CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022272Orig1s027

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	NDA 22272/S-027
Product Name:	OxyContin
PMR/PMC Description:	2923-1: Postmarket Adverse Event and Medication Error Reporting To assess the serious risks of respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors associated with the use of OxyContin in opioid-tolerant pediatric patients aged 11-17, and to assess the serious risks of respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors associated with the use of the product in children who are either younger than the approved age range or who do not meet the labeled criteria for opioid tolerance, provide reports of all postmarket adverse events occurring in children aged 17 and younger related to respiratory depression, accidental injury, overdose, misuse, accidental exposure, and all medication errors, regardless of outcome. After three years of submitting reports, submit a comprehensive analysis of these adverse event and medication errors reports, and provide an explanation of how you have addressed them.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	08/2015
	Interim Report Submission:	12/2015
	Interim Report Submission:	12/2016
	Interim Report Submission:	12/2017
	Interim Report Submission:	12/2018
	Final Report Submission:	04/2019

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

OxyContin has been marketed for nearly 20 years.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

OxyContin has been studied in opioid-tolerant pediatric patients, mostly in the 11-17 year old age range. Additional safety data is needed in younger patients and those who are not opioid tolerant.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☒ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☒ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Expedited reporting of adverse events related to respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Expedited pharmacovigilance reporting

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

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/s/

DIANA L WALKER
08/13/2015

SHARON H HERTZ
08/13/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	NDA 22272/S-027
Product Name:	OxyContin

PMR/PMC Description:

2923-2: Drug utilization

Conduct a nationally representative drug utilization study of sufficient detail to characterize use of OxyContin in children aged 17 years and younger. The data from this study will provide a denominator for the risks assessed in PMR #2923-1and any future safety studies and clinical trials used to assess those risks. The following analyses should be conducted with the data collected:

1) Total number of prescriptions dispensed across all settings of care
   a. stratify by age group (0-1, 2-5, 6-10, 11-17), indication, setting of care, and prescriber specialty, and geographic location
   b. provide characteristics of dose dispensed (mean, median, range)

2) Total number of unique patients receiving dispensed prescriptions across all settings of care

   a. stratify by age group (0-1, 2-5, 6-10, 11-17), indication, setting of care, and prescriber specialty
      i. provide unique incident users every quarter-year
   b. patient demographics of users of the product
   c. clinical characteristics of users of the product (including what percentage of patients are opioid tolerant at the time they get the OxyContin prescription)

3) Duration of therapy (include definitions of allowable gaps in drug therapy in calculating duration of therapy)

   a. total and stratified by indication
   b. exploration of possible 'intermittent' use
   c. percentage of patients switching from immediate-release opioids to OxyContin
   d. percentage of patients switching from other extended-release opioids to OxyContin
   e. dose adjustments over time

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	10/2015
	Interim Report Submission:	01/2016
	Interim Report Submission:	12/2016
	Interim Report Submission:	12/2017

Final Report Submission: 12/2108

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☒ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

OxyContin has been marketed for nearly 20 years.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

OxyContin has been studied in opioid-tolerant pediatric patients, mostly in the 11-17 year old age range. Additional safety data is needed in younger patients and those who are not opioid tolerant.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Various data sources will be accessed to define the extent of OxyContin utilization in the pediatric population.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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Continuation of Question 4

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☐ Other (provide explanation)

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☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

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/s/

DIANA L WALKER
08/13/2015

SHARON H HERTZ
08/13/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Review

From:	Amy M. Taylor, MD, MHS Medical Officer Division of Pediatric and Maternal Health
Through:	Linda L. Lewis, MD Acting Deputy Director Division of Pediatric and Maternal Health
NDA Number:	22272/S-027
Sponsor:	Purdue Pharma
Drug:	OxyContin® (oxycodone hydrochloride)
Dosage form and route of administration:	extended-release tablets, oral
Indication:	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Consult request:	The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) requests DPMH's input on the proposed labeling changes for OxyContin®.

Background

OxyContin was original approved on April 5, 2010 for adults. On November 4, 1998 a Written Request (WR) was issued for pharmacokinetic and pharmacodynamic studies of immediate release and controlled-release oxycodone. On December 31, 2001, a new WR was issued which added safety and efficacy studies in opioid naïve and opioid tolerant patients. On May 13, 2009, A new WR was issued which changed the safety and efficacy study of opioid tolerant patients to an open-label, safety and PK study. This WR was amended on November 18, 2010 and November 14, 2011. The studies requested in the final amended WR were:

Study 1: Pharmacokinetic study of an age-appropriate formulation of oxycodone in opioid-naïve patients from birth up to < 4 years of age.

Study 2: Efficacy, safety, and pharmacokinetic study of an age-appropriate formulation of immediate-release (IR) oxycodone in opioid-naïve patients from 5 years up to ≤ 16 years of age.

Study 3: Open-label, safety and pharmacokinetic study of an oxycodone extended-release tablet in opioid-tolerant patients from 6 years to ≤ 16 years of age with moderate to severe pain requiring around-the-clock opioid therapy for an extended period of time.

Reviewer comment: The study conducted by the sponsor of opioid tolerant patients aged 6 to 16 years included very few patients less than 11 years. Currently, the Division is considering approval only in patients 11 years and older.

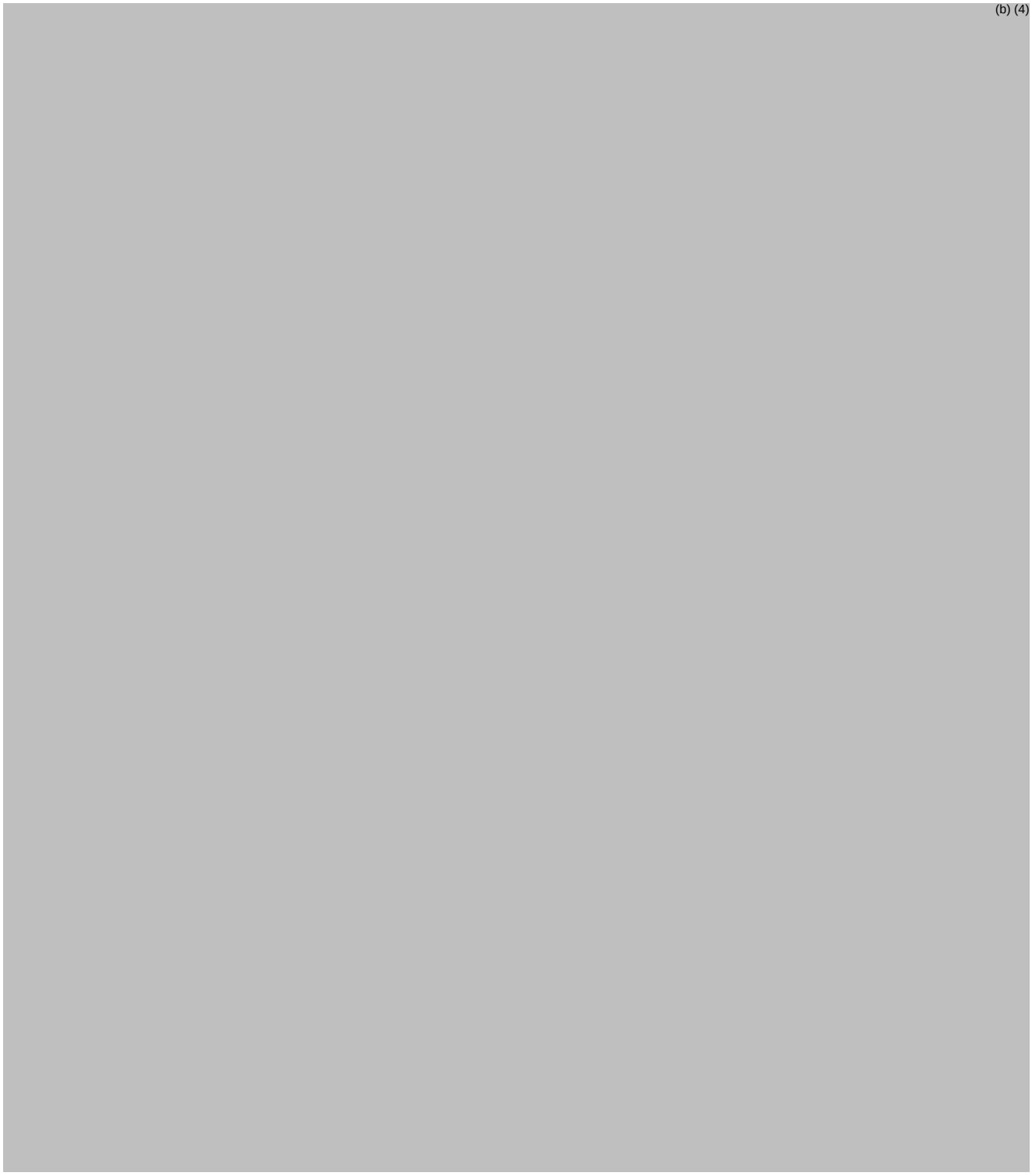
Sponsor's proposed pediatric specific labeling with DPMH comments and edits
Highlights
Use in Specific Populations

(b) (4)

(b) (4)

(b) (4)

(b) (4)



(b) (4)

Reviewer comment: Labeling will continue to be negotiated with the sponsor and as a result the final labeling may be different.

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/s/

AMY M TAYLOR
06/09/2015

LINDA L LEWIS
06/11/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 27, 2015
To:	Sharon Hertz, MD Acting Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Koung Lee, RPh, MSHS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name, Dosage Form (established name):	OXYCONTIN (oxycodone hydrochloride extended-release tablets)
Route:	for oral use
Application Type/Number:	NDA 022272/S-027
Applicant:	Purdue Pharma L.P.

1 INTRODUCTION

On December 8, 2014, Purdue Pharma L.P. submitted for the Agency's review a Prior Approval Supplement (S-027) to New Drug Application (NDA) 022272 for OXYCONTIN (oxycodone hydrochloride extended-release tablets). This labeling supplement provides proposed revisions to the Prescribing Information to include pediatric dosing, adverse reactions, and clinical study data.

OXYCONTIN (oxycodone hydrochloride extended-release tablets) was originally approved on April 5, 2010 and is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on May 20, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for OXYCONTIN (oxycodone hydrochloride extended-release tablets).

2 MATERIAL REVIEWED

- Draft OXYCONTIN (oxycodone hydrochloride extended-release tablets) MG received on December 8, 2014, and received by DMPP and OPDP on May 20, 2015.
- Draft OXYCONTIN (oxycodone hydrochloride extended-release tablets) Prescribing Information (PI) received on December 8, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 20, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
05/27/2015

KOUNG U LEE
05/27/2015

BARBARA A FULLER
05/27/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **May 21, 2015**

To: **Diana Walker, Ph.D., RHPM**

Sharon Hertz, MD, Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: **Koung Lee, Regulatory Review Officer,**
Office of Prescription Drug Promotion (OPDP)

Through: **Samuel M. Skariah, Team Leader -** OPDP

cc: **Olga Salis, Senior Regulatory Project Manager** - OPDP

Subject: **NDA 22272/S-027 OXYCONTIN Professional Labeling**

As requested in the DAAAP's consult dated April 29, 2015, OPDP has reviewed the Oxycontin prescribing information. As described in DAAAP's consult request, this labeling supplement adds pediatric labeling revisions in response to a pediatric written request.

OPDP has reviewed the proposed substantially complete version of the prescribing information emailed by DAAAP on May 15, 2015. OPDP's comments are included in the attached document below.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at 240-402-8686 or by email, Koung.Lee@fda.hhs.gov.

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/s/

KOUNG U LEE
05/21/2015

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: April 29, 2015

TO: Lisa Basham, Regulatory Project Manager
Javier Muniz, M.D., Medical Officer
John Feeney, M.D., Team Leader
Division of Analgesia, Anesthesia, and Addiction Products (**DAAAP**)

FROM John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations (**OSI**)

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation, OSI

SUBJECT: Evaluation of Clinical Inspections

APPLICATIONS: NDA 22272 S-027

APPLICANT: Purdue Pharma, LP

DRUG: Oxycodone Hydrochloride (OxyContin®) Extended-Release Tablet

NME: No

INDICATION: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (no new OxyContin® indication for use proposed in this NDA supplement)

THERAPEUTIC CLASSIFICATION: Priority (Pediatric Written Request)

CONSULTATION REQUEST DATE: January 26, 2015

INSPECTION SUMMARY GOAL DATE: May 1, 2015

REGULATORY ACTION GOAL DATE: June 8, 2015

PDUFA DUE DATE: June 8, 2015

I. BACKGROUND

In NDA 22272 S-027, Purdue Pharma, LP (**Purdue**) seeks to update the OxyContin® label to reflect the findings of three pediatric studies recently completed in response to FDA's 2011 Pediatric Written Request (**PWR**). Purdue proposes no new proposed indication for use; OxyContin® is currently approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Purdue requests priority review (granted) in seeking six months of pediatric exclusivity (b) (4).

According to PWRs 1 and 2, Studies OXP1005 and OXP3003 were conducted in hospitalized opioid-naive subjects. According to PWR 3, Study OTR3001 was conducted in opioid-tolerant subjects (hospitalized or out-patients) selected to assure ethnic diversity: 2034 patients were pre-screened worldwide (nine countries), of whom 155 were enrolled and treated (United Kingdom, Greece, Guatemala, Hungary, Israel, New Zealand, Spain, and United States). Two oxycodone formulations were used in the three studies, reformulated OxyContin and immediate-release oral solution.

The three pediatric studies were audited at good clinical practice (**GCP**) inspections of three clinical investigator (**CI**) sites selected for large site subject enrollment. Four specific study-sites were audited in support of this NDA review; two studies were audited at inspection of one site (Studies OXP3003 and OXP1005 at Site 0033A), and two sites were inspected in auditing one study (Sites 1360A and 1863A in Study OTR3001). The three audited studies are described briefly below, with emphasis on study features relevant to the inspectional observations.

Study OTR3001

An Open-label, Multicenter Study of the Safety of Twice Daily Oxycodone Hydrochloride Controlled-Release Tablets in Opioid Experienced Children from Ages 6 to 16 Years Old, Inclusive, with Moderate to Severe Malignant and/or Nonmalignant Pain Requiring Opioid Analgesics

This Phase 3, open-label, single-arm study was conducted between February 2011 and July 2014 at 101 CI sites worldwide in 173 opioid-tolerant subjects, of whom 155 were treated and 122 completed the study.

The primary study objective was to characterize the safety of oxycodone controlled-release (**CR**) tablets in opioid-tolerant pediatric subjects (6-16 years of age) with moderate to severe (malignant or non-malignant) pain requiring opioid therapy. The study consisted of open-label treatment for up to four weeks, as either out-patient or in-patient.

Subjects and Treatment

The study treatment consisted of oral oxycodone CR every 12 hours (tablet strengths of 10, 15, 20, 30, or 40 mg) for a total daily dose of 20-240 mg in subjects meeting the following eligibility criteria:

- Opioid-tolerant subjects of age 6-16 years expected to require on-going around-the-clock opioid treatment equivalent to 20-240 mg of oxycodone daily for at least two weeks for the management of moderate to severe malignant or nonmalignant pain
- Had tolerated opioid therapy for at least five consecutive days prior to study entry using 20-240 mg daily of oxycodone (or equivalent) for at least 48 hours
- Subjects excluded for any contraindication to opioid use; eligible opioid-tolerant post-operative subjects not dosed with oxycodone CR until at least five days after surgery

Study Endpoints

- Efficacy assessment consisted of pain scores, Functional Disability Inventory (**FDI**), Parent/Caregiver-assessed Global Impression of Change (**PGIC**), and supplemental opioid analgesic use.
- In assessing pain and pain relief, subjects of age 6-12 years completed the Faces Pain Scale-Revised (**FPS-R**), and subjects of age12-16 years completed the visual analogue scale (**VAS**).

- Safety assessment consisted of adverse event (**AE**) monitoring, physical examination, vital signs, body weight, pulse oximetry (**SpO2**), clinical laboratory testing, and somnolence evaluation using University of Michigan Sedation Scale (**UMSS**).
- Study data (efficacy and safety) were summarized by age group, assessor status (self, parent, or caregiver), and/or assessment time (in relation to initiation of study treatment) using descriptive statistics, with 95-percent confidence intervals as applicable.

Sponsor-Reported Outcome

- AEs were as expected for opioid treatment (most commonly vomiting, nausea, and headache), with headache as the most frequently reported treatment-related AE leading to study discontinuation.
- Most of the serious AEs (**SAEs**) and four deaths were considered to be unrelated to study treatment. Clinical evaluations (including vital signs and laboratory testing) revealed no apparent safety concerns.
- Treatment with oxycodone CR provided sustained pain control in subjects 6-16 years of age. The magnitude of pain relief appeared to be greater for older patients (12-16 years of age).
- The use of supplemental opioid medication tended to be more prevalent for the younger age group (78%) relative to the older age group (73%).
- Both age groups: The most frequently used supplemental opioid medications were hydrocodone, oxycodone, hydromorphone, and morphine (as expected, consistent with clinical experience). There were no significant changes in respiratory rate, hemoglobin oxygen saturation, or somnolence.

Study OXP3003

A Multi-Center, Double-Blind, Randomized, Dose-Ranging Study in Pediatric Patients 5 to ≤ 16 Years of Age, Receiving Morphine As Standard Supplemental Pain Medication, to Evaluate the Pharmacokinetics, Safety and Efficacy of Oxy Pediatric Liquid (1 mg/ml) versus Placebo in the Treatment of Acute Moderate to Severe Pain

This Phase 3, double-blind, randomized, placebo-controlled, dose-ranging study was conducted between January 2003 and April 2004 at 30 CI sites (United States, Canada, England, Finland, and the Netherlands) in 74 subjects, of whom 68 received randomized treatment and 54 completed the study.

The primary study objectives were to: (1) characterize the pharmacokinetics (**PK**) of Oxy Pediatric Liquid® (1 mg/mL) using population PK (after initial and repeated dosing) in subjects 5-16 years of age; and (2) evaluate the safety of Oxy Pediatric Liquid® in this subject age group. Purdue notes that this study was terminated early in March 2004 for administrative reasons unrelated to safety or efficacy of the investigational medication.

Subject Selection

- In-patient subjects of age 5-16 years, opioid naive at study entry (or pre-operatively), with current or expected moderate to severe pain requiring opioid analgesia for at least two days
- Per CI judgment, subjects were excluded for: (1) any contraindication to the use of opioids, (2) significant hepatic or renal dysfunction, or (3) for any reason, including the inability to receive morphine as needed to achieve adequate analgesia.

Treatment Groups and Regimen

Subjects were stratified into two age groups, 5-11 and 12-16 years, and randomized in 2/3/3 ratio, respectively, to receive placebo or Oxy Pediatric Liquid (0.1 or 0.2 mg/kg) every six hours for 18-24 hours (4-5 doses). All subjects could receive patient-controlled analgesia (**PCA**) or oral morphine sulfate as supplemental pain medication.

Study Endpoints

- Pain intensity scores (numerical rating of 0-10): (1) baseline, (2) after first dose, (3) 0.5, 1.0, 2.0, and 3.0 hours post-dose immediately before and one hour after each dose, and (4) end of study
  - o Pain intensity scores were recorded whenever a nurse assisted with PCA-morphine: (1) number of doses and total amount of morphine in a one-hour period, and (2) route of administration
  - o Use of all other supplemental pain medications (non-PCA opioid and acetaminophen) were documented to include: (1) exact clock time and amount of each dose, and (2) route of administration
- Analysis using the Jonckheere-Terpstra (**JT**) test and descriptive statistics: (1) mean and maximum pain scores, (2) mean post-dose pain scores at one and six hours, and (3) supplemental pain medication use
- PK evaluation: Up to eight blood samples were collected over the study to determine the concentrations of oxycodone, oxycodone metabolites, and morphine (at least one hour between sampling).
- Safety assessment: AE monitoring clinical laboratory testing, vital signs, physical examination, hemoglobin oxygen saturation, and somnolence

Sponsor-Reported Outcome

- The most common treatment-related AEs observed in > 5% of all subjects were: nausea, vomiting, pyrexia, headache, and pruritus. A total of 36 out of 65 patients (55%) in the safety population had treatment-related AEs, most of which were mild in severity (three severe events).
- There were no deaths in the study. Five SAEs were seen in four subjects (all recovered): pericardial effusion, cholangitis, pneumonia, and pyrexia. There were no unexpected safety findings.
- Statistically significant lower pain scores were observed for the active treatment (both dose groups) relative to placebo, after either single or multiple dosing. The most commonly used supplemental opioid medications were fentanyl (91%) and morphine (95%).
- For the active treatment relative to placebo, less use of: (1) supplemental PCA-morphine, statistically significant; (2) supplemental acetaminophen, statistically significant; and (3) supplemental opioid medications overall, statistically not significant, and overall use pattern similar to that of PCA-morphine

Study OXP1005

A Multi-Center, Inpatient, Open-Label, Dose-Ranging Study to Characterize the Pharmacokinetics and Safety of an Oral Liquid Formulation of Oxycodone in Patients from Birth to 4 Years of Age, Who Require Opioid Analgesia

This Phase 1, open-label, dose-escalation study was conducted between January 2003 and April 2004 at 26 CI sites (United States, Canada, England, Scotland, Finland, and the Netherlands) in 66 subjects, of whom 60 received treatment and 50 completed the study.

The primary study objectives were to: (1) characterize the PK of Oxy Pediatric Liquid® (1 mg/mL) using population PK (after initial and repeated dosing) in subjects from birth to four years of age; and (2) evaluate the safety of Oxy Pediatric Liquid® in this subject age group. Purdue notes that this study was terminated early in March 2004 for administrative reasons unrelated to safety or efficacy of the investigational medication.

Subject Selection

- In-patient subjects from birth to four years of age, opioid naive at study entry (or pre-operatively), with current or expected moderate to severe pain requiring opioid analgesia for at least two days
- Subjects under one year of age had to have a gestational age $\geq$ 36 weeks and body weight $\geq$ 2.5 kg. Subjects were excluded for any contraindication to the use of opioids.

- Per CI judgment, subjects were excluded for: (1) any contraindication to the use of opioids, (2) significant hepatic or renal dysfunction, impaired respiratory reserve, or cardiovascular instability, or (3) for any reason, inability to receive morphine as needed to achieve adequate analgesia.

Treatment Groups and Regimen

Subjects were stratified into three age groups: (1) birth to 30 days, (2) 31 days to six months, and (3) seven months to four years. Oxy Pediatric Liquid® was given every six hours up to seven doses in escalating doses: (1) 0.05 mg/kg, (2) 0.10 mg/kg, and (3) 0.2 mg/kg. For inadequate pain relief, supplemental pain medication was given: morphine (preferred, oral or PCA-morphine), acetaminophen, or a non-steroidal anti-inflammatory drug (**NSAID**).

Study Endpoints

- Pain intensity scores (numerical rating of 0-10): (1) baseline, (2) after first dose, (3) 0.5, 1.0, 2.0, and 3.0 hours post-dose immediately before and one hour after each dose, and (4) end of study
  - Pain intensity scores were recorded whenever a nurse assisted with PCA-morphine: (1) number of doses and total amount of morphine in a one-hour period, and (2) route of administration
  - Use of other supplemental pain medication (oral morphine, acetaminophen, NSAID): (1) exact clock time and amount of each dose, and (2) route of administration
- Analysis using the JT test and descriptive statistics: (1) mean and maximum pain scores, (2) mean post-dose pain scores at one and six hours, and (3) supplemental pain medication use
- PK evaluation: Blood samples (nine if > 5 kg, four if $\leq$ 5 kg) were collected over the study to determine the concentrations of oxycodone and its metabolites (at least one hour between sampling).
- Safety assessment: AE monitoring clinical laboratory testing, vital signs, physical examination, hemoglobin oxygen saturation, and somnolence

Sponsor-Reported Outcome

- The most common treatment-related AEs observed in $\geq$ 5% of all subjects were: vomiting (8%), pyrexia (8%), decreased hemoglobin (7%), tachycardia (5%), and hypertension (5%).
- A total of 30 out of 60 patients (50%) in the safety population had treatment-related AEs: (1) seven (58%), < 30 days; (2) 11 (46%), 31 days to six months; and (3) 12 (50%), seven months to four years.
- There were no deaths in the study. SAEs were seen in two subjects (both recovered): obstructive apnea, loss of appetite, abdominal pain, and pyrexia.
- Three subjects were discontinued form the study due to AEs (all recovered): sedation, vomiting, and obstructive sleep apnea. There were no unexpected safety findings.
- The most commonly used supplemental opioid medications were fentanyl (80%) and morphine (68%). Use of PCA-morphine increased with increasing doses of Oxy Pediatric Liquid®.
- Total supplemental opioid medication use was higher for higher dose groups (in particular, 0.2 mg/kg) than for the lowest dose group (0.05 mg/kg).
- After initial dosing (first six hours), more subjects in the 0.1 mg/kg group used acetaminophen than in the other dose groups, but less overall than in the 0.05 mg/kg and 0.2 mg/kg groups.
- Across all dosing intervals, mean pain intensity scores were low for all dose groups. Pain intensity scores were higher for higher dose groups.

II. INSPECTIONS

The following four study-sites were identified for GCP audit based on relative importance of the study to the NDA and on large site (subject) enrollment. No special concerns were identified for protocol violations, AEs, or CI conflicts of interest. The outcomes of the four inspections are shown below.

Clinical Investigator		Study, Site, Enrollment	Inspection Outcome
1	Peter Szmuk, M.D. University of Texas-Southwestern 1935 Medical District Drive Dallas, Texas	Study OTR3001 Site 1863A 15 subjects	April 7-17, 2015 Pending, preliminary VAI
2	Andrea L. D. Orsey, M.D. Connecticut Children's Medical Center 282 Washington Street Hartford, Connecticut	Study OTR3001 Site 1360A 17 subjects	March 11-24, 2015 Pending, preliminary VAI
3	Gregory B. Hammer, M.D. Stanford Medical Center 300 Pasteur Drive, H3580 Stanford, California	Study OXP3003 Site 0033A 26 subjects Study OXP1005 Site 0033A 26 subjects	April 9-17, 2015 Pending, preliminary VAI

Pending = preliminary results based on communication with field investigator
VAI = voluntary action indicated (minor GCP violations)

1. Peter Szmuk, M.D.

a. What was inspected:

- Records review: local institutional review board (**IRB**) oversight and sponsor monitoring, clinical investigator (**CI**) financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, study blind, treatment compliance, and data verification
- Data verification: major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study OTR3001, Site 1863A: 15 subjects were screened, 15 were enrolled, and 11 completed the study. Records were reviewed in detail for 10 subjects. The following deficiencies were observed.

Cited on Form FDA 483

- For Subject 9001, the initially adequate IC was not supplemented by a re-signed copy of the IC document (**ICD**) upon availability of a modified version of the ICD.

- Subjects were screened in consultation with the sponsor. For each subject, selected medical information redacted for subject identity was sent to the sponsor for eligibility adjudication, and if accepted by the sponsor, the screening assessment for that subject was formally completed and the subject was enrolled into the study. This screening practice was cited for not consulting the IRB about sharing selected subject information with the sponsor (as third party, not subject or CI), even if the information shared had been adequately redacted to protect subject confidentiality.

  OSI Comments: This pre-screening practice is consistent with the 100% screening/enrollment rate observed at this CI site. The citation was about not obtaining IRB review and approval, and not necessarily about screening practice inconsistent with GCP.

- Subject eligibility worksheets (including laboratory worksheets) were not signed by the study staff at subject screening (signed later) for 10 of the 15 enrolled subjects, and CI review and confirmation of subject eligibility was consistently not documented on the worksheets (or elsewhere) for 11 of the 15 enrolled subjects.
- A serious adverse event (**SAE**) of sustained migraine in Subject 9006 was not reported to the sponsor until six days later (protocol specifies SAE reporting within 24 hours)
- Febrile neutropenia with back pain requiring hospitalization was not immediately recognized as serious and not reported to sponsor as SAE until one month later (protocol specifies evaluating all AEs as potential SAEs, and SAE reporting within 24 hours).
- Laboratory tests were not always obtained according to the study protocol: (1) no urinalysis for Subjects 9011, 9012, 9013, and 9014; (2) no electrolytes for Subject 9009.
- Findings of the screening physical examination for Subject 9015 were not adequately documented, including no documentation of Tanner Stage of Development Score and inadequate documentation for the examination of the eyes, abdomen, and lymph nodes.
- Insomnia and lip numbness reported by Subject 9003 at Visit 2 were not reported to the sponsor, and not documented in the study records as AEs.
- Vincristine chemotherapy administered to Subject 9010 during this study of Oxy Pediatric Liquid® for pain control was not reported as a concomitant medication.

Uncited Discussion Items

- Paper source records not optimally organized to facilitate tracking and/or review
- Not completing diary review when the subject is still available, to clarify any discrepancies
- Old diary not collected consistently before issuing a new one
- Isolated instances of minor inconsistent pain scoring
- Vital signs not taken at exact times as specified in the protocol
- Calcium levels not corrected for albumin

All deficiency observations (cited or verbal) appear minor, isolated, or otherwise unlikely to be significant. Many appear to reflect poor recordkeeping of otherwise adequate study conduct. Overall, the study conduct appears to be GCP-compliant, including for IC, AE reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. All audited endpoint data were verifiable among source records, case report forms (**CRFs**), and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

Note: The findings noted above are based on preliminary communication with the field investigator.

2. Andrea L. D. Orsey, M.D.

a. What was inspected:

- Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, study blind, treatment compliance, and data verification
- Data verification: major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study OTR3001, Site 1360A: 21 subjects were screened, 17 were enrolled, and 16 completed the study. Records were reviewed for all subjects, including detailed review for all enrolled subjects. The following deficiencies were observed.

Cited on Form FDA 483

- Dose calculations were not shown on dose calculation worksheets. All doses were verifiable and accurate as specified in the study protocol.
- Subjects 0075014 and 0075020: OxyContin® was used as supplemental medication, prior to availability of protocol version that permits use of OxyContin® as supplemental medication.
- Subject 0075014: The original informed consent (**IC**) document was not available for review (copy available for review).

Uncited Discussion Items

- Incomplete drug accountability log (bottle numbers not listed)
- Study notes about IC written by staff who did not participate in obtaining IC
- AEs documented by staff not documented to be qualified to evaluate AEs

Overall, the study records showed that all deficiency observations (cited or verbal) reflected poor recordkeeping of otherwise adequate study conduct, including adequate informed consent, AE reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

Note: The findings noted above are based on preliminary communication with the field investigator.

3. Gregory B. Hammer, M.D.

a. What was inspected:

- Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, study blind, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study OXP3003, Site 0033A

27 subjects were screened, 26 were enrolled, and 24 completed the study. Records were reviewed for all enrolled subjects, including a detailed review for 10 subjects completing study. The following deficiencies were observed.

Cited on Form FDA 483

- Subject 26006 with a body weight of 14.5 kg was enrolled without special documentation, in violation of the protocol which specifies a body weight ≥ 15 kg unless exempted.
- The temperature log for the freezer did not include temperature records for the first nine of the total 15 months of PK blood sample storage.

  OSI Comments: The inadequate freezer temperature log may indicate more than inadequate recordkeeping and may include inadequate PK blood sample handling and storage for much of the study period (nine of 15 months). A comparison of the PK data from this CI site with those from other CI sites may be helpful in evaluating the reliability of the PK data from this CI site.

- The parent of Subject 26023 was consented using an IC document (**ICD**) intended for a different study (Study OXP1005). Assent was not documented for the seven year old Subject 26004.

Uncited Discussion Items

- A few days before the FDA inspection, the sponsor notified the CI that some subjects who received propofol had been enrolled without the sponsor's written concurrence (as specified in protocol) to deviate from the protocol-specified exclusion criterion of CYP3A4 inhibitor receipt within 24 hours of anticipated enrollment. The sponsor apparently identified this subject eligibility concern at post-study data review. The sponsor did not identify which subjects and did not seek an explanatory reply from the CI. The CI disagreed that the sponsor's concurrence was necessary, and documented (as part of study records) that propofol was not on the list of protocol-prohibited drugs and is not commonly considered a CYP3A4 inhibitor.

  OSI Comments: This sponsor-identified concern does not appear to be a true protocol deviation, as discussed by the CI at inspection and documented as part of study records. Suggestive evidence that propofol competitively inhibits CYP3A4 has been reported in the literature, but the clinical significance of the implicated extent and mechanism of inhibition remains unclear. Propofol is not (yet) generally considered a CYP3A4 inhibitor and is currently not labeled as a CYP3A4 inhibitor. The sponsor's reporting practices appear to reflect due-diligence, to report any unclear concern about subject eligibility in the NDA, and to accordingly notify the CI.

- For some subjects, IC was obtained using an incorrect (outdated) version of the correct ICD for Study OXP3003.
- Errors on study records were occasionally (isolated instances) corrected using WiteOut, making it difficult to track, interpret, or otherwise audit the correction.

All deficiency observations (cited or verbal) appear minor, isolated, or otherwise unlikely to be significant. Many appear to reflect poor recordkeeping (including disorganized documentation) of otherwise adequate study conduct. Overall, the study conduct appears to be GCP-compliant, including for IC, AE reporting, and drug accountability. IRB oversight was adequate and sponsor monitoring appeared acceptable. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

Study OXP1005, Site 0033A

29 subjects were screened, 26 were enrolled, and 23 completed the study. Records were reviewed for all enrolled subjects, including detailed review for 10 subjects completing study. The following deficiencies were observed.

Cited on Form FDA 483

- Subject 34015 born at 29 weeks (gestation) was enrolled at age of six months. The protocol specifies gestational age ≥ 36 weeks for a child under one year of age.
- The temperature log for the freezer in which (PK) blood samples were stored did not include the first nine of the total 15 months of storage.

  OSI Comment: This CI site participated in both Studies OXP3003 and OXP1005. The comment about the same observation noted above for Study OXP3003 applies also to Study OXP1005.

Uncited Discussion Items

- For Subject 34001, the following concomitant medications were not reported in the NDA, apparently due to the sponsor's mishandling of two pages of the CRFs: acetaminophen (fever), calcium chloride and potassium chloride (electrolyte balance), fentanyl (pain), milrinone (post-operative blood pressure control), and sodium bicarbonate (acidosis prophylaxis).
- A few days before FDA inspection, the sponsor notified the CI that some subjects (not identified) had been enrolled without the sponsor's written concurrence for potentially exclusionary conditions. The CI disagreed that the sponsor's concurrence was necessary, and documented (as part of study records) that the following conditions (sponsor's concerns) were clearly NOT protocol deviations as applicable to each subject at time of enrollment:
  - Clinically significant hepatic dysfunction, as evidenced by bilirubin ≥ 18mg/dl, aspartate aminotransferase (**AST**) ≥100 IU/L, and/or alanine aminotransferase (**ALT**) ≥ 80 IU/L

    CI response: Transiently elevated bilirubin and/or liver enzymes, typical following cardiac surgery, do not indicate clinically significant hepatic dysfunction in the subjects enrolled.
  - Receipt of propofol within 24 hours of expected enrollment, in deviation of the study protocol which specifies the receipt of a CYP3A4 inhibitor as an exclusion criterion.

    CI response: Propofol was not on the list of protocol-prohibited drugs, and is not commonly thought of as a CYP3A4 inhibitor.
  - Insertion of a Blalock-Taussig (**BT**) shunt within 30 days of expected enrollment, in deviation of the study protocol which specifies subject exclusion for insertion of any intracardiac or intracranial experimental device within 30 days of expected enrollment.
  - ***CI response:*** The BT shunt is a small synthetic tube inserted during the Blalock surgical procedure. Neither the Blalock procedure nor the BT shunt is experimental.

  OSI Comments: These sponsor-identified concerns do not appear to be true protocol deviations, as discussed by the CI at inspection and documented as part of study records.

  - *Section 9.3.2 of the study protocol specifies the following exclusion criterion: "Clinically significant hepatic dysfunction as evidenced by: bilirubin ≥ 18 mg/dL, and/or AST ≥ 100 IU/L and ALT ≥ 80 IU/L."*
    - *The wording of this criterion is unclear in that it specifies clinically significant hepatic dysfunction as evidenced by the laboratory values, and not necessarily the laboratory values themselves. Elevated levels of bilirubin, AST, and ALT are not specific for hepatic dysfunction, particularly transiently elevated levels.*

- *The CI appears to have attributed the laboratory values to non-exclusionary conditions within the overall clinical setting of infants ranging in age from the neonate to four years of age with complex medical conditions and pain "severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate," and not to clinically significant hepatic dysfunction.*
- *In responding to the sponsor's notification, the CI's refers to transiently elevated laboratory values and cardiac surgery. Neither the sponsor's notification nor the CI's response are specific for subjects, clinical setting, or timing of the laboratory values.*
- *In the NDA listing for protocol deviations assigned by the sponsor to this CI site (not reported by this CI site to the sponsor), the sponsor listed the following 11 subjects as having exclusionary "bilirubin and/or AST and ALT": Subjects 002, 005, 006, 010, 012, 015, 017, 018, 019, 023, and 024.*
- *Communication is on-going with the sponsor and the CI to obtain more specific information about this particular sponsor concern, and to further evaluate the GCP implications of this inspectional observation, if any, for the CI, the sponsor, and/or the NDA.*

o *Suggestive evidence that propofol competitively inhibits CYP3A4 has been reported in the literature, but the clinical significance of the implicated extent and mechanism of inhibition remains unclear. Propofol is not (yet) generally considered a CYP3A4 inhibitor and is currently not labeled as a CYP3A4 inhibitor.*

o *The BT shunt mimics patent ductus arteriosus and may relieve severe neonatal/congenital cyanosis as a temporizing measure, by shunting blood from the systemic to the pulmonary circulation. The BT shunt is currently used during the Blalock procedure as part of clinically accepted standard of care.*

The sponsor's reporting (of enrolling subjects with) these subject conditions as (deviations to) protocol-specified subject exclusion criteria appears to reflect the sponsor's due-diligence, to report any/all unclear concerns about subject eligibility in the NDA, and to accordingly notify the CI in preparation for the FDA inspection.

- Errors on study records were occasionally (isolated instances) corrected using WiteOut, making it difficult to track, interpret, or otherwise audit the correction.

All deficiency observations (cited or verbal) appear minor, isolated, or otherwise unlikely to be significant. Many appear to reflect poor recordkeeping (including disorganized documentation) of otherwise adequate study conduct. Overall, the study conduct appears to be GCP-compliant, including for IC, AE reporting, and drug accountability. IRB oversight was adequate and sponsor monitoring appeared acceptable. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

Note: The findings noted above are based on preliminary communication with the field investigator.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

Three pediatric studies (OTR3001, OXP3003, and OXP1005) were conducted by Purdue in fulfillment of FDA's 2011 PWR. In this NDA 22272 S-027, Purdue seeks to update the OxyContin® label to reflect the pediatric study findings, without proposing a new OxyContin® indication for use. As PWR studies, all three studies were audited in support of this priority NDA review.

Four study-sites were audited at GCP inspections of three CI sites selected for large site (subject) enrollment. Two studies were audited at one CI site (Studies OXP3003 and OXP1005 at Site 0033A), and two CI sites were inspected in auditing one study (Sites 1360A and 1863A for Study OTR3001). In the three audited studies combined, 283 subjects were treated at 157 study-sites, of whom case records for 84 subjects (30% of 283) were reviewed at audit of four study-sites (2.5% of 157), including detailed review for 47 subjects (17% of 283).

For all four study-sites audited, the observed GCP deficiencies consisted of those cited on Form FDA 483 and additional uncited discussion items. Whether cited or verbally discussed, most were minor, and all were isolated and/or otherwise unlikely to be significant. Study conduct appeared adequate at all three CI sites inspected, as did IRB oversight and sponsor monitoring of CI's study conduct. All audited study data were verifiable among source records, CRFs, and NDA data listings. The data from the four audited study-sites appear reliable as reported in the NDA.

Note: For all three CI sites inspected, the establishment inspection report (**EIR**) has not been received from the field office and the final inspection outcome remains pending. Upon receipt and review of each EIR, an addendum to this clinical inspection summary (**CIS**) will be forwarded to the review division if the final inspection outcome differs from the preliminary outcome reported in this CIS. Otherwise, OSI's inspection close-out correspondence with each CI copied to the review division will indicate EIR review completion without new significant findings.

{See appended electronic signature page}

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/s/

JONG HOON LEE
04/29/2015

JANICE K POHLMAN
04/30/2015

KASSA AYALEW
04/30/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 022272 BLA#	NDA Supplement #: S- 027 BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Animal Rule Confirmatory Study (SE7) ☒ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☒ Pediatric
Proprietary Name: OXYCONTIN Established/Proper Name: oxycodone hydrochloride extended-release Dosage Form: tablets Strengths: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg		
Applicant: Purdue Pharma L.P. Agent for Applicant (if applicable):		
Date of Application: 12/10/14 Date of Receipt: 12/10/14 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 6/10/15	Action Goal Date (if different): 6/8/15	
Filing Date: 2/8/15	Date of Filing Meeting: 1/14/15	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s):		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☐ Priority ☒ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 029038	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☐	☒		Priority review due date reflected in DARRTS (6 months) rather than 180 days for PWR response.
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☒		

1 page has been withheld as (b)(4) immediately following this page

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☐	☐	☒	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☒	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☐	☒		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☒	☐		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☐	☒	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	Already member of ER/LA opioid class REMS.
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	Pending
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☐	☐	☒	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	PMHS for PeRC and Pediatric Exclusivity Meetings
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/14/15

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Basham	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	John Feeney		Y
Division Director/Deputy	Sharon Hertz		Y
Office Director/Deputy	Curtis Rosebraugh/Mary Parks		N
Clinical	Reviewer:	Javier Muniz	Y
	TL:	John Feeney	Y
~~Social Scientist Review (*for OTC products*)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~OTC Labeling Review (*for OTC products*)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~Clinical Microbiology (*for antimicrobial products*)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
Clinical Pharmacology	Reviewer:	Srikanth Nallani	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:		
	TL:	Freda Cooner	Y

~~Nonclinical (Pharmacology/Toxicology)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~Statistics (carcinogenicity)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~Immunogenicity (assay/assay validation)~~ ~~*(for protein/peptide products only)*~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~Product Quality (CMC)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~Biopharmaceutics~~	~~Reviewer~~	———	———
	~~TL:~~	———	———
~~Quality Microbiology~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~CMC Labeling Review~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~Facility Review/Inspection~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~OSE/DMEPA (proprietary name, carton/container labels))~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~OSE/DRISK (REMS)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~OC/OSI/DSC/PMSB (REMS)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———

~~Bioresearch Monitoring (OSI)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~Controlled Substance Staff (CSS)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~Other reviewers/disciplines~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
Other attendees	Kevin Krudys		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
~~**CONTROLLED SUBSTANCE STAFF**~~ ~~• Abuse Liability/Potential~~ ~~**Comments**:~~	~~☐ Not Applicable~~ ~~☐ FILE~~ ~~☐ REFUSE TO FILE~~ ~~☐ Review issues for 74-day letter~~
~~**CLINICAL MICROBIOLOGY**~~ ~~**Comments**:~~	~~☐ Not Applicable~~ ~~☐ FILE~~ ~~☐ REFUSE TO FILE~~ ~~☐ Review issues for 74-day letter~~
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
~~**NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)**~~ ~~**Comments**:~~	☐ ~~Not Applicable~~ ☐ ~~FILE~~ ☐ ~~REFUSE TO FILE~~ ☐ ~~Review issues for 74-day letter~~

~~**IMMUNOGENICITY** (protein/peptide products only)~~ ~~**Comments**:~~	☐ ~~Not Applicable~~ ☐ ~~FILE~~ ☐ ~~REFUSE TO FILE~~ ☐ ~~Review issues for 74-day letter~~
~~**PRODUCT QUALITY (CMC)**~~ ~~**Comments**:~~	☐ ~~Not Applicable~~ ☐ ~~FILE~~ ☐ ~~REFUSE TO FILE~~ ☐ ~~Review issues for 74-day letter~~
~~**New Molecular Entity (NDAs only)**~~ • ~~Is the product an NME?~~	☐ ~~YES~~ ☐ ~~NO~~
~~**Environmental Assessment**~~ • ~~Categorical exclusion for environmental assessment (EA) requested?~~ ~~**If no**, was a complete EA submitted?~~ ~~**If EA submitted**, consulted to EA officer (OPS)?~~ ~~**Comments**:~~	☐ ~~YES~~ ☐ ~~NO~~ ☐ ~~YES~~ ☐ ~~NO~~ ☐ ~~YES~~ ☐ ~~NO~~
~~**Quality Microbiology**~~ • ~~Was the Microbiology Team consulted for validation of sterilization?~~ ~~**Comments**:~~	☐ ~~Not Applicable~~ ☐ ~~YES~~ ☐ ~~NO~~

Facility Inspection • Establishment(s) ready for inspection? • Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	_____
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• ~~Is a comprehensive and readily located list of all clinical sites included or referenced in the application?~~	☐ ~~YES~~ ☐ ~~NO~~
• ~~Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?~~	☐ ~~YES~~ ☐ ~~NO~~

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Sharon Hertz

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): 3/12/14

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☒	If priority review:

	• notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74 N/A
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter N/A
☐	Update the PDUFA V DARRTS page (for applications in the Program) N/A
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

LISA E BASHAM
02/04/2015

PARINDA JANI
02/04/2015