to IR oxycodone) of ALO-02 is likely to result in limited abuse potential when taken as directed, as demonstrated in study B4531008.
- As demonstrated from epidemiology studies with Oxycontin, no one ADF can completely address the issue of prescription drug abuse and having multiple ADFs with different mechanisms creates additional hurdles for misuse and abuse in the community. There is incremental benefit to public health by having earlier availability of multiple ADFs.

Will the FDA reconsider Pfizer's request for a priority review upon NDA submission?

Discussion:

The Sponsor restated the information in the response above, and asked the Division whether a request for priority review would be considered. The Division stated that the best way to assure priority review would be to conduct a study comparing ALO-02 to a marketed formulation and showing an improvement in the abuse-deterrent properties. Head-to-head data showing the potential for better abuse deterrence is required, and not simply an argument that abuse deterrence is an unmet need. The Division confirmed that the Sponsor can submit a request for priority review in the NDA submission and that the Division will review the request package.

Question 15:

The planned NDA will be submitted in electronic Common Technical Document (eCTD) format in accordance with the International Conference on Harmonization (ICH) and FDA guidance on electronic submissions. A summary of the proposed eCTD format and outline of the Table of Contents (TOC) for the NDA application are provided in Appendix 1.1.

Does the Agency concur with the format and placement of the information in the electronic submission of the planned NDA?

Division Response: Yes, we agree.

Pfizer Response: No further discussion is required at the meeting.

Discussion:

There was no further discussion of this question.

Additional Biopharmaceutics Comments:

You must submit the full development and validation report of the proposed dissolution method for both oxycodone and naltrexone for the Agency to review. Some general guidelines for the dissolution method are as follows:

a) Dissolution Method:

Provide the dissolution method report including the complete dissolution profile data collected during the development and validation of the proposed dissolution method. A detailed description of the optimal in vitro dissolution methodology and the developmental parameters (i.e., solubility data for the drug substance across the pH range, selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.) that were used to identify this method as most appropriate should be included in the report. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The dissolution profile should be complete and cover at least 80% of drug dissolved or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend using at least twelve samples per testing variable. The dissolution data (individual, mean, SD, profiles) should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim). The testing conditions used for each test should be clearly specified. Also, include the testing conducted to demonstrate the discriminating capability of the selected test as well as the validation data for the test method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). The chosen method should be discriminating and sensitive enough to reject lots that would have less than acceptable clinical performance.

b) Dissolution Acceptance Criteria:

Provide the dissolution profile data from the clinical and stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values). For setting of the drug dissolution acceptance criteria, the following points should be considered:

- The in vitro dissolution specifications should encompass the timeframe over which at least 80% of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.
- Data from lots used in the clinical trials and primary stability studies must be used.
- For extended release products the establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data must be set. The acceptance criteria ranges must be based on the overall dissolution data generated at these times.
- In general, the selection of the dissolution acceptance criteria ranges is based on mean target value $\pm 10\%$ and NLT 80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.

- The dissolution acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.

3.0 ACTION ITEMS

1. The Sponsor agreed to submit the dissolution method to the Agency for review.
2. The Sponsor agreed to submit relevant literature supporting the safety of the excipients to the Agency, to follow the excipient guidance, and to balance the supportive literature with additional studies as required.
3. The Sponsor agreed to submit the release profiles and in vitro data results for alcohol interaction.
4. The Agency will review this and provide comments on the need for further alcohol interaction studies. If time permits, these comments will be added as a postmeeting note to the meeting minutes.

4.0 ATTACHMENTS AND HANDOUTS

Attachment 1: Additional Comments for Pre-NDA Stage of Drug Development

Attachment 1: Additional Comments for Pre-NDA Stage of Drug Development

Nonclinical Comments

1. Include a detailed discussion of the nonclinical information in the published literature in your NDA submission and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.
2. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 draft guidance for industry, *Applications Covered by Section 505(b)(2)*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408, available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).

Note that you may only rely on the Agency's finding of safety and/or effectiveness as it is reflected in the approved labeling for the listed drug(s). You may not reference data in the Summary Basis of Approval or other FDA reviews obtained via the Freedom of Information Act or publically posted on the CDER website to support any aspect of your development program or proposed labeling of your drug product. Reviews are summary data only and do not represent the Agency's previous finding of safety and effectiveness.

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

3. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.

4. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance for industry, *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients*.

As noted in the document cited above, “the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently **proposed level of exposure, duration of exposure, or route of administration.**” (emphasis added).

5. Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.

Adequate qualification would 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 of appropriate duration to support the proposed indication.
6. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative *in vitro* bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled “Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.” Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.
 7. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), 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 Q3B(R2) qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.
 8. Failure to submit adequate impurity qualification or justification for the safety of new excipient use at the time of NDA submission can result in a Refusal-to-File or other adverse action.

Chemistry, Manufacturing and Control (CMC) Comments

1. Include a well-documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.
2. Include at least 12 months of real time data and 6 months of accelerated data in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to cover the proposed expiry dating.
3. Provide a list of all manufacturing and testing facilities and their complete addresses in alphabetical order, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number and facsimile number at the site. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester etc.) of each facility, the site CFN numbers and designate which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.
4. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.
5. Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis), and in addition, provide graphical plots of critical parameters and trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.

The Abuse Potential section of the NDA is submitted in the eCTD as follows:

Module 1: Administrative Information and Prescribing Information

1.11.4 Multiple Module Information Amendment

This section should contain:

- A summary, interpretation and discussion of abuse potential data provided in the NDA.
- A link to a table of contents that provides additional links to all studies (nonclinical and clinical) and references related to the assessment of abuse potential.
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

Module 2: Summaries

2.4 Nonclinical Overview

This section should include a brief statement outlining the nonclinical studies performed to assess abuse potential.

2.5 Clinical Overview

This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

Module 3: Quality

3.2.P.1 Description and Composition of the Drug Product

This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

3.2.P.2 Description and Composition of the Drug Product

This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

Module 4: Nonclinical Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

4.2.3.7.4 Dependence

This section should include:

- A complete discussion of the nonclinical data related to abuse potential.
- Complete study reports of all preclinical abuse potential studies.

Module 5: Clinical Study Reports

5.3.5.4 Other Study Reports

This section should contain complete study reports of all clinical abuse potential studies.

5.3.6.1 Reports of Postmarketing Experience

This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product

General Clinical Comments

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R).

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - Important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 – Clinical Pharmacology- Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
3. Section 7.5.1 Dose Dependency for Adverse Events
4. Section 7.5.2 Time Dependency for Adverse Events
5. Section 7.5.3 Drug-Demographic Interactions
6. Section 7.5.4 Drug-Disease Interactions
7. Section 7.5.5 Drug-Drug Interactions
8. Section 7.6.4 – Overdose, Drug Abuse Potential, Withdrawal and Rebound

Sites for Inspection

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/contract research organization (CRO) inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Items I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in the submission in the format described, the Applicant can identify the location(s) and/or provide link(s) to the requested information.

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

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring [BIMO] Clinical Data in eCTD Format).

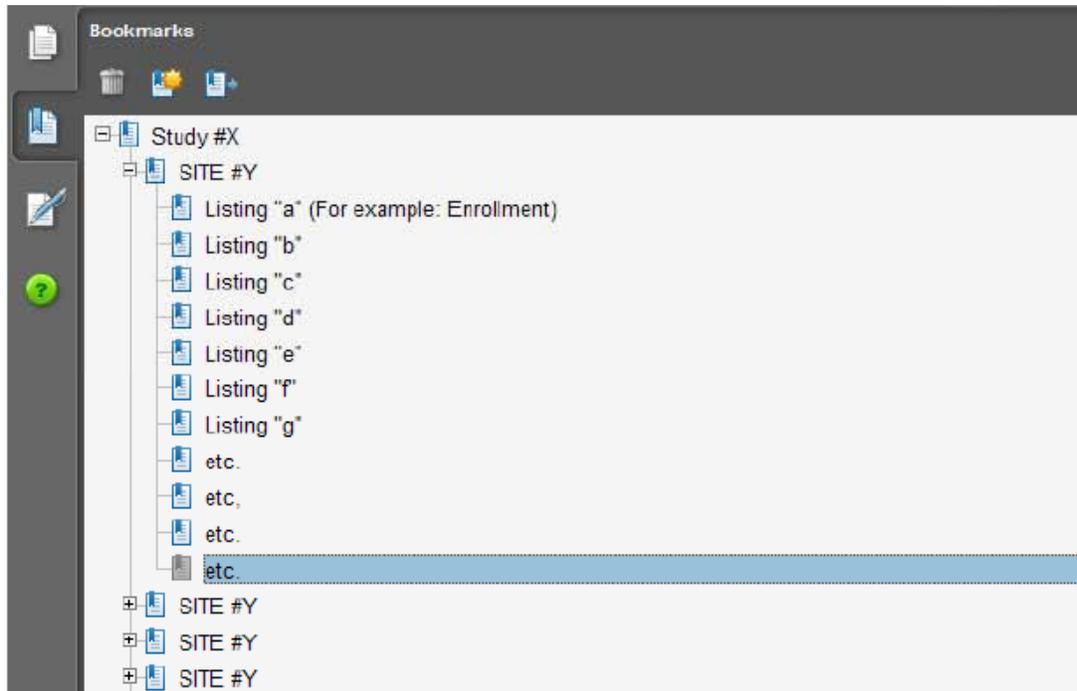
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in the submission, describe the location or provide a link to the requested information).

1. Please include the following information in a tabular format in the original NDA/BLA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal Investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA/BLA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued at each site
3. Please include the following information in a tabular format in the NDA/BLA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety

- reports, or other sponsor records as described in ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
- b. Name, address and contact information of all contract research organizations (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571) you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated case report form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial, provide the original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per-protocol subjects/ non per-protocol subjects and reason not per- protocol
 - e. By subject, listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject, listing of AEs, SAEs, deaths and dates
 - g. By subject, listing of protocol violations and/or deviations reported in the NDA/BLA, including a description of the deviation/violation
 - h. By subject, listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject, listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject, listing of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Subpart 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

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

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



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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

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

FDA eCTD web page

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

For general help with eCTD submissions: ESUB@fda.hhs.gov

Pediatric 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.

Common PLR Labeling Errors

Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions)
7. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
8. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

9. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
10. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
11. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]
12. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See Comment 34 Preamble]
13. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
14. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
15. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Contents (Table of Contents):

16. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
17. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
18. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
19. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
20. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, Subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

8.1 Pregnancy
8.3 Nursing Mothers (not 8.2)
8.4 Pediatric Use (not 8.3)

8.5 Geriatric Use (not 8.4)

21. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI):

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>
24. Do not refer to adverse reactions as “adverse events.” Refer to the guidance for industry, *Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)].
28. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
29. Since SPL Release 4 validation does not permit the inclusion of the Medication Guide as a subsection, the Medication Guide or Patient Package Insert should not be a subsection under the Patient Counseling Information section. Include at the end of the Patient Counseling Information section without numbering as a subsection.

30. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
32. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. See guidance for industry, *Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements*. The same applies to PPI and MG.
33. For fictitious examples of labeling in the new format, refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.
34. For a list of error-prone abbreviations, symbols, and dose designations, refer to the Institute of Safe Medication Practices’ website, <http://www.ismp.org/Tools/abbreviationslist.pdf>

SPL Submission

Structured product labeling (SPL) must be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b)]; guidance for industry, *Providing Regulatory Submissions in Electronic Format — Content of Labeling*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>], you are required to submit to FDA prescribing and product information (i.e., the package insert) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

Integrated Summary of Effectiveness

Please refer to the guidance for industry, *Integrated Summary of Effectiveness*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>

Please refer to guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

CDER Data Standards Reference Guide/Checklist

The following resources are intended to assist submitters in the preparation and submission of standardized study data to CDER, available at.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

Dataset Comments

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The integrated safety dataset that must include the following fields/variables:

- a. A unique patient identifier
 - b. Study/protocol number
 - c. Patient's treatment assignment
 - d. Demographic characteristics, including gender, chronological age (not date of birth), and race
 - e. Dosing at time of adverse event
 - f. Dosing prior to event (if different)
 - g. Duration of event (or start and stop dates)
 - h. Days on study drug at time of event
 - i. Outcome of event (e.g., ongoing, resolved, led to discontinuation)
 - j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
 - k. Marker for serious adverse events
 - l. Verbatim term
2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the case report form.
 3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.

4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.
5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the *ICH MedDRA Term Selection: Points to Consider* document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
9. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.
11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.
13. All datasets must contain the following variables/fields (in the same format and coding):
 - a. Each subject must have one unique ID across the entire NDA
 - b. Study number
 - c. Treatment assignment

d. Demographic characteristics (age, race, gender, etc.)

14. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups are not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.
15. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.
16. For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.
17. With reference to the table on the following page, note that the HLG and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLG terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

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

/s/

DIANA L WALKER
04/11/2014



IND 107037

MEETING MINUTES

Alpharma Pharmaceuticals, LLC
c/o King Pharmaceuticals, Inc
4000 CentreGreen Way, Suite 300
Cary, NC 27513

Attention: Victoria Gunto, Ph.D.
Director, Regulatory Affairs, King Pharmaceuticals, Inc

Dear Dr. Gunto:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Oxycodone hydrochloride and Naltrexone hydrochloride Extended-Release Capsules (ALO-02).

We also refer to the teleconference between representatives of your firm and the FDA on November 8, 2010. The purpose of the meeting was to discuss critical development issues related to the ALO-02 combination product.

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

If you have any questions, call me, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, PhD
Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B, End-of-Phase 2

Meeting Date and Time: November 8, 2010, 2:00 p.m., EST

Meeting Location: Teleconference

Application Number: IND 107037

Product Name: ALO-02, Oxycodone HCl and naltrexone HCl ER capsules

Indication: (b) (4)

Sponsor/Applicant Name: Alpharma Pharmaceuticals/King Pharmaceuticals, Inc.

Meeting Chair: Sharon Hertz, M.D., Deputy Director, Division of Anesthesia and Analgesia Products (DAAP)

Meeting Recorder: Diana L. Walker, Ph.D., Regulatory Project Manager

FDA ATTENDEES

Bob Rappaport, M.D.	Director, DAAP
Sharon Hertz, M.D.	Deputy Director, DAAP
Neville Gibbs, M.D.	Medical Officer
R. Daniel Mellon, Ph.D.	Pharmacology/Toxicology Supervisor
Suresh Doddapaneni, Ph.D.	Clinical Pharmacology Team Leader
Craig Bertha, Ph.D.	Product Quality Reviewer
Patrick Marroum, Ph.D.	Biopharmaceutics Supervisor
Dionne Price, Ph.D.	Biometrics Team Leader
Jonathan Norton, Ph.D.	Biometrics Reviewer
Silvia Calderon, Ph.D.	Controlled Substances Staff Team Leader
Diana L. Walker, Ph.D.	Regulatory Health Project Manager

SPONSOR ATTENDEES

Eric Carter	Chief Science Officer
Veeraindar Goli	Senior Director, Clinical Research
Vicki Gunto	Director, Regulatory Affairs
Wendy Hamon	Project Manager
Michael Lamson	Senior Director, Pharmacokinetics and Clinical Research
Paul Meisner	Senior Director, Clinical Research
Kenneth Sommerville	Vice President, Clinical Development
Kenneth Touw	Senior Vice President, Regulatory Affairs

1.0 BACKGROUND

The purpose of this meeting is to seek the Division of Anesthesia and Analgesia Products (DAAP) input and agreement on key aspects of the ALO-02 development program. The objectives of this meeting are to obtain input on the Chemistry, Manufacturing, and Controls (CMC) plans and protocols, and to review the ALO-02 clinical development plan and confirm that the approach presented is consistent with the expectations to support the development of an abuse deterrent extended-release oxycodone product. The Sponsor received the Preliminary Meeting Comments letter responding to the questions in the meeting briefing package in advance of the meeting, and chose to focus on Questions #9 and #10. Additional discussion outside of the questions is included at the end of the meeting minutes.

Comments and questions posed by the Sponsor are in *italicized font*, and pre-meeting preliminary responses from the Agency are in **bold font**. Discussion during the meeting is presented in normal font.

2.0 DISCUSSION

FDA General Comments:

CHEMISTRY, MANUFACTURING AND CONTROLS

(b) (4)
The formulation of ALO-02 that is planned for the Phase 3 clinical trials and NDA registration stability batches differs from that used in the pilot pharmacokinetic study (Study ALO-02-09-1001). These differences include (b) (4)

Additionally, commercial plans include the development of several strengths of ALO-02. (b) (4)

The proposed dosage strengths for the oxycodone HCl and naltrexone HCl content in the capsules are 10/1.2 mg, (b) (4) 20/2.4 mg, 30/3.6 mg, 40/4.8 mg, 60/7.2 mg and 80/9.6 mg. Pertinent information about the manufacturing and controls proposed for ALO-02 is presented in Section 3 of this briefing package.

Question 1: Does the Division concur with the proposed strengths of ALO-02 planned for registration? If not, what changes does the Division suggest?

FDA Response

The dose range for the oxycodone component appears to be acceptable. Whether the doses of naltrexone are appropriate will be assessed during the review of the NDA with particular attention paid to the occurrence of withdrawal symptoms in the study population.

Discussion: There was no further discussion of this question.

Question 2: *Does the Division concur with the proposed ALO-02 manufacturing process, including process scales, in-process controls and specifications for intermediates? If not, what changes does the Division suggest?*

FDA Response

The registration/primary stability batches should be prepared (b) (4)

Evaluation of in-process controls and specifications for intermediates will be undertaken during the review of the data presented in your NDA.

Discussion: There was no further discussion of this question.

Question 3: *Does the Division concur with the proposed specifications for acceptance of both active pharmaceutical ingredients (APIs), oxycodone HCl and naltrexone HCl at the site of drug product manufacture? If not, what changes does the Division suggest?*

FDA Response

The specifications for oxycodone HCl contain all of the parameters that we would recommend for use in the formulation of the drug product. The evaluation of the acceptance criteria for all parameters will be undertaken during review of the data in the NDA.

(b) (4)

In terms of safety qualification, the drug substance impurity (b) (4) contains a structural alert for mutagenicity. Genotoxic or carcinogenic impurities, or impurities that contain a structural alert for genotoxicity, must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product 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. If levels cannot be reduced, adequate qualification would 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.

We note that the proposed impurity specification of NMT (b) (4) % may be deemed adequate if you can provide in vitro dissolution data for this drug product to show that (b) (4) is not released from the product such that levels would not exceed 1.5 mcg/day when the product is used as labeled up to the maximum theoretical daily dose of (b) (4) g/day oxycodone.

Discussion: There was no further discussion of this question.

Question 4: *Does the Division concur with the proposed specifications for ALO-02? If not, what changes does the Division suggest?*

FDA Response

The drug product specification includes the parameters expected for the proposed type of dosage form. However, justification for not following ICH Q6A for identity testing should be provided in the application. Evaluation of the proposed acceptance criteria will be done at the time of NDA review.

In terms of safety qualification, several of your proposed drug product stability specifications exceed the ICH Q3B(R2) qualification threshold of NMT 0.2%. Any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as described in the ICH Q3A(R2) and ICH Q3B(R2) guidances at the time of NDA submission.

Adequate qualification would include:

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

Discussion: There was no further discussion of this question.

Question 5: *Does the Division concur with the proposed in vitro studies to support the dissolution method and specifications for ALO-02? If not, what additional data do the Division suggest be collected?*

FDA Response

Submit a full dissolution method development report for review. The proposed specifications appear to be (b) (4) recommended by the IVIVC guidance. Provide data to justify the proposed dissolution specifications and follow the recommendations of the IVIVC guidance on setting dissolution specifications. If an IVIVC is present and is found to be acceptable, then this IVIVC should be used to justify the proposed specifications.

Discussion: There was no further discussion of this question.

Question 6: *Does the Division concur with the proposed studies to examine the effect of physical and chemical manipulation of ALO-02 for the purpose of misuse of oxycodone HCl? If not, what additional data do the Division suggest be collected?*

FDA Response

Although complete protocols are not provided, the solvent extraction studies (3.1.3.4.1) appear to be acceptable (b) (4) studies (3.1.3.4.2) also appear reasonable. However, in these studies looking at temperature effects, should partial extraction be evident at the time points indicated, it is recommended that additional later time points be assessed until the extractions are complete.

Also, additional consideration should be given to the design of the multiple-step extraction studies (3.1.3.4.3) for preparation of a suitable solution for intravenous injection. Additional solvents, particularly (b) (4) should be examined for extraction of the oxycodone base (b) (4) for intravenous injection. In the event that oxycodone HCl can be preferentially extracted (b) (4) from intact pellets, this procedure should also be considered as a potential means of preparing a solution for intravenous injection.

Discussion: There was no further discussion of this question.

Question 7: *The current commercialization strategy includes seven strengths of ALO--02 (in capsule shells of different sizes and colors), two different packaging configurations (bottles (b) (4)) and the use of two possible sites for encapsulation of the ALO-02 pellets into capsule shells. Does the Division concur with the proposed number of batches to be manufactured and included in the stability program to support NDA registration? If not, what changes does the Division suggest?*

FDA Response

Stability data collected as per your bracketed (strengths)/matrixed (batches) protocol should be treated as per ICH Q1E for determination of the appropriate expiry period. Refer to the ICH Q1D guideline for a description of the risks associate with such a reduced design. If it is not the case that long-term and accelerated stability data show little or no variability or change with time, include a statistical analysis of the stability data in your application to support your proposed expiration dating period, and include the input data in the application in a format amenable to analysis by our biometrics team.

Discussion: There was no further discussion of this question.

Question 8: *Does the Division concur with the proposed registration stability protocol, including the amount of stability data planned for submission at the time of the NDA filing? If not, what additional data do the Division suggest be collected?*

FDA Response

The registration stability protocol in Table 22 is acceptable; however, follow the recommendations of ICH Q1A and submit 12 months of stability data at the time of NDA submission. Applications are expected to be complete at the time of submission and we can not guarantee the review of amendments that arrive during the review cycle. Thus, assume that your expiration dating period will be evaluated based solely on the data provided in the original application.

Discussion: There was no further discussion of this question.

Biopharmaceutics Studies

The following biopharmaceutics studies are intended to support the registration of ALO-02:

- *Study 1: relative oral bioavailability of oxycodone from ALO-02 compared with a commercial formulation of oxycodone*
- *Study 2: effects of taking ALO-02 with food or mixing the pellets with applesauce on oxycodone bioavailability and leakage of naltrexone, compared with fasted conditions*
- *Study 3: effects of ethanol (4%, 20%, and 40%) on oxycodone bioavailability and leakage of naltrexone from ALO-02 compared with control (water only)*
- *Study 4: single- and multiple-dose PK of oxycodone and leakage of naltrexone from intact ALO-02 pellets*
- *Study 5: bioavailability/bioequivalence of the ALO-02 formulation proposed for marketing*
- *Study 6: bioavailability of naltrexone following administration of ALO-02 taken whole or crushed compared with a reference dose of a commercial formulation of naltrexone administered orally*

Question 9: *Does the Division have any guidance or recommendations regarding the proposed Biopharmaceutics studies to support the registration of ALO-02?*

FDA Response

In addition to the types of studies above, we recommend that you add a dose-proportionality study as well. Measure the naltrexone and 6 β -naltrexol levels in all of the studies.

Discussion: The Sponsor requested clarification of the need to conduct a dose-proportionality study given that the drug product uses the same pellet formulation for all dosage strengths. The Sponsor has conducted in vitro studies to demonstrate linearity of morphine release, but linearity of naltrexone was not tested since it is sequestered within the formulation. The Agency stated that the main concern is with the naltrexone levels, and the recommendation for a dose-proportionality study is to assess the release of naltrexone at the highest dose level. If the Sponsor has data showing that at the highest dose level, there are no naltrexone levels, then a dose-proportionality study is not needed for this product. The Sponsor indicated that they plan to collect naltrexone PK data for all dose levels during the clinical studies of ALO-02, and plan to conduct in vitro dose linearity studies.

Clinical Pharmacology Studies

The ratio of naltrexone to oxycodone was evaluated in a dose-response study conducted in Canada (first bullet below). Additional Clinical Pharmacology studies for ALO-02 will include those designed to evaluate the abuse potential of tampered ALO-02. Completed and planned studies for ALO-02 include the following:

- naltrexone dose-ranging study (ALO-02-09-2001) to determine the effects of various doses of naltrexone on oxycodone-induced drug liking and euphoria [study completed]*
- three human abuse potential studies to evaluate the oral, intranasal, and intravenous administration routes of abuse in recreational drug abusers*

Question 10: *Does the Division agree that if successful, results from the studies listed above would be appropriate for inclusion in the prescribing information? Does the Division have any other comments regarding the Clinical Pharmacology program?*

FDA Response

Naltrexone and oxycodone are not approved for either intranasal or 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.

From the stand point of evaluating abuse potential, the three human abuse liability studies are acceptable with the understanding that "ALO-02" is the to-be-marketed formulation and that pharmacokinetic parameters will also be determined.

Potential labeling claims are a review issue. Any proposed claims related to abuse deterrent properties arising out of Clinical Pharmacology studies will be dependent on the types of studies, their design, conduct, and robustness of the data in terms of the rigor of the conditions employed in the manipulation(s) of the capsules and the changes in pharmacokinetics seen along with other in vitro tamper resistance data arising out of physical and chemical manipulation of the product.

It is possible that the NDA for ALO-02 may be brought to Advisory Committee in order to assist the Division in determining the adequacy of the studies that were performed to assess the abuse-deterrent properties of the product, the relevance of the findings and how this information should be represented in the label. The Division received clear recommendations from the Advisory Committee Meeting held on October 21 and 22, 2010, that the language included in the label regarding abuse resistance must be based on the specific physiochemical attributes of a particular product and the studies done to evaluate specific routes of abuse.

Discussion: The Sponsor stated that they are not planning on using crushed ALO-02 for the intravenous study in humans, but do plan to administer ALO-02 as crushed pellets intranasally to nondependent recreational drug abusers. The Sponsor stated that the ALO-02 intravenous study

will use the naltrexone and oxycodone APIs while the proposed intranasal study will be a single-dose exposure to the crushed ALO-02 pellets. The Agency noted that there is no approved IV oxycodone or naltrexone product, and, therefore, the appropriate CMC and nonclinical data supporting the manufacturing and safety of the APIs to be used in an IV study must be submitted prior to study initiation. For the proposed intranasal study, because the crushed product includes talc and other excipients, the Agency stated that safety justification for the intranasal route of administration for the crushed tablets will be required to support this proposed clinical study. The Sponsor agreed and indicated their intention to supply these data in support of the IV and intranasal clinical protocols.

Clinical Efficacy and Safety Studies

The following two clinical studies are proposed to support the registration of ALO-02 (b) (4)

[REDACTED] *Alpharma intends to submit the protocol for Study One for a Special Protocol Assessment.*

- **Study One:** *A Multicenter, 12-Week, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Evaluate the Efficacy and Safety of ALO-02 in Opioid-Experienced Subjects With Moderate to Severe Chronic Low Back Pain*
- **Study Two:** *A Multicenter, 12-Month, Open-Label, Single-Arm, Safety Study of ALO-02 in Subjects With Moderate to Severe Chronic Noncancer Pain*

Question 11: *Does the Division agree that these proposed two clinical studies, if successful, will support the registration of ALO-02* (b) (4)

[REDACTED] *If not, please provide additional guidance or recommendations.*

FDA Response

The two proposed studies, a single controlled efficacy study and a long-term safety study, may be adequate to determine the safety and efficacy of ALO-02. The success of these studies is a review issue.

For Study One, you propose a primary imputation method which uses a mixture of last observation carried forward (LOCF) and baseline observation carried forward (BOCF). In July 2010, the National Academy of Sciences (NAS) released a report on missing data which was commissioned by FDA. The report recommends that, “Single imputation methods like [LOCF] and [BOCF] should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified.” A pre-publication version of the report can be found online at http://www.nap.edu/catalog.php?record_id=12955. While your proposed method is not purely LOCF or BOCF, it is a *single imputation method* because each missing observation is filled in with a single value.

The NAS report has prompted a reconsideration of our approach to missing data. Hence we cannot agree to your imputation method. Your full protocol should include a new method which is in line with NAS recommendations.

We note, however, that your current imputation algorithm has at least one feature which has merit: BOCF, based on the screening baseline pain, is used for patients who withdraw due to an adverse event. We support this element of your algorithm because it attributes a high pain score to patients who clearly had a poor clinical outcome when they withdrew. More broadly speaking, we continue to favor methods for handling missing pain data which attribute poor outcomes to those patients who discontinue early. These methods could include both imputation methods and modeling approaches which have the desired effect. It is also appropriate to account for the potential confounding effect of opioid withdrawal in the primary analysis. The advice in the NAS report should be interpreted in this context.

Discussion: There was no further discussion of this question.

Special Population Studies

(b) (4)

No proposed study designs for these studies are presented at this time.

Question 12: Please comment on this proposal for the program for special populations.

FDA Response

- **You must conduct pediatric studies in order to fulfill PREA requirements.**
- **For an opioid indicated for the treatment of chronic pain, a waiver for studies in children under 7 years may be requested.**
- **Safety and pharmacokinetic studies must be conducted in pediatric patients ages 7 to 17 years. Efficacy for this age group may be extrapolated from studies in the adult population.**
- **You may request a deferral for pediatric studies for patients 7 to 17 years old until studies are completed in adults, but must provide a rationale for why pediatric studies cannot be initiated during development for adult use.**
- **A pediatric plan must be submitted with the NDA, and include requests for waivers and deferrals, and a timeline for proposed studies including date of final protocol submission to the Agency, and date of final study report submission.**

Discussion: There was no further discussion of this question.

Exploratory Studies to Evaluate Respiratory Depression

Although the dose response of euphoria and drug liking has been characterized for opioids, less is known about the dose response relationship with respect to other pharmacological effects of opioids, including the primary mechanism of fatal opioid overdose, opioid induced respiratory depression. Respiratory depression and arrest as a manifestation of an opioid overdose

following tampering of extended release oxycodone is a significant public health concern. Tampering with ALO-02 by chewing and crushing or dissolving will release naltrexone with the oxycodone. In addition to mitigating the psychoactive effects of the opioid, naltrexone has the potential to mitigate the respiratory depression associated with an overdose. Alpharma is planning to investigate the effects of naltrexone on oxycodone-induced respiratory depression in a naltrexone dose-ranging study (Section 4.3.4). Depending upon the outcome of the initial investigation, Alpharma intends to seek specific DAAP input and guidance. Other studies of respiratory function may then be planned.

Question 13: *These studies will evaluate mitigation of respiratory depression by naltrexone. Does the Division have any comments regarding the development pathway for evaluation of this possibly unique feature of the ALO-02 drug product?*

FDA Response

We have not previously assessed the mitigation of respiratory depression in this context. However, in addition to pharmacokinetic studies, clinical endpoints including measures of respiratory drive and ventilation must be included in clinical studies; these include measures such as respiratory rate, oxygen saturation, and end-tidal carbon dioxide.

You must be able to demonstrate that the mitigation of respiratory depression is clinically significant. You must address the duration of action of the naltrexone, and what will happen to the patient when the naltrexone wears off and there is continued systemic exposure to oxycodone.

Discussion: There was no further discussion of this question.

Additional Nonclinical Comment:

Your NDA must include adequate safety justification for the maximum theoretical daily exposure to excipients in the product formulation taking into consideration that the maximum theoretical daily dose of oxycodone in an opioid tolerant individual is (b) (4) grams per day. We refer you to the following guidance document: Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Additional Regulatory Comment:

We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-voll.pdf>)).

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

Additional Discussion

The Agency asked the Sponsor whether, given the similarity of this product to EMBEDA, there will be some naltrexone exposure. The Sponsor stated that they do not expect patients to experience exposure to naltrexone.

The Agency stated that reports of patients experiencing withdrawal after taking EMBEDA have been received, and informed the Sponsor that based on the experience thus far with EMBEDA, prospective data on the possibility of inducing withdrawal when taking ALO-02 will likely be required. The Sponsor noted that based on its safety monitoring programs, they believe that the withdrawal seen with EMBEDA is related to tampering or misuse, such as chewing or crushing. The Agency stated that not all cases may be classified as resulting from manipulation, and reiterated that the Sponsor should look into the issue of withdrawal as they go forward with product development.

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/s/

DIANA L WALKER
11/19/2010