CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-272

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Sheetal Agarwal, Ph.D.**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: **04/29/09**	IND No.: 29,038 SDN.:687	Related NDA Nos. 20-553 (SDN 351), 22-272 (SDN 60)	Submission Date: 04/16/2010	
NAME OF DRUG: Oxycontin	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	
NAME OF THE SPONSOR: Purdue Pharma				

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW):*
☒ PHASE IV RELATED		DDI study protocol employing Oxycontin 10 mg (ER) with 200 mg bid ketoconazole

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ . See comments below
☐Medical ☐Chemist ☐Pharm-Tox	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ . See submission cover letter
☐Micro ☐Pharmacometrics ☐Others		☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)		[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

The submitted study protocol OTR1023 for a drug-drug interaction study employing Oxycontin and ketoconazole as a Phase 4 post marketing commitment for approval of Oxycontin is acceptable from a Clinical Pharmacology perspective. No further action is indicated at this time.

BACKGROUND:

This review pertains to the final drug-drug interaction protocol # OTR1023 submitted to the Agency on 04/16/2010. This DDI study is designed to fulfill the Post Marketing Commitment outlined in the Agency's letter dated September 2, 2009 in reference to the approval of supplement # S-060 that was submitted on December 13, 2007. A draft of protocol OTR1023 was submitted on September 11, 2009 (NDA 20533/SDN 340) and reviewed by Dr. Sayed Al Habet (see review in DARRTS dated 09/30/00).

The following Clinical Pharmacology related comment was conveyed to the sponsor at the time of initial review of the draft protocol:

"Although, a drug interaction is expected between ketoconazole and oxycontin, the magnitude of resulting increase in oxycodone exposure is unknown. In order to protect the healthy volunteers participating in this study from the opioid side effects resulting from a potential interaction, we advice that you provide naltrexone blockade to the participating volunteers. We recommend that naltrexone at a dose of 50 mg be administered during the study at the following time points in relation to oxycontin dosing: 12 hours pre-dose, 12 hours, 24 and 36 hours post-dose."

It should be noted that the final protocol does not contain any major amendments to the study design reviewed by Dr. Al Habet which would materially affect the clinical pharmacology assessments.

Purdue did not include naltrexone blockade in their final protocol but provided an acceptable rationale to the Agency via email on April 27, 2010 to the project manager, Ms. Lisa Basham. Dosing in this study was planned to be started on April 28, 2010. Attachment 1 is an extract of Purdue's rationale, while attachment 2 contains the final protocol synopsis.

ATTACHMENT 1: RATIONALE PROVIDED BY PURDUE PHARMA FOR NOT INCLUDING NALTREXONE BLOCKADE IN THE DRUG-DRUG INTERACTION STUDY

[April 26, 2010] FDA Comment on proposed study OTR1023:

"Although, a drug interaction is expected between ketoconazole and OxyContin, the magnitude of resulting increase in oxycodone exposure is unknown. In order to protect the healthy volunteers participating in this study from the opioid side effects resulting from a potential interaction, we advise that you provide naltrexone blockade to the participating volunteers. We recommend that naltrexone at a dose of 50 mg be administered during the study at the following time points in relation to OxyContin dosing: 12 hours pre-dose, 12 hours, 24 and 36 hours post-dose."

[April 27, 2010] PPLP Response:

OTR1023 is a drug-drug interaction study in which 10 mg OxyContin (oxycodone hydrochloride controlled-release [CR]) tablets will be administered to subjects with and without concomitant ketoconazole administration to assess the impact of this potent azole CYP3A4 inhibitor on oxycodone pharmacokinetics. We considered inclusion of naltrexone blockade in protocol OTR1023 but elected not to include it based upon the considerations summarized below.

In a published report, Hagelberg et al (Eur J Clin Pharmacol. 2009 Mar;65(3):263-71 attached in email) examined the interaction between oxycodone and the potent azole CYP3A4 inhibitor voriconazole in 12 healthy subjects. Oxycodone was administered as single 10 mg immediate-release (IR) capsule (Oxynorm) doses. In the presence of voriconazole, mean peak oxycodone (Cmax) increased from 18.1 to 30.5 ng/mL. This corresponds to a 1.7-fold increase in Cmax on average (range 1.4 – 2.4x). Mean total oxycodone exposure (AUCinf) increased from 102 to 363 ng.h/mL. This corresponds to a 3.6-fold increase in AUCinf on average (range 2.7 – 5.6x).

Adverse events were described by Hagelberg et al as follows:

> "All subjects completed the study. Eight of the 12 subjects experienced adverse events on day 3. Adverse events were headache (n=5), nausea (n=3), vomiting (n=1), dizziness (n=2), extreme fatigue (n=1) and itch (n=1). Three subjects received paracetamol (1,000 mg) for headache 12 h after oxycodone dosing, and one received tropisetrone 2 mg iv for nausea 5 h after dosing. All cases of nausea or vomiting were reported during the voriconazole phase. Number of reports of headache did not differ between voriconazole and control phases."

PPLP concluded that although the increase in oxycodone exposure following co-administration with voriconazole was associated with more AEs, there were no significant safety concerns raised by the observed AEs following the administration of 10 mg IR oxycodone under CYP3A4 inhibition, beyond those applicable whenever an opioid is administered under experimental conditions.

We hypothesize that since ketoconazole and voriconazole are both potent azole CYP3A4 inhibitors, they will have similar effects on oxycodone pharmacokinetics. We further hypothesize that the magnitudes of the increases in Cmax and AUC noted by Hagelberg et al are the best available predictions of the magnitude of effect likely to be characterized in OTR1023. These hypotheses are supported by observed

effects of these CYP3A4 inhibitors on sirolimus exposure in healthy subjects. Voriconazole produced increases in sirolimus exposure of 7-fold and 11-fold for Cmax and AUC, respectively (Vfend Package Insert attaached in email). Ketoconazole produced increases in sirolimus exposure of 4.4-fold and 11-fold for Cmax and AUC, respectively (Floren et al. Clin Pharm Ther (1999) 65, 159–159 attached in email).

In OTR1023, oxycodone is administered in CR form as a 10 mg OxyContin dose. In the absence of CYP3A4 inhibition, this dose is expected to produce a mean Cmax of approximately 9.4 ng/mL and an AUCinf of approximately 108 ng.h/mL. It should be noted that this expected peak exposure (Cmax) is approximately 50% of that expected for a 10 mg IR oxycodone dose, while total oxycodone exposure (AUCinf) is similar for CR and IR formulations. Thus, use of a CR dosage form (OxyContin) provides a 2-fold reduction in expected Cmax, with and without CYP3A4 inhibition. Since the intensity of opioid AEs is typically related to Cmax, this margin is relevant to the safety and tolerability of oxycodone dosing in OTR1023.

In a prior PPLP single-dose crossover study OC93-0801 [submitted to IND 29,038 on October 7, 1994, Serial Number 188]), both 20 and 40 mg OxyContin doses and 20 mg IR oxycodone doses were administered to healthy subjects (n=24) without naltrexone blockade. Mean oxycodone Cmax and AUC following 40 mg OxyContin administration were 39.3 ng/mL (range 23.9 – 87.5) and 421 ng.h/mL (range 244 – 921), respectively. The OC93-0801 study report states that most AEs were mild or moderate in intensity and that there were no discontinuations due to adverse experiences. It further states that a dose-response was observed between 20 mg (n=22) and 40 mg (n=24) OxyContin doses, with 97 and 197 AEs reported, respectively, for the two treatments.

The prior safety and tolerability experience in OC93-0801 with 40 mg OxyContin administered without naltrexone represents the safety and tolerability that is expected in OTR1023 assuming ketoconazole were to produce approximately a 4-fold increase in Cmax (vs. the 1.7-fold increase noted with voriconazole) and AUC (vs. the 3.6-fold increase noted with voriconazole).

Administration of 50 mg naltrexone blockade is believed by our investigators to be associated with tolerability issues, reflected by reported AEs, and can even lead to subject discontinuations in rare instances.

While exclusion of naltrexone is advantageous in permitting a ‘cleaner’ assessment of the effect of ketoconazole on oxycodone pharmacokinetics, this consideration only applies if the conclusion is reached that naltrexone blockade is not required to minimize the opioid agonist effects anticipated in this study. Based upon the considerations summarized above, we concluded that naltrexone blockade is not required in this study. Therefore co-administration of naltrexone was not included in protocol OTR1023.

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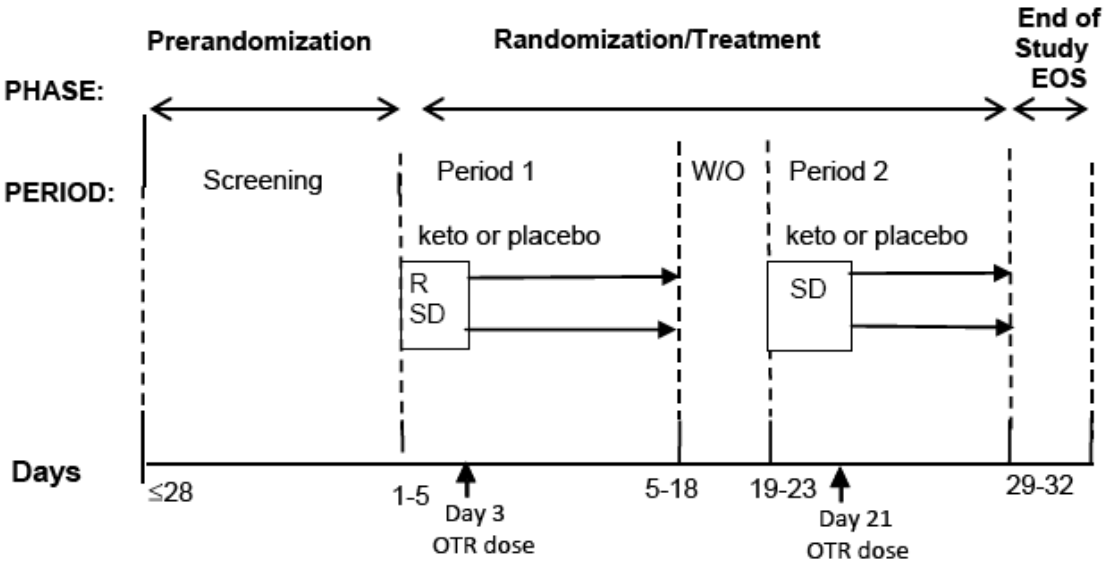
ATTACHMENT 2: FINAL PROTOCOL SYNOPSIS

Name of Company: Purdue Pharma L.P.		
Name of Finished Product: Oxycodone Tamper Resistant Tablets	**Name of Active Ingredient:** Oxycodone hydrochloride	
Full Title of the Study: A Single-Center, Randomized, Open-label, Crossover Study to Assess the Pharmacokinetics of Oxycodone and Its Metabolites During Co-Administration of OTR and Ketoconazole, a CYP3A4 Inhibitor, in Healthy Subjects.		
Investigator(s)/Center(s): Thomas Murtaugh, M.D. / (b) (4)		
Objectives: 1. To assess the pharmacokinetics of oxycodone and its metabolites (noroxycodone, oxymorphone, and noroxymorphone) in the presence and absence of ketoconazole. 2. Safety evaluation of concomitant administration of oxycodone and ketoconazole in healthy subjects.		
Study Design (Methodology): A single center, randomized, open-label, 2-treatment, 2-period crossover study examining OTR (10 mg) with ketoconazole tablet (200 mg, q12h) administration vs. OTR (10 mg) with placebo tablet (q12h) administration.		
Study Design Graphic:  R = Randomization (Period 1 only) SD = Study drug administration according to RAS W/O = 14 day washout starting from last dose of ketoconazole or placebo (day 5 to 18) keto = ketoconazole 200 mg tablet b.i.d		
Number of Subjects: A sufficient number of subjects (up to 30) will be randomized to complete approximately 20.		
Indication and Criteria for Inclusion/Exclusion: Healthy male and female subjects aged 18 to 50 years, inclusive, with no clinically significant medical history, who are deemed suitable to take part in this clinical study by the Investigator.		

Treatments, Doses, and Modes of Administration:

OTR 10 mg tablet, Ketoconazole 200 mg oral tablet, and placebo tablet (administered q12h). All treatments will be administered orally with 8 oz. (240 mL) water.

Treatments will be administered in an open-label fashion. Subjects will be dosed in an upright position, and will remain upright for 4 hours afterwards. Treatment administrations will be separated by a 14 day washout period.

Concomitant Medication:

Naloxone HCl challenge test (administered on Day -1, Period 1 check-in).

The use of concomitant medications during this trial is discouraged, unless necessary to treat adverse events or unless approved on a case-by-case basis prior to randomization (e.g., hormonal contraceptives). The use of any concomitant medications should be approved by the sponsor in advance, in writing, when possible.

Duration of Treatment and Study Duration:

Screening and baseline period will be up to 28 days prior to administration of study medication (in this case either ketoconazole or placebo administration).

In Period 1 subjects will be administered ketoconazole or placebo in a randomized fashion on days 1-4. On day 3, the subjects will receive a single oral dose of OTR. This will be followed by a washout period lasting 14 days (days 5 to 18). In Period 2 subjects will be administered ketoconazole or placebo in a crossover fashion on days 19-22. On day 21, the subjects will receive a single oral dose of OTR.

Subjects will be confined to the study facility during Periods 1 and 2.

Subjects will have end of study procedures (EOS) performed 7-10 days after last dose of ketoconazole or placebo or upon discontinuing from the study.

The total duration of the study is approximately 60 days.

Treatment Schedule:

Pre-Randomization Phase:

Screening: Subjects will be screened within 28 days of Period 1 check-in. Drug and alcohol screens, physical exam, 12- lead ECG, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate and oral temperature), SpO_2, medical and medication history, clinical laboratory testing and inclusion/exclusion criteria will be evaluated. Subjects are not allowed to consume apple juice, orange juice or grapefruit juice during the treatment period.

Randomization Phase:

On Day -1, Period 1 Check-in only, subjects will receive a Naloxone HCl challenge test. Vital signs and SpO_2 will be measured prior to and following the Naloxone HCl challenge test.

For each Period, subjects will check into the unit the day prior to dosing. At check-In, subjects will have chemistry (fasting for at least 4 hours), hematology and urinalysis tests performed. Urine pregnancy test (for women of childbearing potential), vital signs, SpO_2, and alcohol and urine drug screens will be performed.

Period 1 (Days 1 to 5)

Ketoconazole (200 mg) or placebo administration will begin on Day 1 and will be given twice a day at approximately 8 AM and approximately 8 PM through Day 4. Throughout Period 1, vital signs, SpO_2 and HDYF? will be performed as per study flow chart.

On Day 3 at approximately 8 AM, OTR 10 mg tablet will be administered following an overnight fast. Subjects will continue fasting until 4 hours post-dose. Blood samples for PK analysis will be drawn at pre-dose, and at pre-determined time points through 48 hours post-dose.

On Day 4, blood samples for the determination of ketoconazole levels will be drawn at approximately 8 AM, prior to ketoconazole or placebo administration.

On Day 5, vital signs, SpO_2 and HDYF? will be performed as per study flow chart and the subject will then be discharged with instructions to return on Day 18.

Wash-out Period (Days 5 to 18)

During this period, the investigator will ensure that provisions are made for the subjects to contact the study site in case of adverse events during the washout period. Such reporting of adverse events and the investigator's response will be accurately documented, and the Purdue Pharma L.P. study monitor will be notified immediately.

Baseline 2 (Day 18)

On Day 18, subjects will be confined to the study unit. Vital sign evaluation, safety laboratory tests (serum chemistries including liver function tests, hematology, and urinalysis); urine pregnancy testing (if female), urine drug screening, and alcohol testing will be performed.

Period 2 (Days 19 to 23)

On Day 19, the subjects will be crossed over to the opposite treatment schedule. Subjects who were given ketoconazole during Period 1 will be given placebo in Period 2, and those given placebo in Period 1 will be given ketoconazole during Period 2.

Ketoconazole (200 mg) or placebo administration will begin on Day 19 and will be given twice a day at approximately 8 AM and approximately 8 PM through Day 22. Throughout Period 2, vital signs, SpO_2 and HDYF? will be performed as per study flow chart.

On Day 21 at approximately 8 AM, OTR 10 mg tablet will be administered following an overnight fast. Subjects will continue fasting until 4 hours post-dose. Blood samples for PK analysis will be drawn at pre-dose, and at pre-determined time points through 48 hours post-dose.

On Day 22, blood samples for the determination of ketoconazole levels will be drawn at approximately 8 AM, prior to OTR and ketoconazole administration.

On Day 23, vital signs, SpO_2 and HDYF? will be performed as per study flow chart and the subject will then be discharged with instructions to return for End of Study procedures.

Adverse events (AEs) and concomitant medications will be recorded throughout the study.

Note: for clarity, OTR is assigned as the study drug for determination of adverse event causality. Ketoconazole and placebo are considered distinct from study drug in this determination.

End of Study Visit: Subjects will return to the unit 7 to 10 days after receiving their last dose of ketoconazole or placebo or upon discontinuation from the study for their end of study (EOS) procedures. EOS procedures will include a physical exam, 12- lead ECG, vital signs, SpO_2, and laboratory tests.

Criteria and Methods for Evaluation:

Analysis Populations:

The enrolled population is the group of subjects who provide informed consent.

The randomized safety population is the group of subjects who are randomized, receive study drug, and have at least one post dose safety assessment.

The full analysis population for PK metrics will be the group of subjects who are randomized, receive study drug, and have at least one valid PK metric for that treatment. Subjects experiencing emesis within 12 hours after dosing may be excluded from PK analysis. Subjects and profiles/metrics excluded from the analysis set will be documented in the Statistical Analysis Plan.

Oxycodone Concentration Measurements: Blood samples for determining the concentrations of oxycodone and its metabolites (noroxycodone, oxymorphone, and noroxymorphone) in plasma, will be obtained for each subject at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 28, 32, 36, and 48 hours post study drug administration during each of the study Periods.

Bioanalytical methods:

Plasma oxycodone and its metabolites (noroxycodone, oxymorphone, and noroxymorphone) concentrations will be quantified using a validated liquid chromatography tandem mass spectrometric method.

Safety Assessments: Safety will be assessed using recorded adverse events, clinical laboratory test results, vital signs, SpO_2, physical examinations, and electrocardiograms (ECG).

Statistical Methods:

Pharmacokinetic Metrics: Plasma concentrations of oxycodone and its metabolites (noroxycodone, oxymorphone, and noroxymorphone) will be analyzed to determine the following pharmacokinetic metrics: AUCt, AUCinf, Cmax, tmax, tlag, $t1/2_Z$, and LambdaZ. Descriptive statistics will be tabulated by treatment, as applicable, for all pharmacokinetic metrics.

Safety Analysis:

All safety data (AEs, clinical laboratory results, vital signs, SpO_2 and ECGs) will be listed for subjects in the enrolled and safety populations. Results of clinical laboratory evaluations that lie outside the normal range will be flagged on the listings as high or low.

Subjects' AEs will be categorized into preferred terms and associated system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be defined as AEs that start after, or increase in severity after, a dose of study drug. Treatment-emergent AEs that occur during the washout period up to the point of dosing the next study drug will be assigned to the previous treatment dosed. Treatment-emergent AEs will be summarized by presenting the incidence of AEs for each treatment group by the MedDRA preferred term, nested within System Organ Class for the safety population.

Laboratory, vital signs and SpO_2 will be summarized by treatment and time-point for the safety population.

Sample Size Rationale:

No formal sample-size calculations were performed. A sufficient number of subjects (up to 30) will be randomized to complete approximately 20 subjects.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22272	PMR/PMC-1	PURDUE PHARMA INC	OXYCONTIN

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

/s/

SHEETAL S AGARWAL
04/30/2010

SURESH DODDAPANENI
04/30/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Sheetal Agarwal, Ph.D.**	**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**

DATE: 03/15/10	IND No.: Serial No.:	NDA No. 22-272 SDN: 50	Submission Date: 02/05/10	

NAME OF DRUG Oxycontin®	PRIORITY CONSIDERATION	Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Purdue Pharma

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☒ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
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☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW):* Labeling changes related to drug-drug interactions following published reports
☐ PHASE IV RELATED		

REVIEW ACTION

☒ NAI (No action indicated)	☐ Oral communication with Name: [ ]	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox ☐ Micro ☐ Pharmacometrics ☐ Others (Check as appropriate and attach e-mail)		☐ See submission cover letter
		☐ OTHER *(SPECIFY BELOW)*: [ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

BACKGROUND:

This is a Class I resubmission of NDA 22272 pertaining to reformulated oxycontin formulation. The original NDA submission and the complete response submission were previously reviewed by Dr. Sayed Al Habet (see reviews dated 5/23/2008 and 9/1/2009 for complete details regarding clinical pharmacology aspects of this product). Pertinent Clinical Pharmacology relevant labeling language was negotiated with the sponsor in the last previous cycle. However, subsequent to this, Drug-Drug interaction data between coadministration of oxycodone and rifampin from the following publication came to light; **Nieminen TH et al. Rifampin greatly reduces the plasma concentrations of intravenous and oral oxycodone. Anesthesiology. 2009;110:1371-1378.**

This review captures the labeling changes related to this interaction and other minor appropriate modifications suggested by this reviewer. Attachment contains the proposed labeling changes (additions indicated by underlined text and deletions indicated by strikethrough text).

Following is a discussion of the rifampin and oxycodone interaction study. In this four-session, paired, crossover study, twelve volunteers were given 600 mg oral rifampin or placebo once daily for 7 days.

Oxycodone was given on day 6. In the first part of the study, 0.1 mg/kg oxycodone hydrochloride was given intravenously. In the second part of the study, 15 mg oxycodone hydrochloride was given orally. Concentrations of oxycodone and its metabolites noroxycodone, oxymorphone, and noroxymorphone were determined for 48 h. Psychomotor effects were characterized for 12 h by several visual analog scales. Analgesic effects were characterized by measuring the heat pain threshold and cold pain sensitivity.

Plasma profiles and PK parameters are listed in Figure 1 and Tables 1 and 2 extracted from the publication.

Rifampin decreased the AUC of intravenous oxycodone by 53%, increased the mean plasma Cl by 2.2-fold, and decreased its t½ from 3.7 to 2.4 h. Rifampin decreased the mean AUC and Cmax of oral oxycodone by 86% and 63%, respectively. The mean oral bioavailability of oxycodone was decreased from 69% to 21% by rifampin. Rifampin increased the Cmax of noroxycodone by 2.7-fold after intravenous oxycodone and by 2.0-fold after oral oxycodone compared with the control values. The corresponding metabolite–to–parent drug AUC ratios (AUCm/AUCp) were increased 2.4-fold and 7.6-fold, respectively. Rifampin reduced the AUC of oxymorphone to approximately 5–10% of the corresponding control value after intravenous and oral administration of oxycodone. Intravenous oxycodone produced no detectable oxymorphone concentrations in two subjects after placebo and in eight subjects after rifampin. After rifampin and oral oxycodone, five of the subjects had every measured oxymorphone concentration below the lower limit of quantification. Rifampin increased the Cmax of noroxymorphone more than twofold in both the intravenous and the oral part of the study. The corresponding metabolite– to–parent drug AUC ratios increased 2.4-fold after intravenous and 9.6-fold after oral oxycodone. In addition, pharmacologic effects of oral oxycodone were attenuated.

Figure 1: Plasma concentrations (mean - SD) of oxycodone and its metabolites in 12 volunteers following intravenous administration of 0.1 mg/kg and oral administration of 15 mg oxycodone hydrochloride after placebo or rifampin. The volunteers were given in randomized order either 600 mg oral rifampin or placebo once daily at 8 PM for 7 days. Oxycodone was given on day 6 at 8 AM, 12 h after the fifth dose of rifampin or placebo. Two more doses of rifampin or placebo were given on days 6 and 7. The oxycodone concentrations are shown both on arithmetic and on a semilogarithmic plot (*inset*).

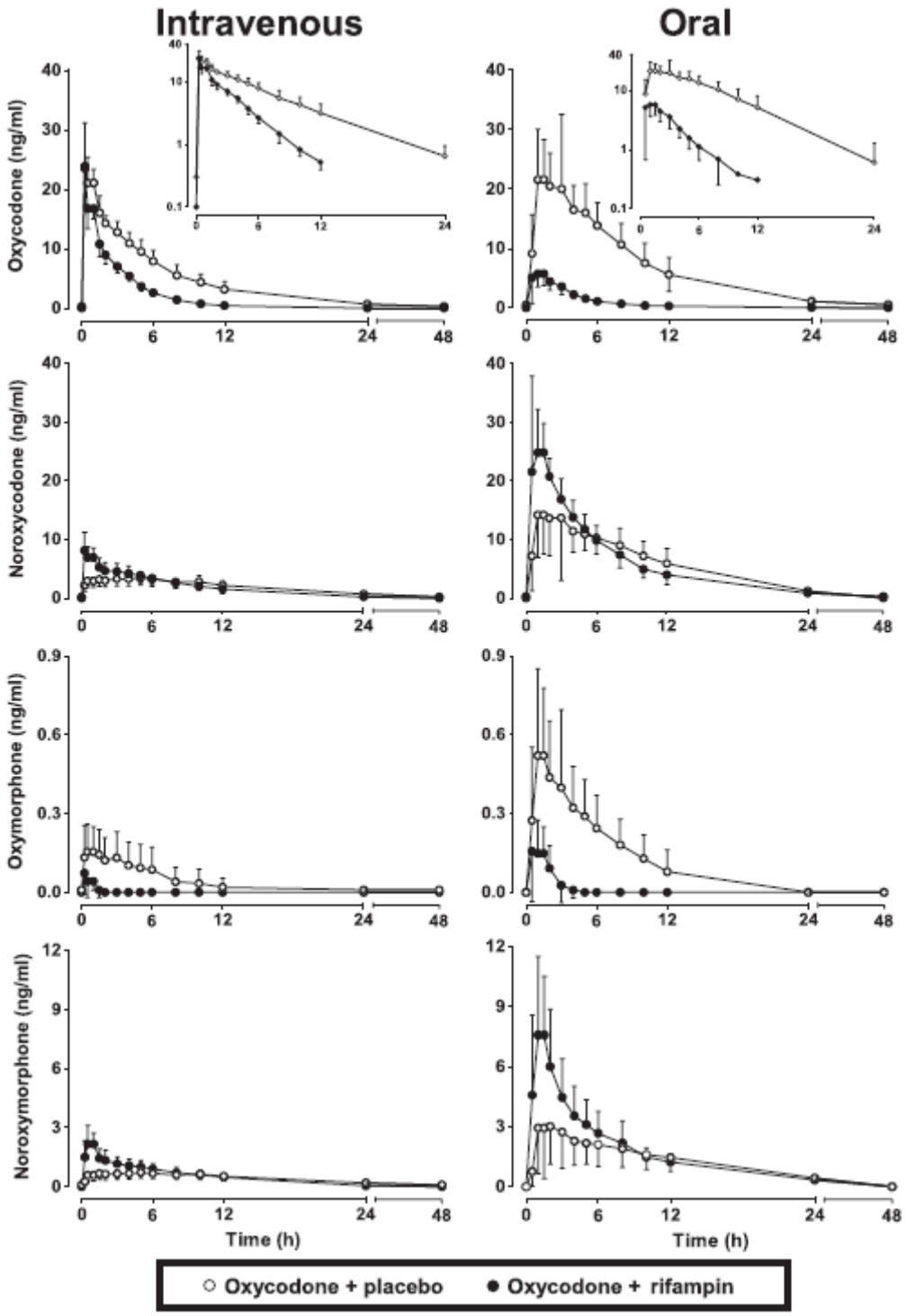

Table 1: Pharmacokinetic Parameters of Oxycodone and Its Metabolites in Volunteers after Intravenous Administration of Oxycodone Following Placebo (Control) or Oral Rifampin

Parameter	Control Phase	Rifampin Phase
Oxycodone		
Cl, l/min	0.90 ± 0.16	1.91 ± 0.29*
V_{ss}, l	307 ± 57	372 ± 68*
$AUC_{0-\infty}$, $\mu g \cdot min \cdot ml^{-1}$	7.3 ± 1.8	3.3 ± 0.5*
$t_{1/2}$, h	3.7 ± 0.9	2.4 ± 0.5*
Noroxycodone		
C_{max}, ng/ml	3.4 ± 1.2	8.4 ± 2.8*
$t_{1/2}$, h	6.7 ± 1.6	4.5 ± 0.6*
t_{max}, h	4.0 (0.5–8.0)	0.25 (0.25–1.5)*
$AUC_{0-\infty}$, $\mu g \cdot min \cdot ml^{-1}$	3.1 ± 1.2	3.1 ± 1.0
AUC_m/AUC_p	0.44 ± 0.18	0.94 ± 0.34*
Oxymorphone		
C_{max}, ng/ml	0.17 ± 0.12	0.07 ± 0.08*
t_{max}, h	0.5 (0.25–3.0)	0.25 (0.25–0.25)
$AUC_{0-\infty}$, $\mu g \cdot min \cdot ml^{-1}$	0.065 ± 0.068	0.003 ± 0.005*
AUC_m/AUC_p	0.01 ± 0.01	0.001 ± 0.001*
Noroxymorphone		
C_{max}, ng/ml	0.7 ± 0.3	2.2 ± 0.9*
t_{max}, h	5.0 (0.5–10.0)	0.5 (0.5–1.5)*
$t_{1/2}$, h	12.5 ± 5.6	6.8 ± 1.1*
$AUC_{0-\infty}$, $\mu g \cdot min \cdot ml^{-1}$	0.82 ± 0.33	0.98 ± 0.31
AUC_m/AUC_p	0.12 ± 0.06	0.32 ± 0.06*

Table 2: Pharmacokinetic Parameters of Oxycodone and Its Metabolites in Volunteers after Oral Administration of Oxycodone Following Placebo (Control) or Oral Rifampin

Parameter	Control Phase	Rifampin Phase
Oxycodone		
C_{max}, ng/ml	26.1 ± 11.0	8.3 ± 2.2*
t_{max}, h	1.5 (1.0–5.0)	1.0 (0.5–3.0)*
$AUC_{0-\infty}$, $\mu g \cdot min \cdot ml^{-1}$	10.7 ± 3.4	1.5 ± 0.6*
Cl/F, l/min	1.35 ± 0.36	10.13 ± 3.43*
V_z/F, l	477 ± 85	2,067 ± 511*
$t_{1/2}$, h	3.8 ± 0.9	2.3 ± 1.3*
F	0.69 ± 0.10	0.21 ± 0.07*
Noroxycodone		
C_{max}, ng/ml	17.7 ± 10.10	31.0 ± 8.3*
t_{max}, h	1.5 (1.0–5.0)	1.0 (0.5–2.0)*
$AUC_{0-\infty}$, $\mu g \cdot min \cdot ml^{-1}$	9.8 ± 3.4	9.3 ± 2.4
AUC_m/AUC_p	0.97 ± 0.39	6.88 ± 2.58*
$t_{1/2}$, h	5.6 ± 1.1	4.3 ± 0.7*
Oxymorphone		
C_{max}, ng/ml	0.61 ± 0.34	0.23 ± 0.16*
t_{max}, h	1.0 (0.5–5.0)	1.0 (0.5–2.0)
$AUC_{0-\infty}$, $\mu g \cdot min \cdot ml^{-1}$	0.24 ± 0.13	0.02 ± 0.02*
AUC_m/AUC_p	0.023 ± 0.010	0.015 ± 0.012
Noroxymorphone		
C_{max}, ng/ml	3.9 ± 2.5	8.6 ± 3.6*
t_{max}, h	1.5 (1.0–4.0)	1.0 (0.5–2.0)*
$AUC_{0-\infty}$, $\mu g \cdot min \cdot ml^{-1}$	2.39 ± 1.11	2.95 ± 1.08*
AUC_m/AUC_p	0.25 ± 0.14	2.19 ± 0.88*
$t_{1/2}$, h	7.8 ± 1.5	6.6 ± 1.0*

5 WARNINGS AND PRECAUTIONS

5.8 Cytochrome P450 3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of OxyContin, drugs that alter (b) (4) CYP3A4 activity may cause changes in (b) (4)-clearance of oxycodone which could lead to an increase or decrease in oxycodone plasma concentrations. The expected clinical results with CYP450 inhibitors would be increased or prolonged opioid effects. If co-administration with OxyContin is necessary, caution is advised when initiating therapy in patients, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved. The expected clinical results with CYP450 inducers would be decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of abstinence syndrome in a patient who had developed physical dependence to oxycodone. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved. *[see Drug Interactions (7.2) and Clinical Pharmacology (12)]*

7 DRUG INTERACTIONS

7.1 Neuromuscular Junction Blocking Agents

OxyContin may enhance the neuromuscular blocking action of true skeletal muscle relaxants (such as pancuronium) and produce an increased degree and/or duration of respiratory depression.

7.2 Agents Affecting Cytochrome P450 Isoenzymes

Inhibitors of CYP3A4:
Since the CYP3A4 isoenzyme plays a major role in the metabolism of OxyContin, drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A published study showed that the co-administration of the antifungal drug, voriconazole, increased oxycodone AUC and C_{max} by 3.6 and 1.7 fold, respectively. Although clinical studies have not been conducted with other CYP3A4 inhibitors, the expected clinical results would be increased or prolonged opioid effects. If co-administration with OxyContin is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP450 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved. *[see Clinical Pharmacology (12.3)]*

Inducers of CYP3A4:

(b) (4)

(b) (4)

CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of abstinence syndrome in a patient who had developed physical dependence to oxycodone. A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and Cmax by 86% and 63% respectively. If co-administration with PERCODAN is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYPP450 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

Inhibitors of CYP2D6:
Oxycodone is metabolized in part to oxymorphone via cytochrome CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not been shown to be of clinical significance during oxycodone treatment.

12.3 Pharmacokinetics

Drug-Drug Interactions

Oxycodone is extensively metabolized by multiple metabolic pathways. CYP3A4 is the major enzyme involved in noroxycodone formation followed by CYP2B6, CYP2C9/19 and CYP2D6. Drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. For example, a published study showed that the co-administration of the antifungal drug, voriconazole, increased oxycodone AUC and Cmax by 3.6 and 1.7 fold, respectively. Similarly, CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of abstinence syndrome in a patient who had developed physical dependence to oxycodone. For example, a published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and Cmax by 86% and 63% respectively.

Oxymorphone is a minor metabolite, its formation is catalyzed primarily by CYP2D6 and to a small extent by CYP2C19. The formation of oxymorphone may be blocked by a

variety of drugs (such as antipsychotics, beta blockers, antidepressants, etc.) that inhibit these enzymes. However, in a study involving ten subjects using quinidine, a known inhibitor of CYP2D6, the pharmacodynamic effects of oxycodone were unchanged. The genetic expression of CYP2D6 may have some influence in the pharmacokinetic properties of oxycodone.

The in vitro drug-drug interaction studies with noroxymorphone using human liver microsomes showed no significant inhibition of CYP2D6 and CYP3A4 activities which suggests that noroxymorphone may not alter the metabolism of other drugs that are metabolized by CYP2D6 and CYP3A4, and such blockade has not been shown to be of clinical significance with oxycodone. *[see Drug Interactions (7.2)]*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22272	ORIG-1	PURDUE PHARMA INC	OXYCONTIN

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

/s/

SHEETAL S AGARWAL
03/17/2010

SURESH DODDAPANENI
03/25/2010

FINAL
(September 1, 2009)
Clinical Pharmacology Review

NDA: 22-272 **Dates of Submission:** March 30, 2009 **(Re-submission)**
November 29, 2007 **(original submission)**

Generic Name	Oxycodone
Brand Name:	**Oxycontin®**
Formulation:	Extended Release Tablets
Strengths:	10, 15, 20, 30, 40, 60, and 80 mg
OCP Division	Division of Clinical Pharmacology II
OND Division	Division of Anesthesia, Analgesia, and Rheumatology Products
Route of Administration:	Oral
Indications:	• Management of moderate to severe pain when a continuous, around-the clock analgesic is needed for an extended period of time. • Not for use as a prn analgesic or in the immediate post-operative period (the first 12 to 24 hours following surgery).
Dosage and Administration:	-Q12h (individualized) -Use low initial doses in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications. –For patients already receiving opioids, use standard conversion ratio estimates.
Type of Submission:	Resubmission
Sponsor:	Purdue Pharma, Stamford, CT
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.

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1.0 Background

OxyContin® 10 mg, 20 mg, and 40 mg strengths were approved on December 12, 1995 (NDA 20-553). Subsequently, 15 mg, 30 mg, and 60 mg strengths were approved on September 18, 2006 and the 80 mg and 160 mg strengths were approved on January 6, 1977 and March 15, 2000, respectively. However, the sponsor discontinued marketing the 160 mg strength. As such, at this time Oxycontin 10, 15, 20, 30, 40, 60, and 80 mg strengths are currently approved and available for marketing.

Due to the concern of abuse liability with the current formulation, the sponsor reformulated the existing extended release formulation purportedly making it more resistant to physical and chemical manipulation. The sponsor is referring to this reformulated product as **OTR** (Oxycodone Tamper-Resistant) tablets. Therefore, this NDA is the subject of this reformulated oxyContin®.

This is a second cycle review for this NDA. In the original submission dated November 29, 2007, the sponsor was seeking the approval of five strengths: 10, 15, 20, 30, and 40 mg tablets (see **Appendix I and II** for clinical pharmacology original and addendum reviews dated April 7, 2008 and May 23, 2008, respectively). However, at that time, the sponsor proposed to continue marketing the 60 and 80 mg strengths in their original form (i.e., not reformulated OTR). In this case there will be two sets of formulations in the market: the first is for 10, 15, 20, 30, and 40 mg OTR formulation and the second set is for 60 and 80 mg non-OTR formulation.

The reason for the two sets of formulations is that the sponsor encountered some technical difficulties during the reformulation of the 60 mg and the 80 mg OTR tablets. The sponsor proposed that the approval of these strengths will be sought after reformulation efforts were successful. The trade name will remain OxyContin®.

The contents of this NDA was discussed at the May 5, 2008 Anesthetic and Life Support Drugs Advisory Committee Meeting (AC Meeting). In the complete response action letter dated October 3, 2008 the Agency listed several deficiencies that needed to be resolved before the NDA can be approved. These include, but not limited to the following:

- The sponsor should provide adequate *in vitro* studies to fully characterize the physical manipulation of the formulation and release characteristics.
- Based on DSI inspection of study # OTR 1005 the sponsor was advised to reanalyze the data excluding six subjects and/or reanalyze the plasma concentration and perform bioequivalence analysis to demonstrate bioequivalency.

Based on the advice received from the agency and at the AC meeting, the sponsor submitted data for the reformulated 60 mg and 80 mg strengths. From this data, the sponsor established bioequivalence of the 80 mg OTR strength with the original

formulation, OxyContin®. Also, dose-propotionality at 40, 60, and 80 mg strengths was demonstrated in this submission.

What Was Submitted?

Based on the above information, in the current resubmission dated March 30, 2009 the sponsor submitted the following studies/information:

Bioequivalence/Dose-propotionality Studies:

Study # OTR1008: This is a bioequivalence study comparing 80 mg single dose of the new formulation (OTR tablet) with the current to be marketed 80 mg OxyContin® tablet in 84 **fed** healthy subjects.

Study # OTR1009: This is a bioequivalence study comparing 80 mg single dose of the new formulation (OTR tablet) with the current to be marketed 80 mg OxyContin® tablet in 84 **fasted** healthy subjects.

Study # OTR1012: This is a dose proportionality study with 40 mg, 60 mg and 80 mg OTR tablets in 54 **fasted** healthy subjects.

Data Re-analayis:

Per the Agency's complete response letter dated October 3, 2008, the sponsor reanalyzed the data from the bioequivalence Study # OTR1005 of 40 mg strength after excluding six subjects that were included in the statistical analysis in the original NDA. This action was necessary to ensure accuracy of the bioequivalence data based on the DSI inspection report.

Effect of Alcohol on Oxycodone release:

To rule out the effect of alcohol on the release of oxycodone from the new OTR formulation, the sponsor submitted additional study specifically on the new 60 mg and 80 mg OTR tablets at alcohol concentration of 4%, 20%, and 40%. It should be noted that the sponsor submitted similar studies for all OTR lower strengths tablets in the original NDA. This study was necessary to also rule out of the potential of dose dumping at the high OTR tablet strengths.

2.0 Summary of Major Clinical Pharmacology Findings:

Bioequivalence Studies:

The 90% CI in both fed and fasted studies after 80 mg strength was within the 80% to 125% limits (**Table 2.1**). Overall, the 90% CI was also within 80% to 125% for 10 mg, 40 mg, and 80 mg strengths in fed and fasted conditions (**Table 2.2**).

Table 2.1 Statistical Summary of the Bioequivalence Data for 80 mg Strength in Fed and Fasted Subjects

Study	Dose	Condition	Cmax		AUCt	
			LS Mean Ratio	90% CI	LS Mean Ratio	90% CI
OTR1008	80 mg	Fed	110	(105.21, 114.47)	94.9	(92.90, 97.02)
OTR1009	80 mg	Fasted	103	(98.67, 106.66)	97.1	(94.41, 99.94)

Table 2.2 Statistical Summary of the Bioequivalence Data for 10 mg, 40 mg, and 80 mg Strengths in Fed and Fasted Subjects (Note: studies OTR1002-1005 were submitted in the original NDA).

Study	Dose	Condition	Cmax		AUCt	
			LS Mean Ratio	90% CI	LS Mean Ratio	90% CI
OTR1002	10 mg	Fed	105.0	[101.06, 108.51]	95.7	[93.85, 97.68]
OTR1003	10 mg	Fasted	102.0	[99.35, 105.42]	98.3	[95.20, 101.48]
OTR1004	40 mg	Fed	99.9	[95.40, 104.52]	92.6	[90.13, 95.13]
OTR1005	40 mg	Fasted	96.6	[92.80, 100.56]	95.5	[92.93, 98.18]
OTR1008	80 mg	Fed	110	[105.21, 114.47]	94.9	[92.90, 97.02]
OTR1009	80 mg	Fasted	103	[98.67, 106.66]	97.1	[94.41, 99.94]

It appears that from both studies the Cmax after 80 mg OTR formulation is slightly delayed and slightly higher than that after Oxycontin in fasted (**Figures 2.1)** and fed **(Figure 2.2**) conditions. The same observation was noted in the original NDA for other strengths. However, this should have minimal clinical significance.

Figure 2.1 Oxycodone Plasma Concentration-Time Profiles in <u>Fasted</u> Subjects (Study # OTR1009)

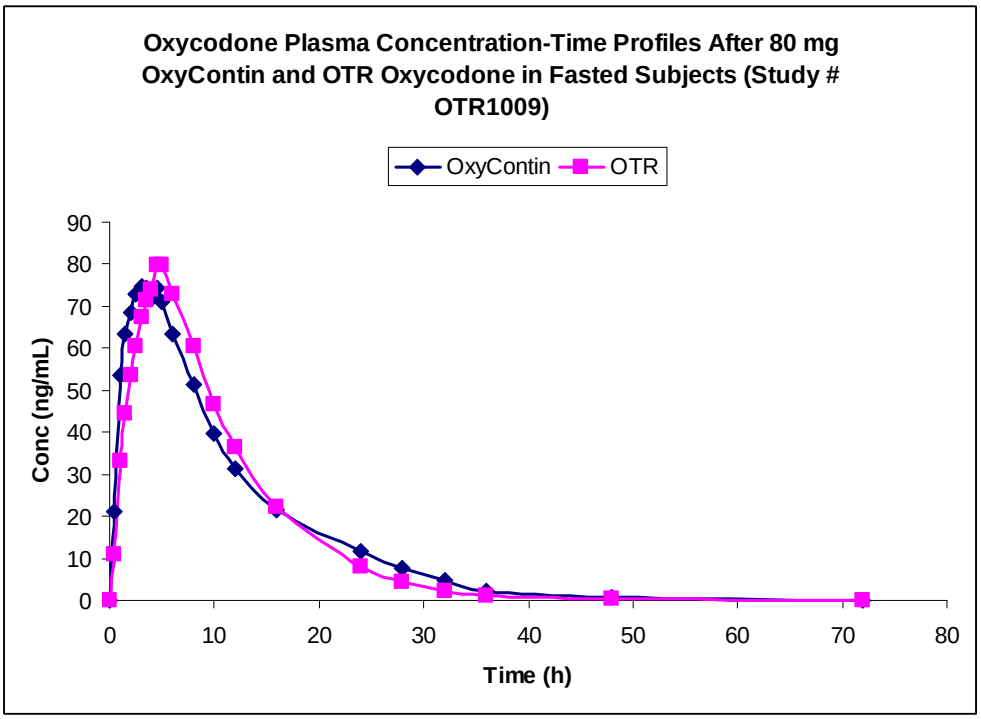
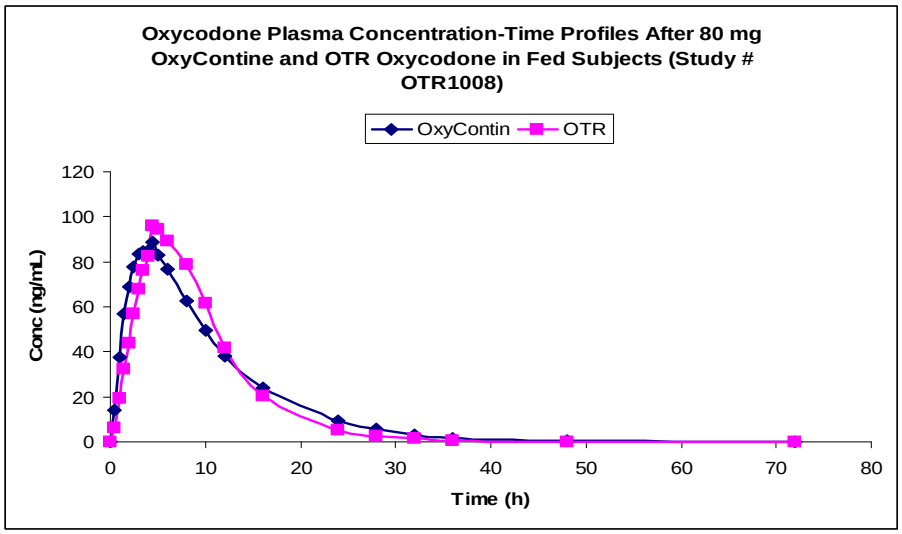


Figure 2.2 Oxycodone Plasma Concentration-Time Profiles in <u>Fed</u> Subjects (Study # OTR1008)



In addition, careful examination of the data across studies reveals that food slightly increases oxycodone Cmax after the administration of both OxyContin® and OTR formulation (**Figures 2.3 and 2.4**).

Figure 2.3 Across Studies Analysis of Effect of Food on Oxycodone Plasma Concentration-Time Profiles After Administration of 80 mg OxyContin® in Healthy Subjects (Studies # OTR1008 and 1009)

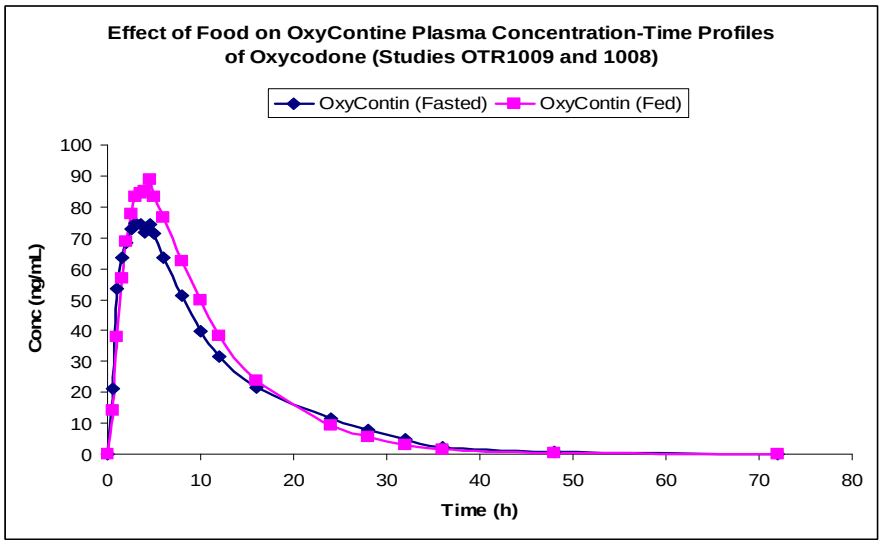
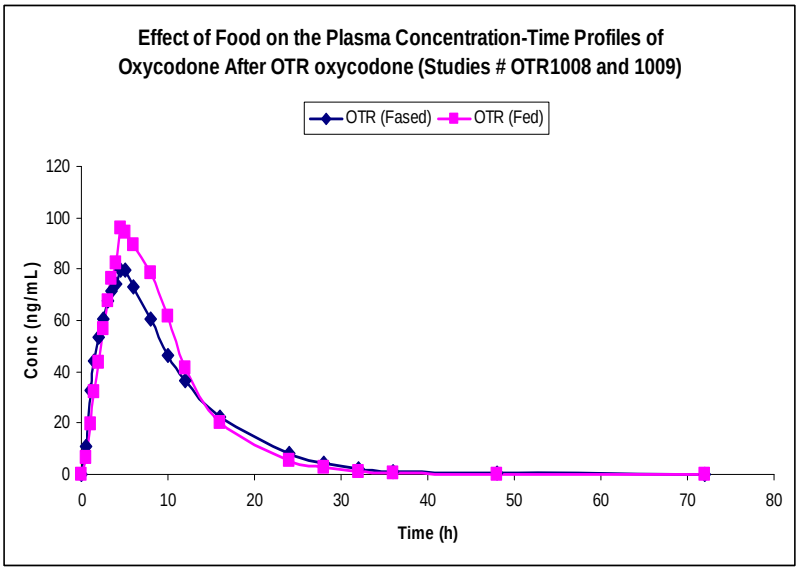


Figure 2.4 Across Studies Analysis of Effect of Food on Oxycodone Plasma Concentration-Time Profiles After Administration of 80 mg OTR Oxycodone Formulation in Healthy Subjects (Studies # OTR1008 and 1009)



Dose Proportionality (40, 60, and 80 mg):

- From current Study OTR1012, oxycodone exposure (Cmax and AUC) was dose proportional after 40 mg, 60 mg, and 80 mg OTR tablets (**Figure 2.5).** Additionally, pooling the data from the current study and the dose proportionality study submitted in the original NDA (Study #OTR1006), there seems to be dose proportionality across all tablet strengths of 10 mg to 80 mg (**Figure 2.6**).

Figure 2.5 Plasma Oxycodone Concentration-Time Profiles Following Single Dose Administration of 40, 60, and 80m g OTR Formulation (Study OTR1012).

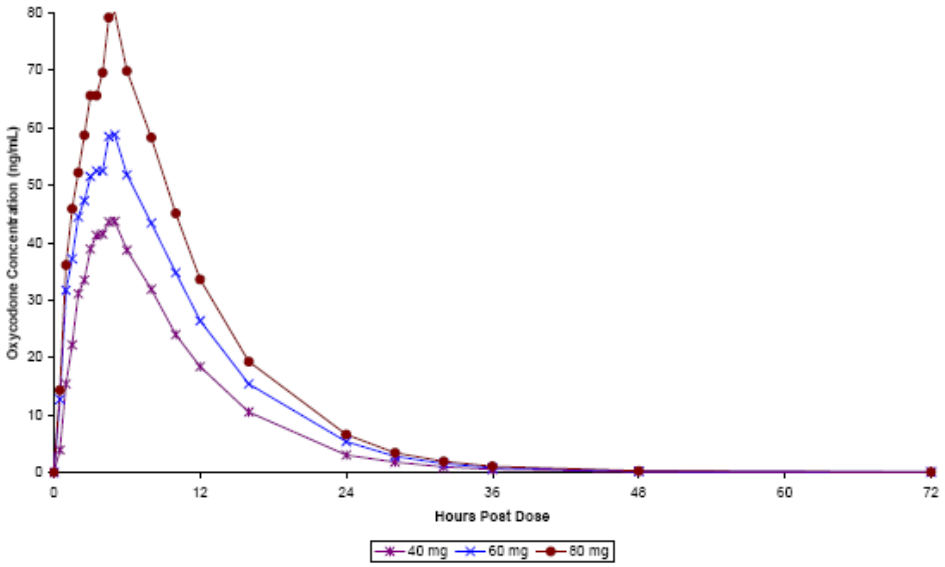
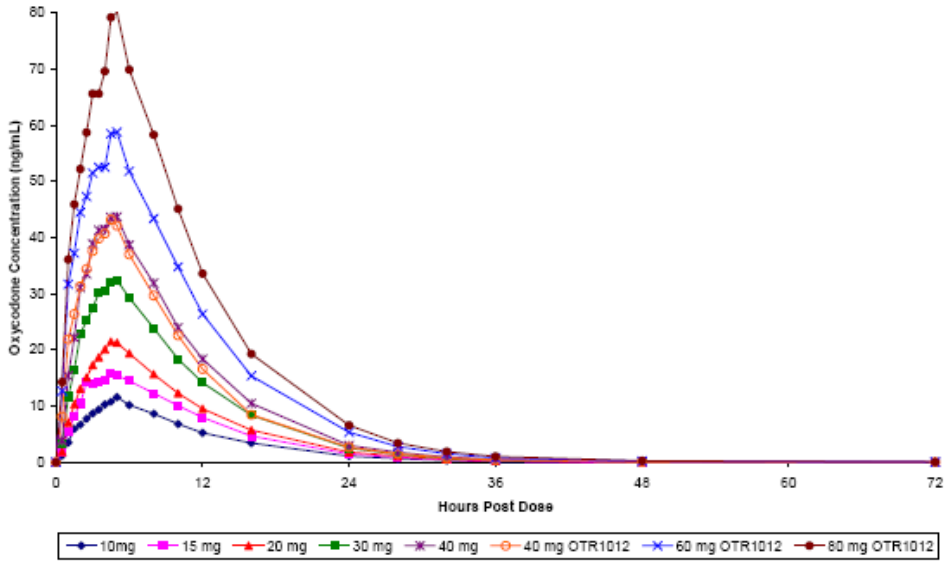


Figure 2.6 Across Studies Plasma Concentration-Time Profiles of Oxycodone Following Single Dose Administration of 10 mg to 80 mg OTR Formulation (data from original NDA "study # OTR1006" and the current resubmission "study # OTR1012").



Effect of Alcohol on Oxycodone Release:

Based on *in vitro* data, there was no effect of alcohol on the release rate of oxycodone from 60 mg and 80 mg OTR formulations (**Figure 2.7 and 2.8**). From this data and the data submitted in the original NDA for 10 mg to 40 mg strengths shows that oxycodone release from OTR formulations is actually in a reverse order with increase in alcohol concentration from 4% to 40%. This confirms that there is no evidence of dose dumping in the presence of alcohol.

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Reanalysis of Bioequivalence Data:

The exclusion of six subjects from the statistical analysis of the data that were submitted in the original NDA from Study # OTR1005 show no difference in Oxycodone plasma concentration-time profiles (**Figure 2.9**). The 90% CI was within 80% and 125% when comparing OTR formulation with the OxyContin® for the 40 mg tablet strengths (**Table 2.3**). Therefore, the exclusion of these six subjects from the analysis did not change the original conclusions from the study that the two formulations are bioequivalent.

Figure 2.9 Mean Oxycodone Plasma Concentration-Time Profile after Exclusion of Six Subjects (Study # OTR1005)

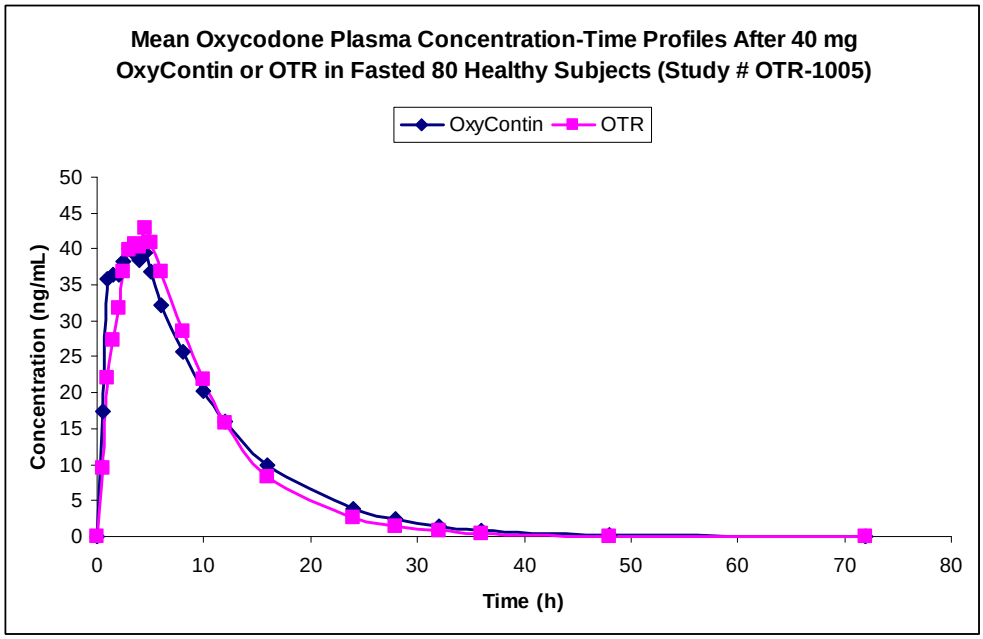


Table 2.3 Reanalysis of Oxycodone PK Data by Exclusion Six Subjects per Agency's Recommendation (Study # OTR1005)

Metric	Units	Comparison	N	Test LS Mean	N	Reference LS Mean	Test/Ref. Ratio	90% Confidence Interval
C_{max}	ng/mL	OTR versus OC	80	46.6	78	48.0	97.0	(93.11, 101.13)
AUC_t	ng*hr/mL	OTR versus OC	80	445	78	468	95.2	(92.48, 97.93)
AUC_{inf}	ng*hr/mL	OTR versus OC	80	447	77	473	94.4	(91.93, 96.92)

Overall Conclusions:

From this resubmission the following conclusions can be made:

- The 80 mg OTR formulation is bioequivalent to the reference, OxyCcontin®, in fed and fasted states.
- The oxycodone Cmax, but not AUC, after OTR appears to be slightly higher and slightly delayed compared to that after the reference, OxyContin®. However, this should have minimal clinical signficance
- Food appears to slightly increase the Cmax, but not the AUC, of oxycodone irrespective of the formulation. As such, current recommendation in the package insert still applies
- Oxycodone exposure (Cmax and AUC) is dose proportional over 10 mg to 80 mg doses of OTR strengths.
- Alcohol does not cause dose dumping for the new OTR formulation. In contrary, the release of oxycodone from OTR is inversely correlated with increase in alcohol concentration from 4% to 40%.

Recommendation:

From the clinical pharmacology perspective, the NDA is acceptable.

3. Individual Study Reports:

4.1 Study # OTR1009 (80 mg OTR vs 80mg OxyContin® in Fasted Subjects)

Objective: To assess the bioequivalence of 80 mg OTR tablet relative to 80 mg OxyContin® in **fasted** healthy subjects.

Design: The study design was similar to that described in all bioequivalence studies submitted in the original NDA (see original clinical pharmacology review in **Appendix I**). Briefly, the study was a single dose, 2-treatment, two-way crossover in 84 healthy subjects with a washout period of at least 6 days as follows:

Treatment A (Test): OTR 80 mg tablet with 240 mL water after over night fast

Treatment B (Reference): OxyContin 80 mg tablet with 240 mL water after over night fast

As in all other bioequivalence studies submitted in the original NDA, subjects received 50 mg oral dose of naltrexone (opioid antagonist) to counteract the effect of oxycodone at -12 hours, 0, 12, 24, and 36 hours after dosing.

Blood samples were collected at appropriate time points over 72 hours for the determination of oxycodone concentration in plasma.

Results:

- There was no major differences in any of the PK parameters or profiles in both treatments (**Figure 3.1.1 and Table 3.1.1**)
- The 90% CIs were within 80% to 125% under fasting conditions (**Table 3.1.2**).

Figure 3.1.1 Oxycodone Plasma Concentration-Time Profiles After 80 mg OxyContin® or OTR Oxycodone in Fasted Subjects (Study # OTR1009) (n=72 Subjects)

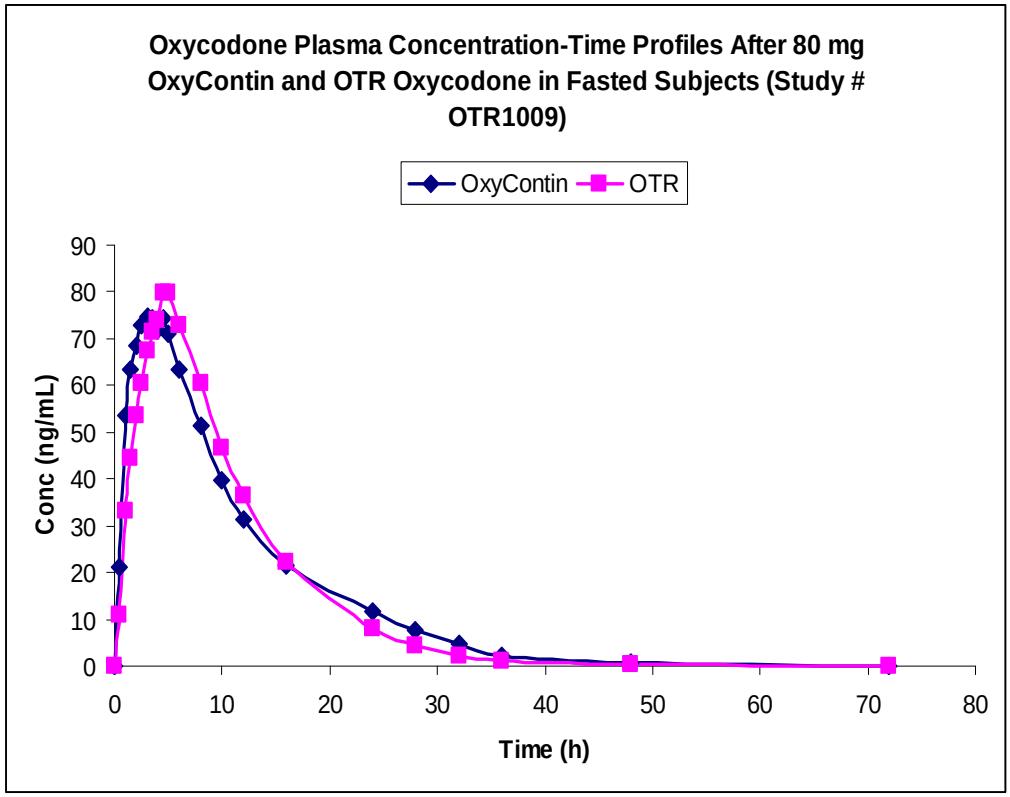


Table 3.1.1 Mean Oxycodone PK Parameters Following 80 mg OxyContin® (Reference) or OTR Oxycodone (Test) in Fasted Subjects (Study # OTR1009)

PK Metric	Units		OxyContin® 80 mg tablet Treatment OC (Reference)	Oxycodone 80 mg TR tablet Treatment TR (Test)
AUC_t	(ng*hr/mL)	Mean	981	964
		SD	243	269
		N	72	78
AUC_{inf}	(ng*hr/mL)	Mean	989	966
		SD	243	269
		N	71	78
C_{max}	(ng/mL)	Mean	83.0	85.1
		SD	20.1	21.5
		N	73	78
t_{max}[a]	(hr)	Median	3.00	4.50
		Min, Max	1.00, 5.02	2.50, 6.00
		N	73	78
λ_z	(1/hr)	Mean	0.129	0.140
		SD	0.0342	0.0376
		N	71	78
$t_{½z}$	(hr)	Mean	5.83	5.51
		SD	1.94	2.56
		N	71	78
t_{lag}	(hr)	Mean	0	0.00641
		SD	0	0.0566
		N	72	78

Source: Table 14.2.2-1 (sequence = All).
[a] Median (min, max) shown for t_{max}.

Table 3.1.2 Statistical Analysis and 90% CI of Oxycodone PK Parameters After 80 mg OxyContin® (Reference) or OTR Oxycodone (Test) in Fasted Subjects (Study # OTR1009)

Metric	Units	LS Mean[a] N	(Test)	N	(Reference)	Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
C_{max}	ng/mL	78	83.0	73	80.9	103	(98.67 , 106.66)	0.0435	0.0196	14
AUC_t	ng*hr/mL	78	933	72	961	97.1	(94.41 , 99.94)	0.0582	0.0103	10
AUC_{inf}	ng*hr/mL	78	936	71	965	97.0	(94.20 , 99.81)	0.0579	0.0105	10

Population: Full Analysis

Note: Test = Oxycodone 80 mg TR tablet; Reference = OxyContin® 80 mg tablet.

[a] Least squares mean from ANOVA. Natural log (ln) metric means calculated by transforming the ln means back to the linear scale, ie, geometric means.

[b] Ratio of metric means for ln-transformed metric (expressed as a percent). Ln-transformed ratio transformed back to linear scale.

[c] 90% confidence interval for ratio of metric means (expressed as a percent). Ln-transformed confidence limits transformed back to linear scale.

[d] Intersubject variability, intrasubject variability, and intrasubject coefficient of variation (expressed as a percent) for ln-transformed metric from ANOVA.

Reviewer's Comments:

- This study provides information on the bioavailability of OTR 80 mg tablet relative to OxyContin® 80 mg tablets in fasted state.
- The two formulations are bioequivalent to each other under fasted condition.
- Examination of the plasma concentration-time profiles show slight delay (right shift) in Tmax after OTR tablet compared to OxyContin®. However, this slight delay in Tmax has little or no clinical implication.

Conclusion:

From this study it can be concluded that the OTR 80 mg tablet is bioequivalent to 80 mg OxyContin® at fasted condition.

3.**2 Study # OTR1008 (80 mg OTR vs 80mg OxyContin® in Fed Subjects)**

Objective: To assess the bioequivalence of 80 mg OTR tablet relative to 80 mg OxyContin® in **fed** healthy subjects.

Design: The study design was similar to the previous study in fasting subjects (Study # OTR1009) and also to all bioequivalent studies submitted in the original NDA (see original clinical pharmacology review in **Appendix I**). The main difference is that dosing was performed after standard breakfast instead of overnight fasting. Briefly, the study was a single dose, 2-treatment, two-way crossover in 84 healthy subjects with a washout period of at least 6 days as follows:

Treatment A (Test): OTR 80 mg tablet with 240 mL water at 30 min after standard breakfast (FDA high-fat breakfast)

Treatment B (Reference): OxyContin 80 mg tablet with 240 mL water at 30 min after standard breakfast (FDA high-fat breakfast)

As in the previous study (Study #OTR1008) and all other bioequivalence studies submitted in the original NDA, subjects received 50 mg oral dose of naltrexone (opioid antagonist) to counteract the effect of Oxycodone at -12 hours, 0, 12, 24, and 36 hours after dosing.

Blood samples were collected at appropriate time points over 72 hours for the determination of oxycodone concentration in plasma.

Results:

- There was no major differences in any of the PK parameters or profiles in both treatments (**Table 3.2.1 and Figure 3.2.1**)
- The 90% CIs were within 80% to 125% under fasting conditions (**Table 3.2.2**).

Figure 3.2.1 Oxycodone Plasma Concentration-Time Profiles After 80 mg OxyContin® or OTR Oxycodone in Fed Subjects (Study # OTR1008) (n=70 Subjects)

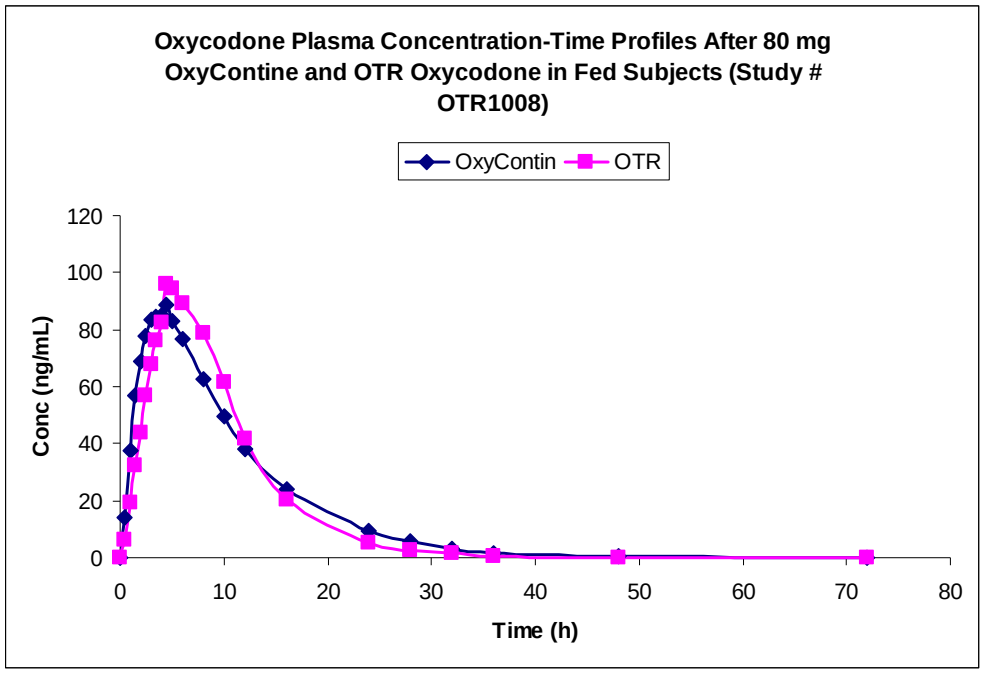


Table 3.2.1 Mean Oxycodone PK Parameters Following 80 mg OxyContin® (Reference) or OTR Oxycodone (Test) in Fed Subjects (Study # OTR1008)

PK Metric	Units		OxyContin® 80-mg tablet Treatment OC (Reference)	Oxycodone 80-mg TR tablet Treatment TR (Test)
AUC_t	(ng*hr/mL)	Mean	1064	1030
		SD	274	267
		N	70	74
AUC_{inf}	(ng*hr/mL)	Mean	1070	1033
		SD	275	269
		N	70	74
C_{max}	(ng/mL)	Mean	97.6	109
		SD	19.9	27.9
		N	70	74
t_{max}[a]	(hr)	Median	3.50	5.00
		Min, Max	1.00, 8.00	2.50, 10.0
		N	70	74
λ_z	(1/hr)	Mean	0.135	0.152
		SD	0.0415	0.0553
		N	70	74
$t_{½z}$	(hr)	Mean	5.94	6.18
		SD	2.90	4.96
		N	70	74
t_{lag}	(hr)	Mean	0.00714	0.0678
		SD	0.0598	0.173
		N	70	74

Source: Table 14.2.2-1 (sequence = All).

[a] Median (min, max) shown for t_{max}.

Table 3.2.2 Statistical Analysis and 90% CI of Oxycodone PK Parameters After 80 mg OxyContin® (Reference) or OTR Oxycodone (Test) in Fed Subjects (Study # OTR1008)

Metric	Units	N	LS Mean[a] (Test)	N	LS Mean[a] (Reference)	Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
C_{max}	ng/mL	74	106	70	96.3	110	(105.21 , 114.47)	0.0301	0.0220	15
AUC_t	ng*hr/mL	74	994	70	1047	94.9	(92.90 , 97.02)	0.0516	0.00570	8
AUC_{inf}	ng*hr/mL	74	996	70	1052	94.7	(92.71 , 96.64)	0.0522	0.00519	7

Population: Full Analysis

Note: Test = Oxycodone 80-mg TR tablet; Reference = OxyContin® 80-mg tablet.

[a] Least squares mean from ANOVA. Natural log (ln) metric means calculated by transforming the ln means back to the linear scale, ie, geometric means.

[b] Ratio of metric means for ln-transformed metric (expressed as a percent). Ln-transformed ratio transformed back to linear scale.

[c] 90% confidence interval for ratio of metric means (expressed as a percent). Ln-transformed confidence limits transformed back to linear scale.

[d] Intersubject variability, intrasubject variability, and intrasubject coefficient of variation (expressed as a percent) for ln-transformed metric from ANOVA.

Reviewer's Comments:

- This study provides information on the bioavailability of OTR 80 mg tablet relative to OxyContin® 80 mg tablets in fed state.
- The two formulations are bioequivalent to each other under fed condition.
- As observed in the previous study (Study #OTR1008) and in all other bioequivalent studies submitted in the original NDA, the plasma concentration-Time profiles show slight delay (right shift) in Tmax after OTR tablet compared to OxyContin®. However, this slight delay in Tmax should have little or no clinical implication.

Conclusion:

From this study it can be concluded that the OTR 80 mg tablet is bioequivalent to 80 mg OxyContin® at fed condition.

3.4 Study # OTR1012 (Dose Proportionality 40 mg, 60mg, and 80 mg OTR in Fasted Subjects)

Objective: To assess the PK and dose proportionality of 40, 60, and 80 mg OTR tablet in **fasted** healthy subjects.

Design: The study design is similar to the other dose proportionality study (Study # OTR1006) that was submitted in the original NDA (see original clinical pharmacology review in **Appendix I**). Briefly, the study was a single dose, 3-treatment, 3-period, crossover in 54 healthy subjects with a washout period of at least 6 days as follows:

Treatment A: OTR 40 mg tablet with 240 mL water after overnight fast.

Treatment B: OTR 60 mg tablet with 240 mL water after overnight fast.

Treatment C: OTR 80 mg tablet with 240 mL water after overnight fast.

As in the previous studies (#OTR1008 and OTR1009) and all other PK studies submitted in the original NDA, subjects received 50 mg oral dose of naltrexone (opioid antagonist) to counteract the effect of Oxycodone at -12 hours, 0, 12, 24, and 36 hours after dosing.

Blood samples were collected at appropriate time points over 72 hours for the determination of oxycodone concentration in plasma.

Results:

- From the current study (Study # OTR1012), oxycodone exposure (Cmax and AUC) was dose proportional after 40 mg, 60 mg, and 80 mg OTR tablets (**Figure 3.4.1 and Tables 3.4.1).**

Figure 3.4.1 Plasma Oxycodone Concentration-Time Profiles Following Single Dose Administration of 40, 60, and 80mg OTR Formulation (Study OTR1012).

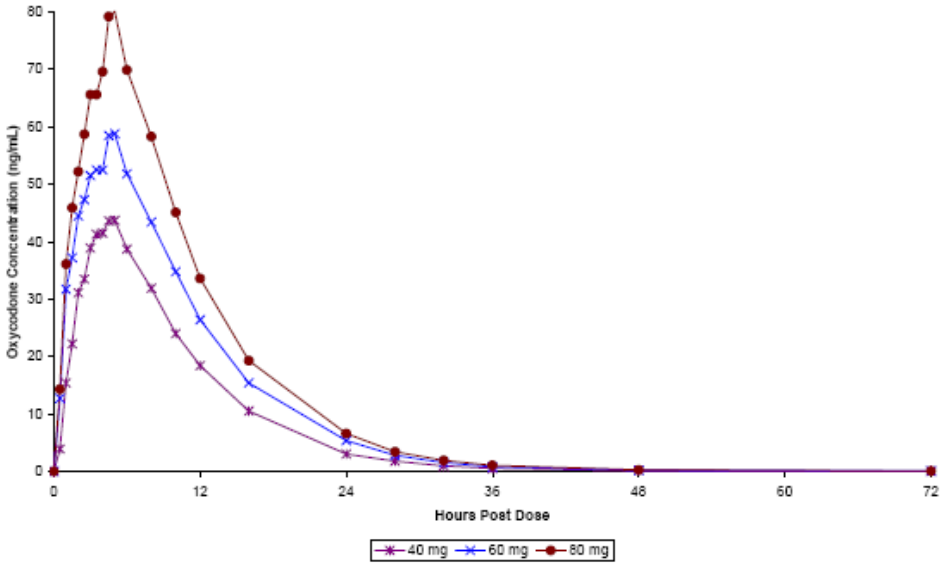


Table 3.2.1 Mean Oxycodone PK Parameters Following 10 mg, 40 mg, and 80 mg OTR Tablets in Fasted Subjects (Study # OTR1012)

PK Metric	Units		40 mg OTR Tablet	60 mg OTR Tablet	80 mg OTR Tablet
AUC_t	(ng*hr/mL)	Mean	464	703	905
		SD	127	156	190
		N	46	50	48
DN AUC_t[a]	(ng*hr/mL)	Mean	116	117	113
		SD	31.8	26.1	23.7
		N	46	50	48
AUC_{inf}	(ng*hr/mL)	Mean	466	705	908
		SD	127	157	190
		N	46	50	48
DN AUC_{inf}[a]	(ng*hr/mL)	Mean	117	118	114
		SD	31.9	26.2	23.8
		N	46	50	48
C_{max}	(ng/mL)	Mean	47.8	64.6	87.1
		SD	12.2	15.2	25.6
		N	46	50	48
DN C_{max}[a]	(ng/mL)	Mean	12.0	10.8	10.9
		SD	3.06	2.54	3.20
		N	46	50	48

(continued)

Source: Tables 14.2.2-1 and 14.2.2-2.
[a] DN indicates a dose-normalized metric, where the metric has been normalized to a dose of 10mg.

Table 3.2.1 (Continued, Study # OTR1012)

PK Metric	Units		40 mg OTR Tablet	60 mg OTR Tablet	80 mg OTR Tablet
t_{max}[b]	(hr)	Median	4.50	4.50	4.50
		Min, Max	2.00, 6.00	2.00, 6.00	2.00, 7.95
		N	46	50	48
λ_z	(1/hr)	Mean	0.134	0.135	0.129
		SD	0.0475	0.0442	0.0487
		N	46	50	48
$t_{½z}$	(hr)	Mean	6.68	6.40	6.93
		SD	4.97	4.38	4.50
		N	46	50	48
t_{lag}	(hr)	Mean	0.0109	0.0100	0.0104
		SD	0.0737	0.0707	0.0722
		N	46	50	48

Source: Table 14.2.2-1.
[b] Median (min, max) presented for t_{max}.

Reviewer's Comments:

- This study provides information on the dose proportionality across three OTR tablet strengths, 40 mg, 60 mg, and 80 mg, in fasted healthy subjects.

- The three strengths demonstrate dose proportionality of oxycodone for both Cmax an AUC.

Conclusion:

From this study it can be concluded that the exposure after the new OTR oxycodone tablets strengths of 40 mg, 60 mg, and 80 mg is dose proportional in healthy subjects at fasting state.

3.5 ADDENDUM To Study # OTR1005 (Bioequivalence of 40 mg Tablet in Fasted Subjects)

Rationale for the Addendum:

This addendum addresses Recommendation # 3 from the Agency's complete response dated October 3, 2008 which states the following:

As noted during Division of Scientific Investigations inspection of Study OTR1005, accuracy of Period 1 oxycodone concentrations for subjects 5040-5042 in run 07307cga14a and subjects 5043, 5044, and 5046 in run 07307cgb14a cannot be assured. Therefore, before data from Study OTR1005 can be accepted, reanalyze and submit the data from Study OTR1005 demonstrating bioequivalence after completely excluding data from subjects 5040, 5041, 5042, 5043, 5044, and 50451. Alternatively, reanalyze the plasma concentrations as identified and confirm the original values."

Sponsor's Response:

The sponsor submitted this addendum to the OTR1005 for the reanalysis of the data after exclusion of all PK data from subjects 5040, 5041, 5042, 5043, 5044, and 5046.

Original Study Design:

Objective:

The primary objective of this study was to establish the BE of OTR 40 mg tablet relative to 40 mg OxyContin® in fasted state.

Study Design:

This was a single dose, 2 periods, 2 treatments, crossover design in 80 healthy subjects as follows:

Treatment A (OTR, Test): 40 mg OTR tablets in fasted state

Treatment B (OxyContin, Reference): 40 mg OTR tablet at fasted state

Similar to all other studies conducted by this sponsor, each subject received 50 mg oral dose of naltrexone (opioid antagonist) to counteract the effect of oxycodone at -12 hours, 0, 12, 24, and 36 hours relative to the time of oxycodone administration.

Blood samples were collected at appropriate time points over 72 hours for the determination of oxycodone.

Results:

- There was no major difference in any of the PK parameter or profiles in both treatments after the reanalysis of the data (**Table 3.5.1)**.

- The 90% CI was also within 80% to 125% for the primary PK parameters (**Table 3.5.2).**

- There was virtually no difference between the primary PK data submitted in the original NDA such as Cmax, AUC, and Tmax (**Table 3.5.3 and Figures 3.5.1 and 2**) and the 90% CI (**Table 3.5.4**).

- Oxycodone plasma concentration-time profiles were identical (superimposed) after 40 mg OxyContin® or OTR tablets before (original submission) and after the exclusion of six subjects (Addendum) from the analysis (**Figures 3.5.3 and 3.5.4**).

Table 3.5.1 Summary of Reanalysis of Oxycodone PK Parameters (Addendum to Study # OTR1005)

PK Metric	Units		OxyContin® 40 mg tablet Treatment OC (Reference)	Oxycodone 40 mg TR tablet Treatment TR (Test)
AUC_t	(ng*hr/mL)	Mean	482	457
		SD	119	117
		N	77	80
AUC_{inf}	(ng*hr/mL)	Mean	484	459
		SD	120	117
		N	77	80
C_{max}	(ng/mL)	Mean	48.7	48.0
		SD	11.0	13.0
		N	78	80
t_{max}[a]	(hr)	Median	2.50	4.00
		(Min, Max)	(0.500, 5.00)	(1.50, 6.00)
		N	78	80
λ_z	(1/hr)	Mean	0.137	0.151
		SD	0.0518	0.0534
		N	77	80
$t_{½z}$	(hr)	Mean	6.21	5.87
		SD	3.54	4.11
		N	77	80
t_{lag}	(hr)	Mean	0.00649	0
		SD	0.0570	0
		N	77	80

Table 3.5.2 Reanalysis Statistical Data and 90% CI of Oxycodone PK Parameters (Addendum to Study # OTR1005)

Metric	Units	Comparison	N	Test LS Mean	N	Reference LS Mean	Test/Ref. Ratio	90% Confidence Interval
C_{max}	ng/mL	OTR versus OC	80	46.6	78	48.0	97.0	(93.11, 101.13)
AUC_t	ng*hr/mL	OTR versus OC	80	445	78	468	95.2	(92.48, 97.93)
AUC_{inf}	ng*hr/mL	OTR versus OC	80	447	77	473	94.4	(91.93, 96.92)

Table 3.5.3. <u>ORIGINAL</u> PK Parameters in Fasted State (Study # OTR1005).

PK Metric	Units		OxyContin® 40 mg tablet Treatment OC (Reference)	Oxycodone 40 mg TR tablet Treatment TR (Test)
AUC_t	(ng*hr/mL)	Mean	477	453
		SD	119	116
		N	82	85
AUC_{inf}	(ng*hr/mL)	Mean	480	454
		SD	120	116
		N	82	85
C_{max}	(ng/mL)	Mean	48.4	47.4
		SD	10.9	12.9
		N	83	85
t_{max}[a]	(hr)	Median	2.50	4.00
		(Min, Max)	(0.500, 5.00)	(1.50, 6.00)
		N	83	85
λ_z	(1/hr)	Mean	0.138	0.151
		SD	0.0510	0.0522
		N	82	85
$t_{½z}$	(hr)	Mean	6.12	5.79
		SD	3.45	4.00
		N	82	85
t_{lag}	(hr)	Mean	0.00610	0
		SD	0.0552	0
		N	82	85

Source: Table 14.2.2-1 (sequence = All)

[a] Median (min, max) shown for t_{max}.

Figure 3.5.4 <u>ORIGINAL</u> Oxycodone Plasma-Concentration Time Profiles in Fasted (Study # OTR-1005)

Metric	Units	LS Mean[a] N	(Test)	N	(Reference)	Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
C_{max}	ng/mL	85	46.1	83	47.7	96.6	(92.80 , 100.56)	0.0411	0.0232	15
AUC_t	ng*hr/mL	85	442	83	463	95.5	(92.93 , 98.18)	0.0585	0.0107	10
AUC_{inf}	ng*hr/mL	85	444	82	468	94.8	(92.42 , 97.24)	0.0568	0.00901	10

Population: Full Analysis

Note: Test = Oxycodone 40 mg TR tablet; Reference = OxyContin® 40 mg tablet.

[a] Least squares mean from ANOVA. Natural log (ln) metric means calculated by transforming the ln means back to the linear scale, i.e., geometric means.

[b] Ratio of metric means for ln-transformed metric (expressed as a percent). Ln-transformed ratio transformed back to linear scale.

[c] 90% confidence interval for ratio of metric means (expressed as a percent). Ln-transformed confidence limits transformed back to linear scale.

[d] Intersubject variability, intrasubject variability, and intrasubject coefficient of variation (expressed as a percent) for ln-transformed metric from ANOVA.

Figure 3.5.1 Oxycodone Plasma-Concentration Time Profiles in Fasted State (Addendum for Study # OTR-1005)

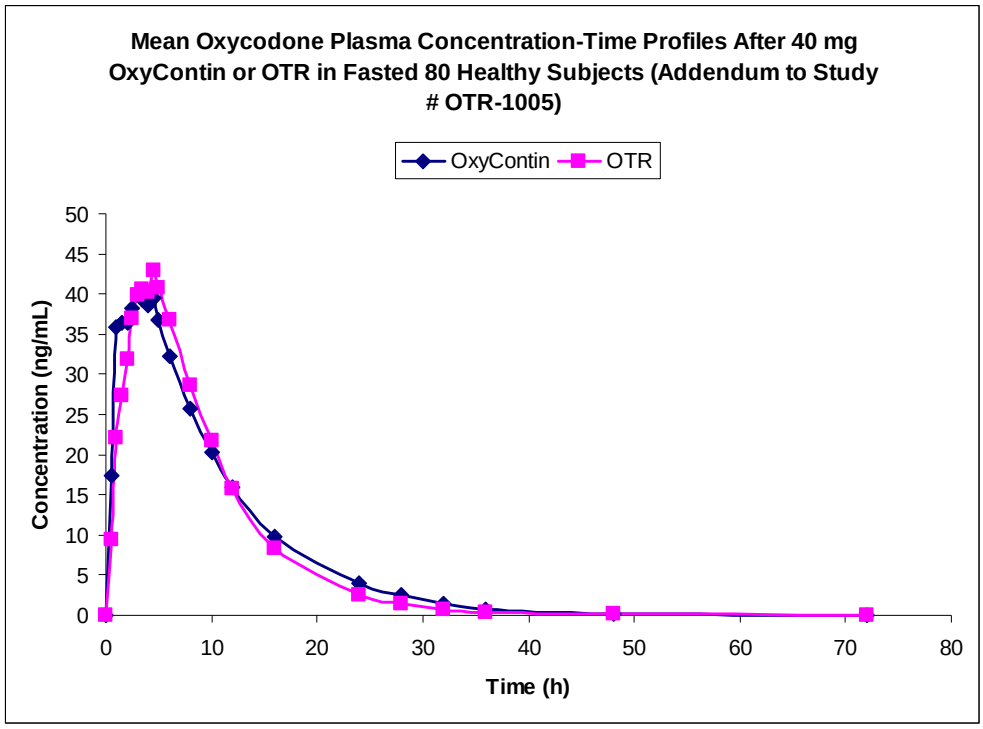


Figure 3.5.2 <u>ORIGINAL</u> Oxycodone Plasma-Concentration Time Profiles in Fasted State (Study # OTR-1005)

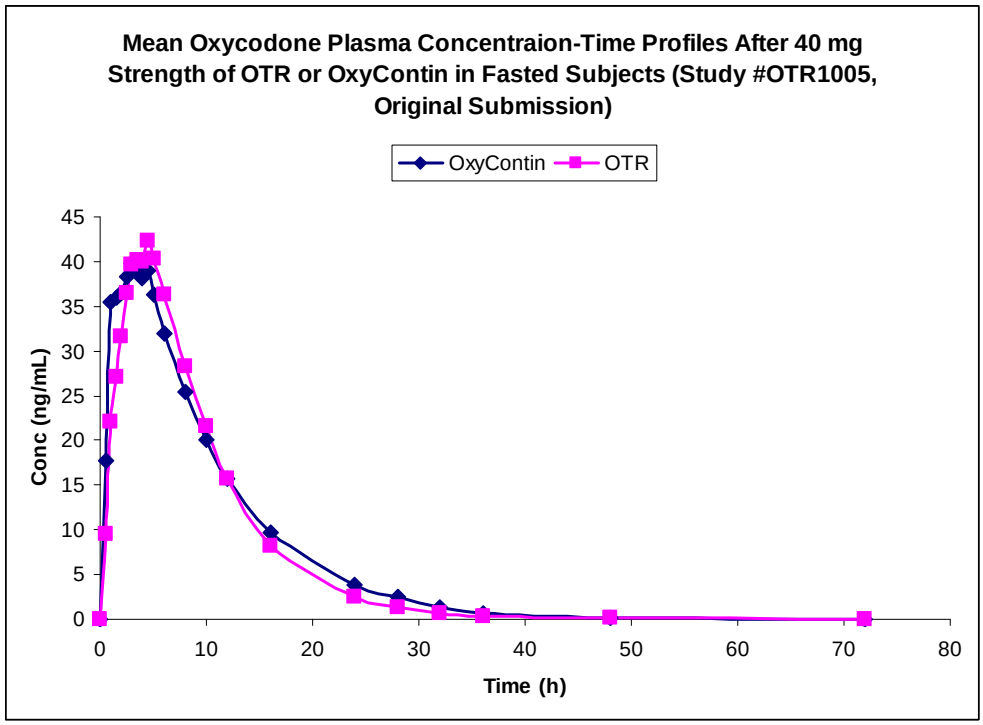


Figure 3.5.3 Comparison in Profiles Between Original Submission and Addendum After OxyContin® 40 mg Tablet (Study # OTR-1005)

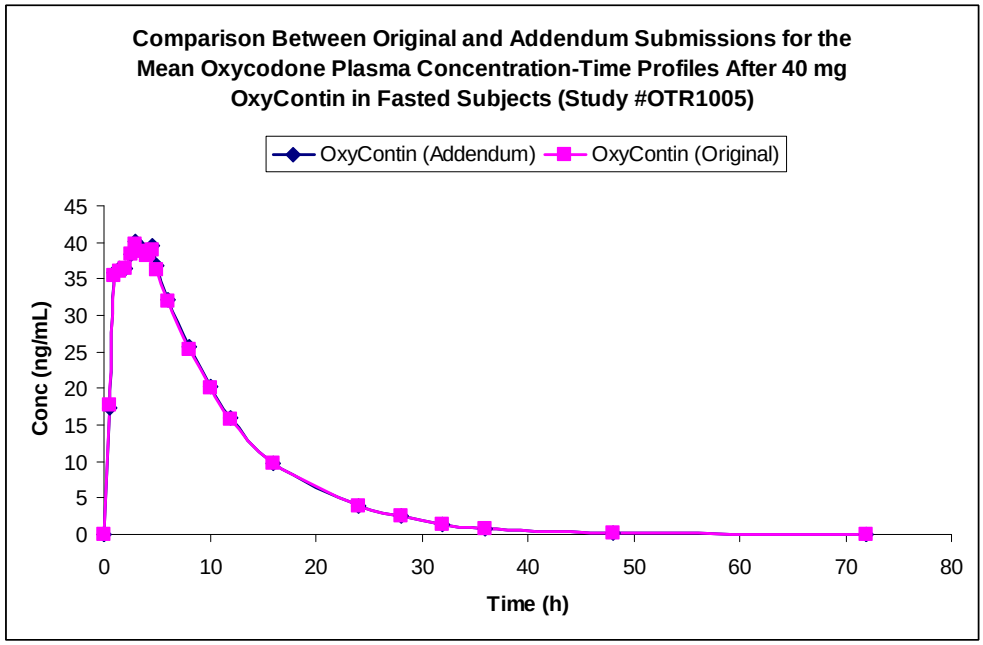
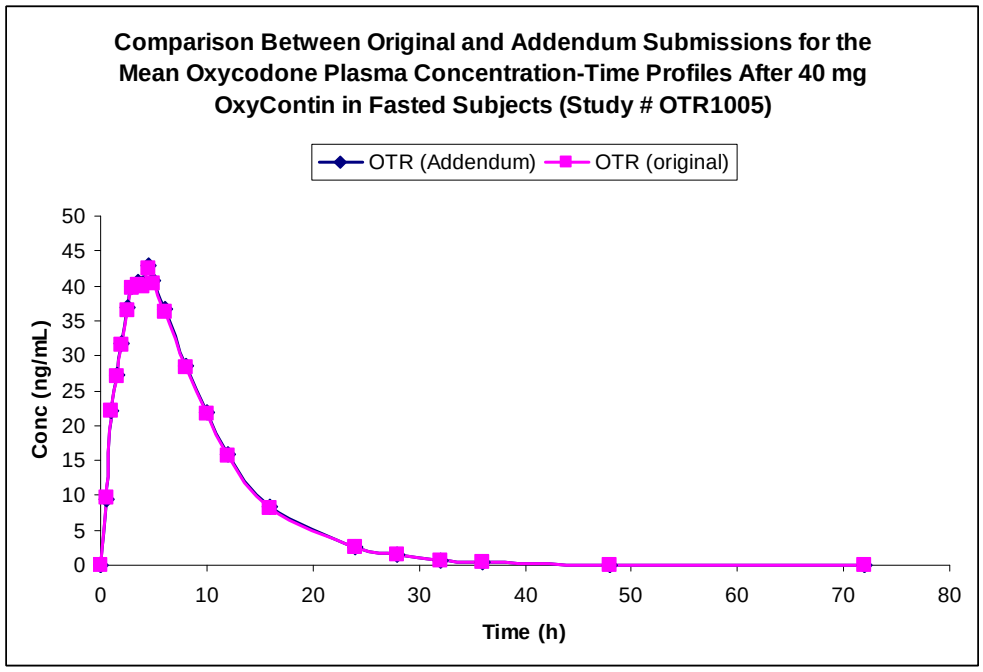


Figure 3.5.4 Comparison in Profiles Between Original Submission and Addendum Following OTR 40 mg Tablet (Study # OTR-1005)



Reviewer's Comments:

- This reanalysis provides confirmatory evidence on the bioavailability of OTR 40 mg tablets relative to Oxycontin® 40 mg tablet in fasted state.

- After the reanalysis of the data, the two formulations are found bioequivalent to each other under fasted condition.

Conclusions:

From this reanalysis it can be concluded that the OTR 40 mg tablet is bioequivalent to 40 mg OxyContin® under fasted condition. Based on this, it is not necessary to change in the original conclusions from this study as stated in the original review.

Recommendation:

The original study and the addendum (reanalysis) are acceptable.

3.6 Effect of Alcohol on Oxycodone Release and Dose Dumping From 60 mg and 80 mg OTR Tablets (*In Vitro* Data)

Rationale:

In the original NDA, the sponsor conducted a specific *in vitro* study to investigate the effect of alcohol on dose dumping on 10, 15, 20, 30, and 40 mg OTR formulation strengths (**Appendix I**). In this resubmission, the sponsor conducted an additional *in vitro* dissolution study on 60 mg and 80 mg OTR strengths.

Design:

The study design and procedure were similar to that used for the other strengths. Briefly, USP Apparatus 1 at a speed of 100 RPM was used. The sampling time points were: 1, 2, 4, 6, 8, 10, and 12 hours. The medium used contained Simulated Gastric Fluid (SGF) without enzymes with 0%, 4%, 20%, and 40% v/v ethanol, respectively.

Results:

- As noted in the original NDA for 10 to 40 mg strengths, the data also clearly show inverse relationship between percent release and ethanol concentration. The higher the ethanol concentration the lower the oxycodone release from the 60 mg (**Figure 3.6.1 Table 3.6.1)** and 80 mg tablets **(Figure 3.6.2 and Table 3.6.2**).
- The similarity factor (f2) for the 4% alcohol compared to SGF for both the 60 mg and 80 mg strengths was approximately 80% (**Table 3.6.1**).

Figure 3.6.1. *In Vitro* Dissolution Profile for 60 mg OTR Strength

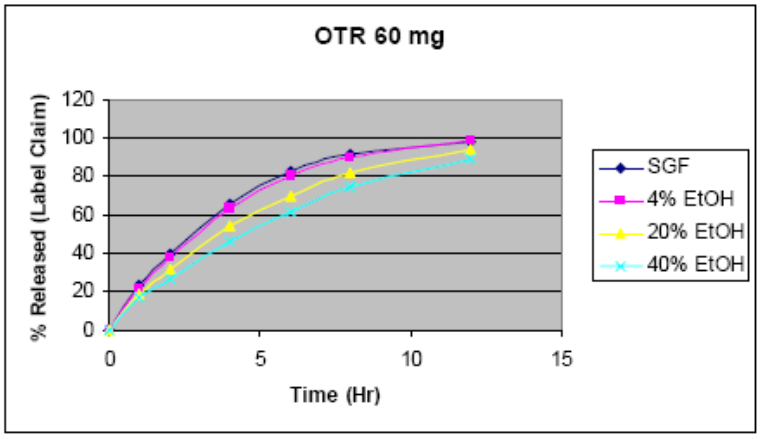


Table 3.6.1 Summary of *In Vitro* Dissolution Data for 60 mg OTR Strength

(b) (4)

*Data was acquired for n=12 tablets therefore the average and range of the first 6 tablets were used for reporting

Figure 3.6.2 *In Vitro* Dissolution Profile for 80 mg OTR Strength

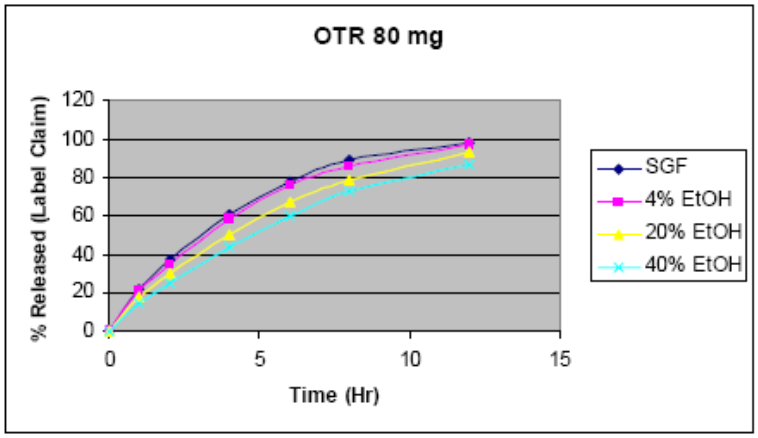


Table 3.6.2 Summary of *In Vitro* Dissolution Data for 80 mg OTR Strength

(b) (4)

*Data was acquired for n=12 tablets therefore the average and range of the first 6 tablets were used for reporting

Table 3.6.3 f2 Similarity Factor for 4% Alcohol compared to SGF (Simulated gastric Fluid)

Product	f_2
OTR 60 mg	79
OTR 80 mg	80

Reviewer's Comments:

- There is clear inverse relationship between alcohol concentration and oxycodone release from OTR formulations.
- Since the f2 was well above 50 it can be concluded that the 4% ethanol profile was similar to that of the SGF. It should be noted that it is not necessary to perform f2 on other alcohol strengths due to the inverse relationship in dissolution profiles as a function of alcohol concentration.
- The data obtained from this study on the 60 mg and 80 mg strengths is similar to that observed for the 10 to 40 mg strengths. Thus, the data is very consistent.

Conclusions:

Based on this *in vitro* data, it can be concluded that there is no evidence that the release of oxycodone was accelerated with alcohol. Conversely, the release was slower in the presence of alcohol. Therefore, no *in vivo* dose dumping can be expected with this formulation. As such, an *in vivo* study is not necessary to further investigate the alcohol interaction potential.

Recommendation:

Since the data from this study is very consistent to the data reported in the original NDA for the other OTR strengths, both studies are acceptable. No dose dumping is expected with OTR formulation.

3.7 Across Studies Analysis:

All bioequivalence studies conducted in this NDA were virtually similar in terms of design, dosing, and administration (**Appendix I**). In the original submission, four bioequivalent studies were conducted for OTR 10 mg and 40 mg strengths relative to OxyContin® 10 mg and 40 mg tablets in fed and fasted subjects (Study # OTR-1002, -1003, -1004, and -1005).

The design of bioequivalence studies in this re-submission for the 80 mg OTR and OxyContin 80 mg tablet in fed and fasted subjects were similar to the other four studies that were submitted in the original NDA (Study # OTR1008 and OTR1009). Similarly, the dose proportionality study at 40 mg, 60 mg, and 80 mg OTR (Study # OTR1012) was similar in design to the study that was submitted in the original NDA for the dosage strengths of 10, 15, 20, 30, 40 mg in fasted subjects (Study # OTR-1006).

Therefore, it feasible to assess dose proportionality across dosage strengths of 10 mg to 80 mg by pooling the data from the current study for 40, 60, and 80 mg (Study # OTR1001) and previous study (Study # OTR1006) for 10, 15, 20, 30, and 40 mg dosage strengths (**Figure 3.7.1-3.7.3 and Table 3.7.1**).

Figure 3.7.1 Across Studies Plasma Concentration-Time Profiles of Oxycodone Following Single Dose Administration of 10 mg to 80 mg OTR Formulation (data from original NDA "study # OTR1006" and the current resubmission "study # OTR1012").

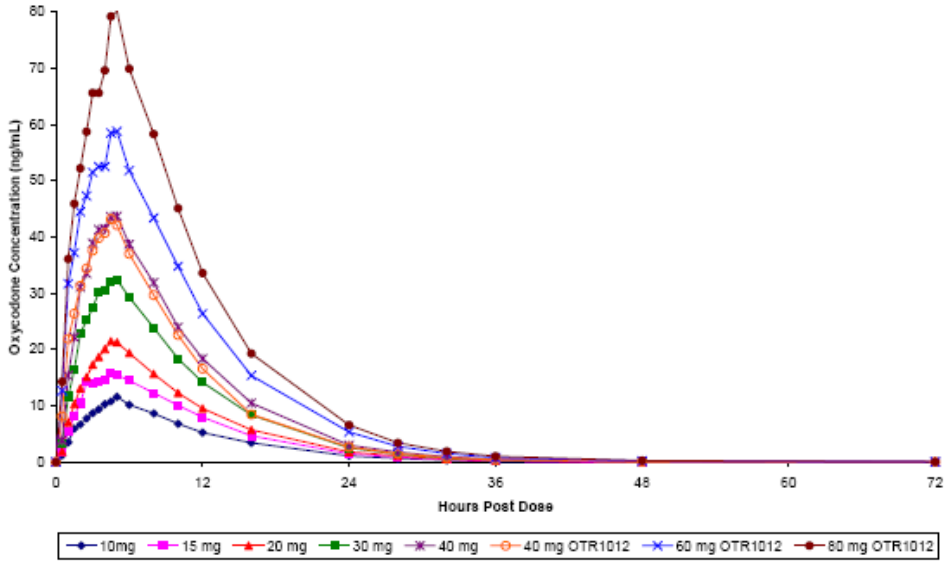


Figure 3.7.2 Across Studies Mean Oxycodone Cmax Values Following Single Dose Administration of 10 mg to 80 mg OTR Formulation (data from original NDA "study # OTR1006" and the current resubmission "study # OTR1012"). Note: two data points for 40 mg strengths (one from each study).

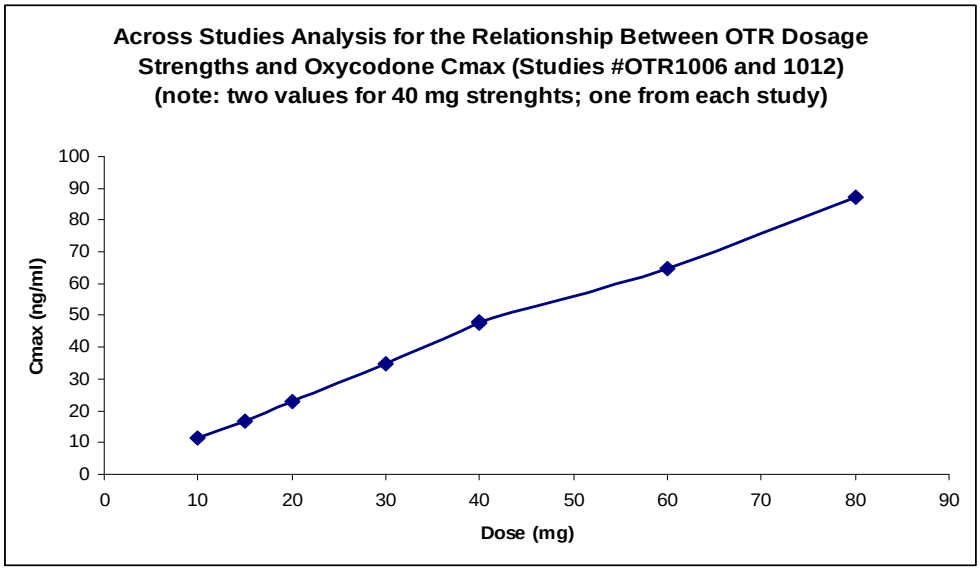


Figure 3.7.3 Across Studies Mean Oxycodone AUC(0-inf) Values Following Single Dose Administration of 10 mg to 80 mg OTR Formulation (data from original NDA "study # OTR1006" and the current resubmission "study # OTR1012"). Note: two data points for 40 mg strengths (one from each study).

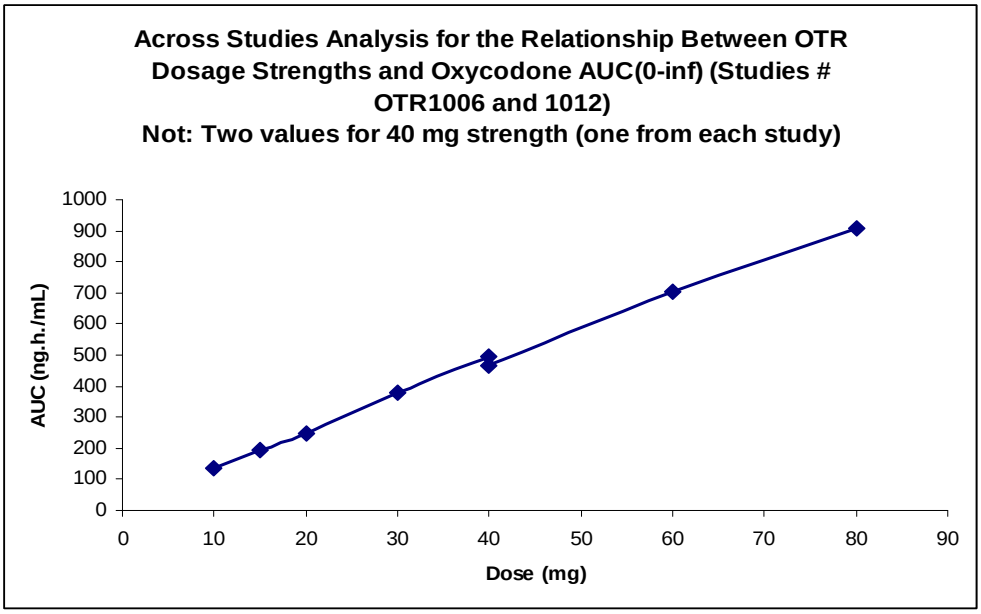


Table 3.7.1 Across Studies Mean Oxycodone Cmax and AUC(0-inf) Following Single Dose Administration of 10 mg to 80 mg OTR Formulation (data from original NDA "study # OTR1006" and the current resubmission "study # OTR1012"). Note: two data points for 40 mg strengths (one from each study).

Dose (mg)	*Cmax (ng/ml)*	*SD (ng/mL)*	*AUC(0-inf) (ng.h/mL)*	*SD (ng/mL)*
10 (OTR1006)	*11.5*	*3.06*	*136*	*37.3*
15 (OTR1006)	*16.8*	*4.91*	*196*	*54.9*
20 (OTR1006)	*22.7*	*5.73*	*248*	*61.1*
30 (OTR1006)	*34.6*	*7.43*	*377*	*91.2*
40 (OTR1006)	*47.4*	*14.0*	*497*	*133*
40 (OTR1012)	*47.8*	*12.2*	*466*	*127*
60 (OTR1012	*64.6*	*15.2*	*705*	*157*
80 (OTR1012	*87.1*	*25.6*	*908*	*190*

The same analysis can be performed for the bioequivalent studies. From the current submission, the 90% CI in both fed and fasted studies after 80 mg strength was within the 80% to 125% (**Table 3.7.2**). Similarly, across studies analysis from the original NDA show that the 90% CI was also within 80% and 125% for 10 mg, 40 mg, and 80 mg strengths in fed and fasted conditions (**Table 3.7.3**).

Table 3.7.2 Statistical Summary of the Bioequivalence Data for 80 mg Strength in Fed and Fasted Subjects

Study	Dose	Condition	Cmax		AUCt	
			LS Mean Ratio	90% CI	LS Mean Ratio	90% CI
OTR1008	80 mg	Fed	110	(105.21, 114.47)	94.9	(92.90, 97.02)
OTR1009	80 mg	Fasted	103	(98.67, 106.66)	97.1	(94.41, 99.94)

Table 3.7.3 Statistical Summary of the Bioequivalence Data for 10 mg, 40 mg, and 80 mg Strengths in Fed and Fasted Subjects (Studies OTR1002, -1003, -1004, and -1005 were submitted in the original NDA).

Study	Dose	Condition	Cmax		AUCt	
			LS Mean Ratio	90% CI	LS Mean Ratio	90% CI
OTR1002	10 mg	Fed	105.0	[101.06, 108.51]	95.7	[93.85, 97.68]
OTR1003	10 mg	Fasted	102.0	[99.35, 105.42]	98.3	[95.20, 101.48]
OTR1004	40 mg	Fed	99.9	[95.40, 104.52]	92.6	[90.13, 95.13]
OTR1005	40 mg	Fasted	96.6	[92.80, 100.56]	95.5	[92.93, 98.18]
OTR1008	80 mg	Fed	110	[105.21, 114.47]	94.9	[92.90, 97.02]
OTR1009	80 mg	Fasted	103	[98.67, 106.66]	97.1	[94.41, 99.94]

It appears that from both studies (Study # OTR1009 and 1008) the Cmax after 80 mg OTR formulation is consistently slightly delayed and slightly higher than that after Oxycontin in fasted state (**Figure 3.7.4)** and fed **(Figure 3.7.5**) conditions. The same observation was noted in the original NDA (**Appendix 1**).

Figure 3.7.4 Oxycodone Plasma Concentration-Time Profiles in <u>Fasted</u> Subjects (Study # OTR1009)

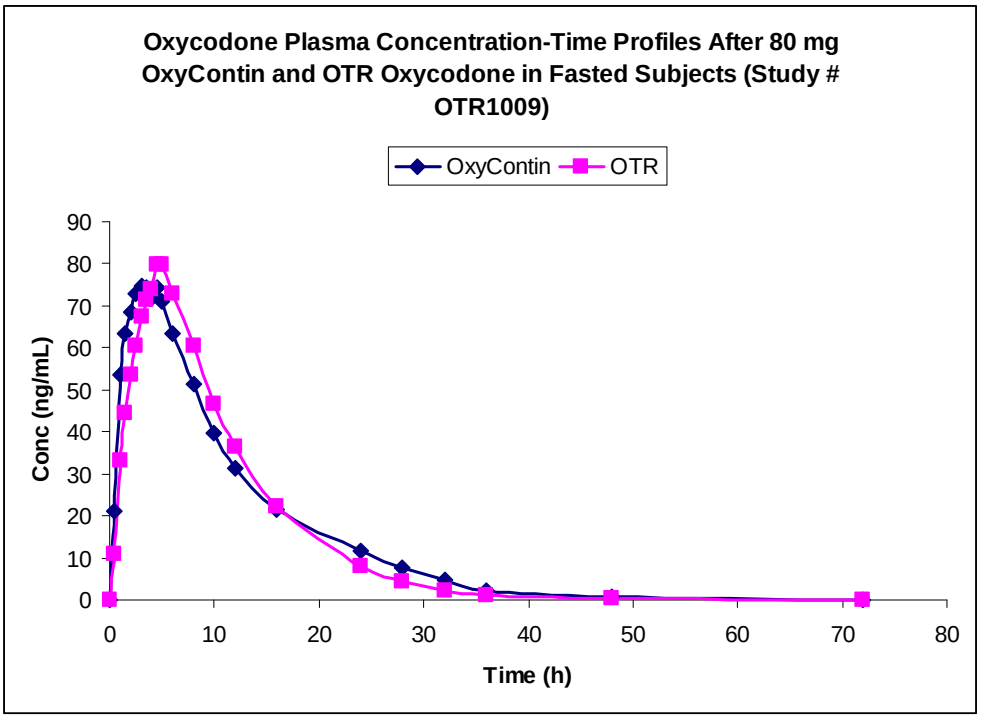
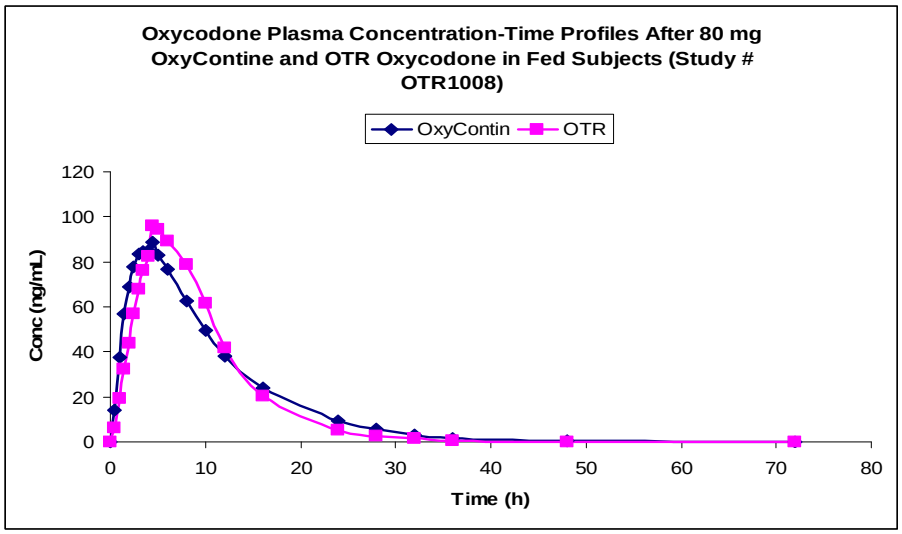


Figure 3.7.5 Oxycodone Plasma Concentration-Time Profiles in Fed Subjects (Study # OTR1008)



In addition, careful examination of the data across studies reveals that food slightly increases oxycodone Cmax after the administration of both OxyContin® and OTR formulation (**Figures 4.7.6 and 4.7.7**).

Figure 3.7.6 Across Studies Analysis of Effect of Food on Oxycodone Plasma Concentration-Time Profiles After Administration of 80 mg OxyContin® in Healthy Subjects (Studies # OTR1008 and 1009)

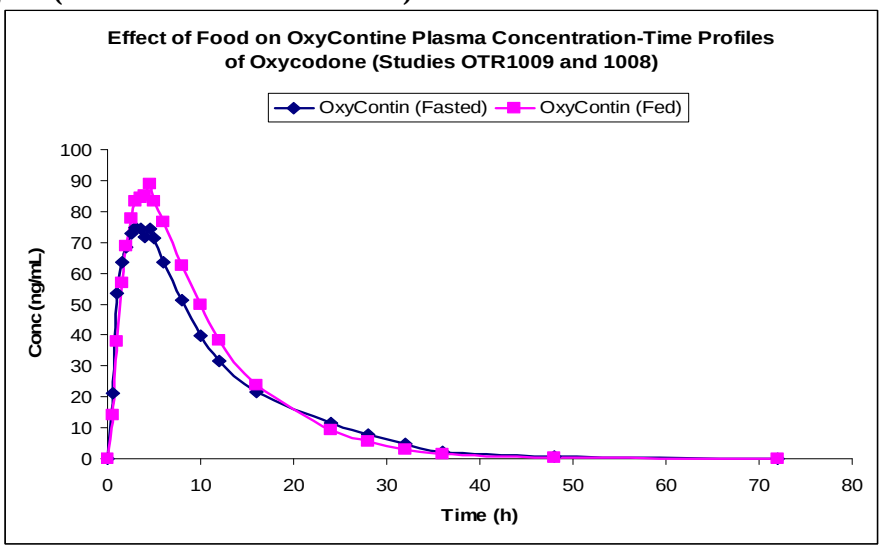
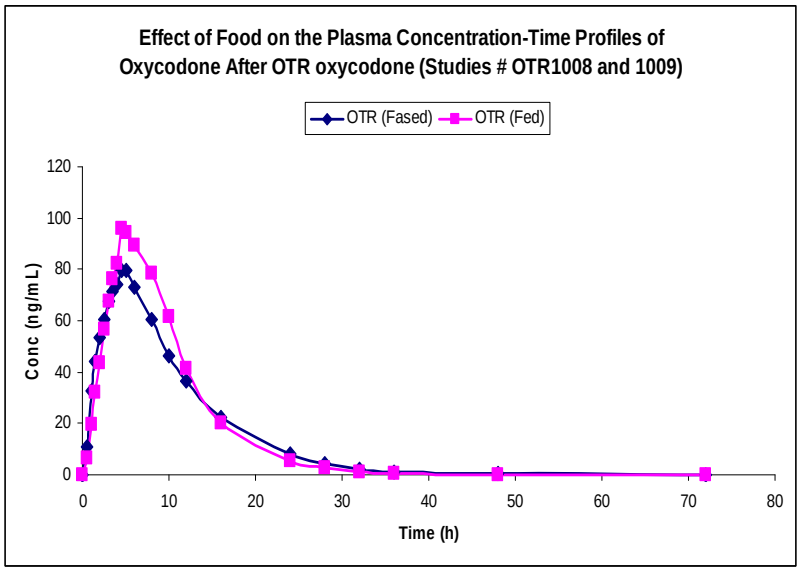


Figure 3.7.7 Across Studies Analysis of Effect of Food on Oxycodone Plasma Concentration-Time Profiles After Administration of 80 mg OTR Oxycodone Formulation in Healthy Subjects (Studies # OTR1008 and 1009)



Overall Summary:

From this analysis it can be stated that the data from all studies are consistent. For instance, in the initial NDA submission, bioequivalence of 10 mg and 40 mg OTR tablet was demonstrated relative to the corresponding OxyContin® tablet strength in both fed and fasted subjects.

The same conclusion was made in the resubmission for the highest 80 mg OTR strength relative to 80 mg OxyContin® tablet. The 90% CI values in the original submission and the re-submission were within 80% and 125% boundaries. Careful examination of the 90% CI values across all studies reveals the tightness and low variability in the data as they fall within a narrow range of approximately 90% to 100%.

Food appears to slightly delay the Tmax and increase Cmax compared to fasting state in all studies. In addition, the Tmax appears to slightly delay and Cmax is slightly increased after OTR formulation compared to OxyContin. These observations were consistent among all studies.

Similarly, examination of the dose proportionality studies demonstrates consistency across studies. For example, the mean Cmax and AUC for the 40 mg strength in both studies are very similar in values (**Table 3.4.1**).

Finally, the *in vitro* release of oxycodone from OTR tablets was inversely correlated with percentage of alcohol in the medium. This phenomenon was observed in the original NDA for the lower strengths and for the higher strength OTR tablets in this submission.

The reanalysis of the data by excluding six subjects from the original study # OTR1005 had no impact on the bioequivalence parameters and final conclusion that was made in the original NDA. The 40 mg OTR strength was equivalent to OxyContin® 40 mg tablet in fasted subjects with and without the data from the six subjects.

4. Labeling Comments

Important Note: Labeling comments will be made directly into the master labeling file posted in the Division's shared drive. These are PRELIMINARY comments specifically for the clinical pharmacology related information. Other comments and edits are pending discussion with the team members and also with the sponsor.

7 DRUG INTERACTIONS

7.1 Neuromuscular Junction Blocking Agents

Opioid analgesics, including OxyContin, may enhance the neuromuscular blocking action of true skeletal muscle relaxants (such as pancuronium) and produce an increased degree and/or duration of respiratory depression.

(b) (4)

43 pp withheld in full immed. after this page as (b)(4) Draft Labeling.

Appendix I

(Original Review Dated April 7, 2008)

Clinical Pharmacology Review

NDA: 22-272	**Dates of Submission:** November 29, 2007
Generic Name	Oxycodone
Brand Name:	**Oxycontin®**
Formulation:	Extended Release Tablets
Strengths:	10, 15, 20, 30, 40, and 80 mg
OCP Division	Division of Clinical Pharmacology II
OND Division	Division of Anesthesia, Analgesia, and Rheumatology Products
Route of Administration:	Oral
Indication:	-Management of moderate to severe pain when a continuous, around-the clock analgesic is needed for an extended period of time. –Not for use as a prn analgesic or in the immediate post-operative period (the first 12 to 24 hours following surgery).
Dosage and Administration:	-Q12h (individualized) -Use low initial doses in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications. –For patients already receiving opioids, use standard conversion ratio estimates.
Type of Submission:	Original NDA; Priority
Sponsor:	Purdue Pharma Stamford, CT
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.

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1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, this NDA is acceptable provided that (i) a mutually acceptable agreement regarding the labeling language can be reached between the Agency and the Applicant and (ii) Division of Scientific Investigation (DSI) audit of study OTR-1005 does not identify any significant issues that would impact the acceptability of the study results for regulatory decision making. At the time of writing this review, DSI inspection report is not available. An addendum to this review will be written summarizing the labeling changes and DSI findings in a separate review.

1.2 Phase 4 Commitment

From the Clinical Pharmacology perspective, no phase 4 commitment is applicable to this NDA.

1.3 Summary of Important Clinical Pharmacology Findings:

OxyContin 10, 20, and 40 mg strengths were approved on December 12, 1995 (NDA 20-553). Subsequently, 15, 30, and 60, mg strengths were approved on September 18, 2006 and the 80 mg and 160 mg strengths were approved on January 6, 1977 and March 15, 2000, respectively. However, the sponsor discontinued marketing the 160 mg strength. As such, at this time Oxycontin 10, 15, 20, 30, 40, 60, and 80 mg strengths are currently approved and available for marketing.

Due to the concern of abuse liability with the current formulation, the sponsor reformulated the existing extended release formulation purportedly making it more resist to physical and chemical manipulation. The sponsor is referring this reformulated product as **OTR** (Oxycodone Tamper-Resistant) tablets. Therefore, this NDA is the subject of this reformulated oxyContin®. In this submission, the sponsor is seeking the approval of six strengths: 10, 15, 20, 30, 40 mg and 80 mg tablets. Of these, 10, 15, 20, 30, and 40 mg tablets are OTR tablets while 80 mg tablet will remain as the original formulation. Due to technical difficulties encountered during the reformulation efforts, sponsor is still working on the 60 mg and 80 mg OTR tablets and has indicated that an approval of these will be sought after reformulation efforts are successful. Until that time, sponsor is not proposing to market the 60 mg strength and is proposing to market the original 80 mg strength. The trade name will remain OxyContin®.

The contents of this NDA will be discussed at the May 5th, 2008 Anesthetic and Life Support Drugs Advisory Committee Meeting. At that the time of writing this review, tentative discussion topics identified were:

- Implications of labeling physical properties of formulation intended to lessen the risk of misuse.
- Labeling when all strengths are not approved

- How resistant to chemical or physical manipulation must a formulation be to warrant inclusion of that information in the label

The sponsor conducted 7 PK studies to determine the bioavailability/bioequivalence of the 10 and 40 mg strengths of OTR formulation relative to the currently marketed formulation under fed and fasting conditions and dose-proportionality of 10, 15, 20, 30, and 40 mg OTR formulation strengths. In addition, the sponsor conducted an *in vitro* dissolution study to investigate the effect of alcohol on dose dumping on OTR formulation. The synopsis of each study is as follows:

Study Designs:

Study # OTR-1001 (Pilot Study): This is a four-way crossover, single dose study, in 22 healthy subjects to characterize the bioavailability of three prototypes **10 mg** tamper resistant oxycodone formulations relative to OxyContin® in **fed and fasted state.**

Study # OTR-1002 (10 mg BE/Fed): This is a single dose, two-period, crossover study to investigate the bioequivalence of OTR **10 mg** tablet relative to OxyContin® under **fed** condition in 82 healthy subjects.

Study # OTR-1003 (10 mg BE/Fasting): This is a single dose, two-period, crossover study to investigate the bioequivalence of OTR **10 mg** tablet relative to OxyContin® under **fasting** condition in 83 healthy subjects.

Study # OTR-1004 (40 mg BE/Fed): This is a single dose, two-period, crossover study to investigate the bioequivalence of OTR **40 m**g tablet relative to OxyContin® under **fed** condition in 74 healthy subjects.

Study # OTR-1005 (40 mg BE/Fasting): This is a single dose, two-period, crossover study to investigate the bioequivalence of OTR **40 m**g tablet relative to OxyContin® under **fasting** condition in 80 healthy subjects.

Study # OTR-1006 (Dose Proportionality/Fasting): This is a single dose, 5 treatment, five-way crossover study to investigate the dose proportionality of OTR tablets 10, 15, 20, 30, and 40 mg strengths under **fasting** condition in 52 healthy subjects.

Summary of Findings:

In the pilot study (OTR1001), one of the three prototypes (**1 B**) was selected for further development. The PK profile of this formulation was similar to the current formulation, under fed and fasted states.

For 10 mg strength, there was no difference in the PK profile between the OTR formulation and the currently approved 10 mg strength in fed (**Figure 1 A**) or fasted (**Figure 1 B**) conditions (Studies # OTR-1002 and OTR 1003). The same conclusion can

be made for the 40 mg strength (**Figures 2 A and B,** Studies # OTR 1004 and OTR 1005).

Figure 1 A and B. Oxycodone Plasma-Concentration Time Profiles of 10 mg Strength in Fed State and Fasted States (Studies # OTR-1002 and 1003)

Figure 1 A (Fed, Study 1002)

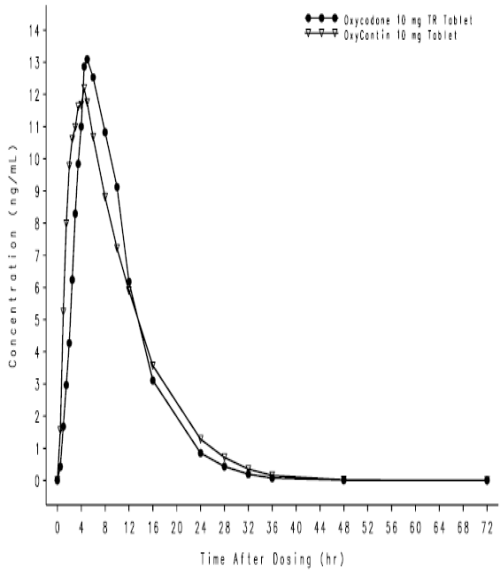


Figure 1 B (Fasted, Study 1003)

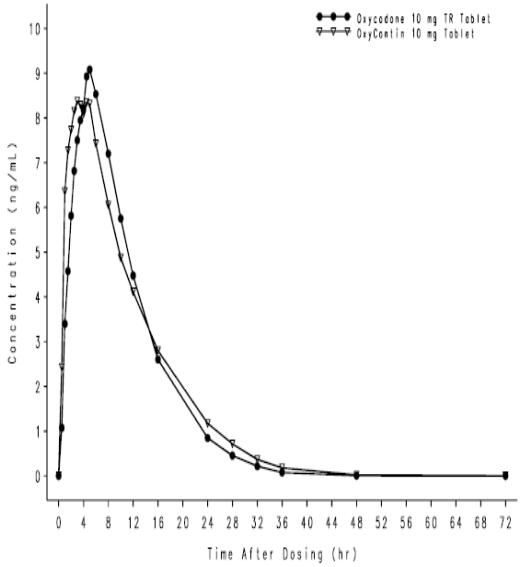


Figure 2 A and B. Oxycodone Plasma-Concentration Time Profiles of 40 mg Strength in Fed and fasted States (Studies # OTR-1004 and 1005)

Figure 2A (Fed, Study 1004)

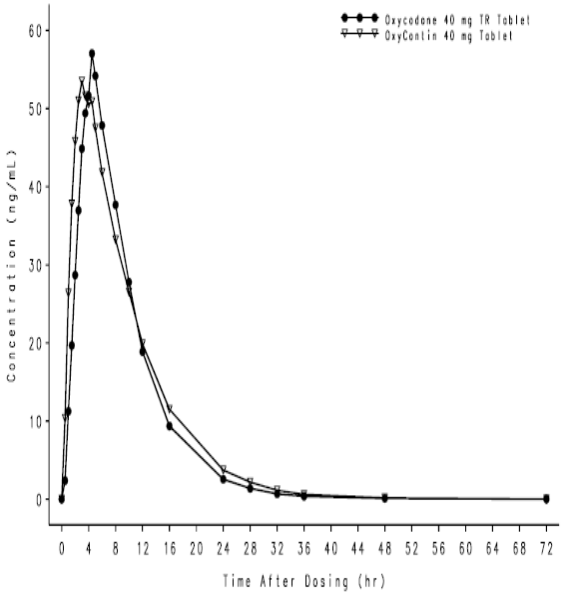
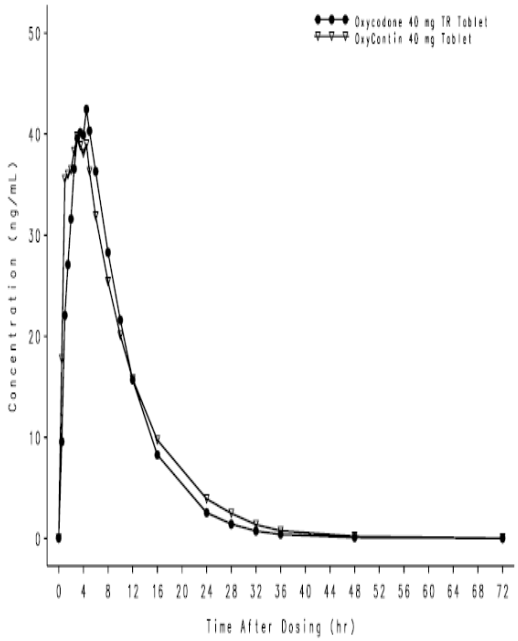


Figure 2 B (Fasted, Study 1005)



The 90% CI's for both Cmax and AUC were within 80% to 125% limits for both 10 mg and 40 mg OTR strengths in fed and fasted states (**Tables 1.3.1 to 1.3.4**). Therefore, from these four studies it can be concluded that the two strengths, 10 mg and 40 mg were bioequivalent to respective reference strengths of original formulation of OxyContin® in fed and fasted conditions.

Table 1.3.1 Statistical Analysis of PK Parameters for the 10 mg strength in Fed State (Study # OTR1002).

Metric	Units	LS Mean[a]				Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
		N	(Test)	N	(Reference)					
C_{max}	ng/mL	79	13.9	81	13.3	105	(101.06 , 108.51)	0.0243	0.0180	13
AUC_t	ng*hr/mL	79	138	81	145	95.7	(93.85 , 97.68)	0.0460	0.00562	8
AUC_{inf}	ng*hr/mL	79	139	81	146	95.6	(93.73 , 97.53)	0.0456	0.00557	7

Population: Full Analysis

Note: Test = Oxycodone 10 mg TR tablet; Reference = OxyContin® 10 mg tablet.

[a] Least squares mean from ANOVA. Natural log (ln) metric means calculated by transforming the ln means back to the linear scale, i.e., geometric means.

[b] Ratio of metric means for ln-transformed metric (expressed as a percent). Ln-transformed ratio transformed back to linear scale.

[c] 90% confidence interval for ratio of metric means (expressed as a percent). Ln-transformed confidence limits transformed back to linear scale.

[d] Intersubject variability, intrasubject variability, and intrasubject coefficient of variation (expressed as a percent) for ln-transformed metric from ANOVA.

Table 1.3.2 Statistical Analysis of PK Parameters for the 10 mg strength in Fasted State (Study # OTR1003).e

Metric	Units	LS Mean[a]				Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
		N	(Test)	N	(Reference)					
C_{max}	ng/mL	81	9.36	81	9.15	102	(99.35 , 105.42)	0.0423	0.0126	11
AUC_t	ng*hr/mL	81	107	81	109	98.3	(95.20 , 101.48)	0.0432	0.0146	12
AUC_{inf}	ng*hr/mL	81	108	81	110	98.0	(94.94 , 101.19)	0.0427	0.0146	12

Source: Table 14.2.3-1.

Note: Test = OTR 10 mg tablet; Reference = OxyContin® 10 mg tablet.

[a] Least squares mean from ANOVA. Natural log (ln) metric means calculated by transforming the ln means back to the linear scale, i.e., geometric means.

[b] Ratio of metric means for ln-transformed metric (expressed as a percent). Ln-transformed ratio transformed back to linear scale.

[c] 90% confidence interval for ratio of metric means (expressed as a percent). Ln-transformed confidence limits transformed back to linear scale.

[d] Intersubject variability, intrasubject variability, and intrasubject coefficient of variation (expressed as a percent) for ln-transformed metric from ANOVA.

Table 1.3.3 Statistical Analysis of PK Parameters for the 40 mg strength in Fed State (Study # OTR1004).

Metric	Units	LS Mean[a] N	(Test)	N	(Reference)	Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
C_{max}	ng/mL	76	59.8	80	59.9	99.9	(95.40 , 104.52)	0.0356	0.0274	17
AUC_t	ng*hr/mL	76	517	80	558	92.6	(90.13 , 95.13)	0.0606	0.00928	10
AUC_{inf}	ng*hr/mL	76	519	80	560	92.6	(90.11 , 95.09)	0.0605	0.00922	10

Population: Full Analysis

Note: Test = Oxycodone 40 mg TR tablet; Reference = OxyContin® 40 mg tablet.

[a] Least squares mean from ANOVA. Natural log (ln) metric means calculated by transforming the ln means back to the linear scale, i.e., geometric means.

[b] Ratio of metric means for ln-transformed metric (expressed as a percent). Ln-transformed ratio transformed back to linear scale.

[c] 90% confidence interval for ratio of metric means (expressed as a percent). Ln-transformed confidence limits transformed back to linear scale.

[d] Intersubject variability, intrasubject variability, and intrasubject coefficient of variation (expressed as a percent) for ln-transformed metric from ANOVA.

Table 1.3.4 Statistical Analysis of PK Parameters for the 40 mg strength in Fed State (Study # OTR1004).

Metric	Units	LS Mean[a] N	(Test)	N	(Reference)	Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
C_{max}	ng/mL	76	59.8	80	59.9	99.9	(95.40 , 104.52)	0.0356	0.0274	17
AUC_t	ng*hr/mL	76	517	80	558	92.6	(90.13 , 95.13)	0.0606	0.00928	10
AUC_{inf}	ng*hr/mL	76	519	80	560	92.6	(90.11 , 95.09)	0.0605	0.00922	10

Population: Full Analysis

Note: Test = Oxycodone 40 mg TR tablet; Reference = OxyContin® 40 mg tablet.

[a] Least squares mean from ANOVA. Natural log (ln) metric means calculated by transforming the ln means back to the linear scale, i.e., geometric means.

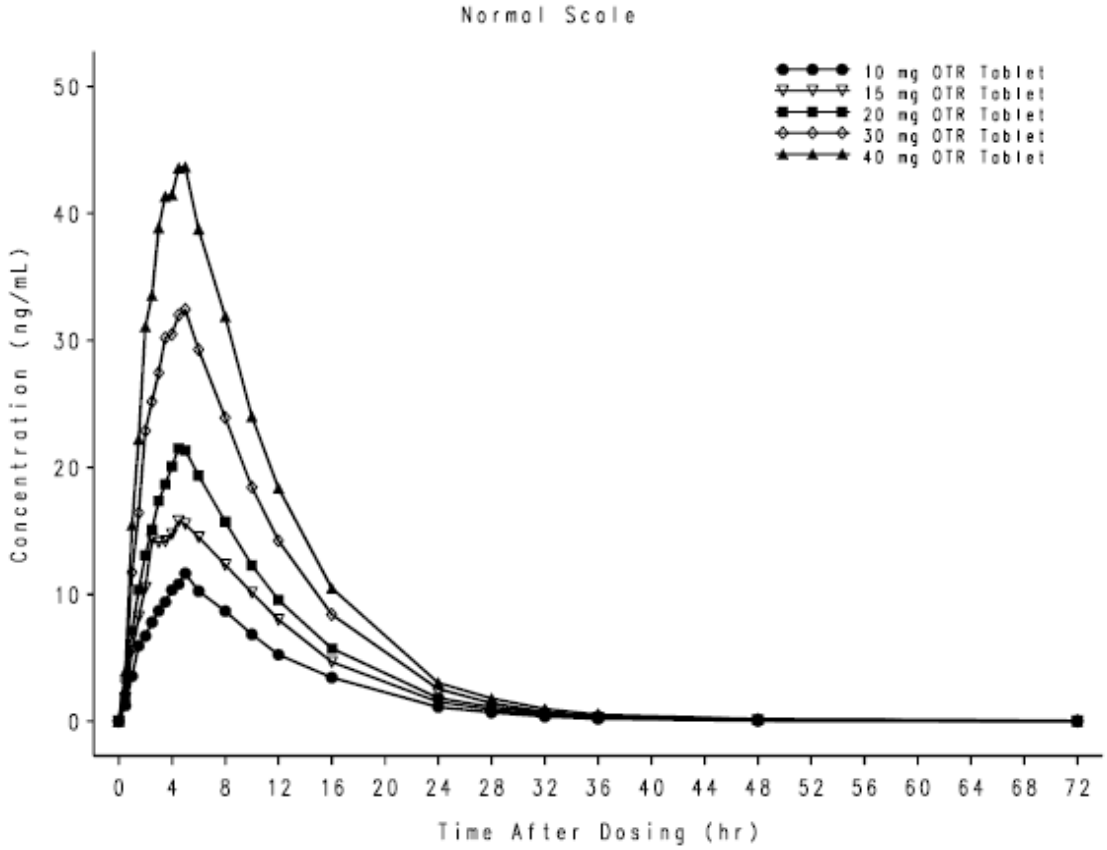
[b] Ratio of metric means for ln-transformed metric (expressed as a percent). Ln-transformed ratio transformed back to linear scale.

[c] 90% confidence interval for ratio of metric means (expressed as a percent). Ln-transformed confidence limits transformed back to linear scale.

[d] Intersubject variability, intrasubject variability, and intrasubject coefficient of variation (expressed as a percent) for ln-transformed metric from ANOVA.

The dose proportionality of all five OTR strengths, 10, 15, 20, 30, and 40 mg was assessed in the fasting state (Study # OTR-1006). Dose proportionality was demonstrated across all the five doses. Since 10 mg and 40 mg strengths were bioequivalent and there is dose-proportionality in this range across the two formulations (strengths), the two formulations are adequately linked in the dose range of 10 mg through 40 mg from the clinical pharmacology perspective.

Figure 3. Oxycodone Plasma-Concentration Time Profiles For Five OTR Strengths at Fasted State (Study # OTR-1006)



Based on *in vitro* dissolution data, there was no evidence of dose dumping or effect of alcohol on the OTR formulation. The data showed an inverse relationship between alcohol concentration (4%, 20% and 40%) and dissolution (drug release) profiles. As such, no *in vivo* study investigating the alcohol interaction is needed.

In terms of pediatric indications, the sponsor is requesting deferral to assess the safety and effectiveness of the product in pediatric population.

Per prior agreement between the Agency and the sponsor, if the two formulations are adequately linked by bioequivalence data, then no new clinical data were required. As such, no Clinical efficacy and safety studies were conducted in support of the OTR formulation.

Overall Conclusions:

Based on the data submitted in this NDA the following conclusions can be made:

- OTR 10 mg and 40 mg strengths are bioequivalent to the reference, currently marketed formulation in both fed and fasted states.

- OTR 10, 15, 20, 30, and 40 mg strengths demonstrated dose proportionality with respect to both Cmax and AUC. Since, there is dose-proportionality in this dose range for the currently approved formulation as well; the two products are satisfactorily linked in the dose range of 10 mg and 40 mg.

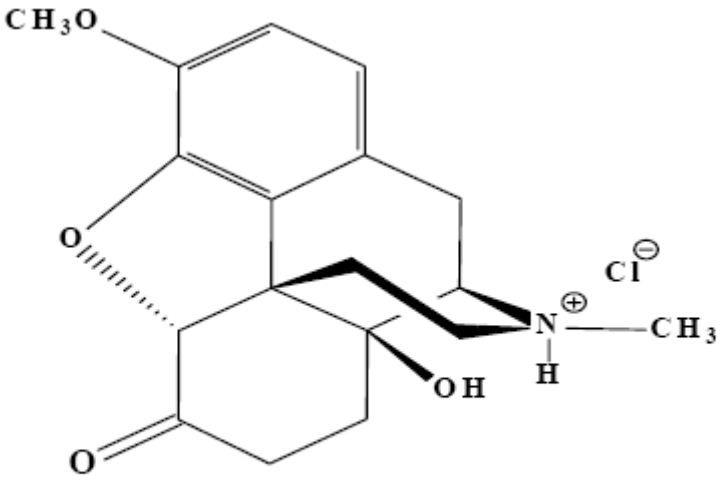
- Based on acceptable *in vitro* dissolution data, there was no evidence of dose dumping in the presence of different concentrations of alcohol (4% through 40% V/V). As such, no *in vivo* study is needed to investigate the alcohol interaction potential.

2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Oxycodone is an old opioid analgesic approved for the treatment of acute and chronic pain. The structural formula for oxycodone hydrochloride is shown below:



$C_{18}H_{21}NO_4 \bullet HCl$ MW 351.83

The drug is available in the market as immediate release and extended release tablets. The most relevant formulation to this NDA is the extended release formulation approved with the trade name, OxyContin® (oxycodone hydrochloride controlled-release), tablets at the following strengths: 10, 15, 20, 30, 40, 60, and 80 mg.

The new modified formulation (Oxycodone Tamper Resistant -OTR) will be available at the following five strengths: 10, 15, 20, 30, and 40 mg. The 80 mg strength will not be available as OTR. **However, it will remain in the market as the original formulation of OxyContin® 80mg.**

The sponsor conducted several PK/BE studies to link the proposed formulation with the currently marketed formulation of OxyContin® in fed and fasted states. In addition, *in vitro* dissolution studies were conducted with and without alcohol to investigate the potential of dose dumping. These studies will be discussed in more detail in the following sections of the review.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

Oxycodone is a pure opioid agonist. It is mainly used as analgesic to control moderate to severe pain.

Indications:

The primary indication of OxyContin® is for relief of moderate to severe pain when a continuous around the clock analgesic is needed for an extended period of time.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The product is administered Q12 hours with an individualized dosage dependent on the needs of the patient and the patients prior opioid analgesic use.

2.1.4 What are the Core Studies Submitted in this NDA?

In this NDA, 7 studies were submitted characterizing the PK of the new formulation under fed and fasted conditions.

Specifically, there were two main objectives from this program. The first is to establish the bioequivalence of 10 mg and 40 mg OTR tablets to the approved formulation of OxyContin® tablets under fed and fasted conditions (Studies OTR 1002, 1003, 1004, and 1005). The second objective is to establish the dose proportionality of all five strengths (10, 15, 20, 30, and 40 mg) under fasted condition (Study OTR-1006).

An *in vitro* dissolution/alcohol study was conducted to demonstrate the lack of dose dumping effect by alcohol on the extended release characteriscts of the formulation.

2.2 General Clinical Pharmacology

Based on the data from the studies submitted in this NDA and the historical data, the PK of oxycodone is summarized below.

Oxycodone is a pure *mu* opioid receptor agonist to produce analgesia. Its activity is primarily related to the parent drug, oxycodone. However, the drug is extensively metabolized to noroxycodone, oxymorphone, and noroxymorphone metabolites. However, these metabolits are rapidly glucuronidated and eliminated primarily in urine as both conjugated and unconjugated metabolites. The drug is metabolized mainly by CYP3A4 and CYP2D6.

The oral bioavailability of oxycodone is approximately 60% to 87%, suggesting low pre-systemic metabolism. The steady state is achieved within 24 to 36 hours of repeat administration of extended-release formulation.

From this NDA, dose proportionality was demonstrated between 10 to 40 mg dose range (see below, Study # 1006). Food does not appear to have significant effect on the absorption of oxycodone. The plasma protein binding is 45%.

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

No biological biomarker was used in this NDA. All data in this NDA were presented as comparative PK.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

All data in this NDA were based on measurement of the parent drug, oxycodone.

As stated earlier, oxycodone is extensively metabolized. Therefore, it is excreted mainly as metabolites in urine. However, based on the historical data, the metabolites have little clinical significance in terms of analgesia compared to the parent drug, oxycodone.

2.2.3 Exposure Response
2.2.3.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

The focus of this NDA development program is to demonstrate the comparative bioavailability for the OTR tablet relative to the marketed formulation of OxyContin®. Therefore, no PK/PD data was acquired in this submission to establish the relationship between oxycodone dose and efficacy.

2.2.3.3 Does this Drug Prolong the QT or QTc Interval?

No formal QTc study was conducted in this NDA to investigate the effect of oxycodone on QTc.

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters of oxycodone and its metabolites? How do the PK parameters change with time following chronic dosing?

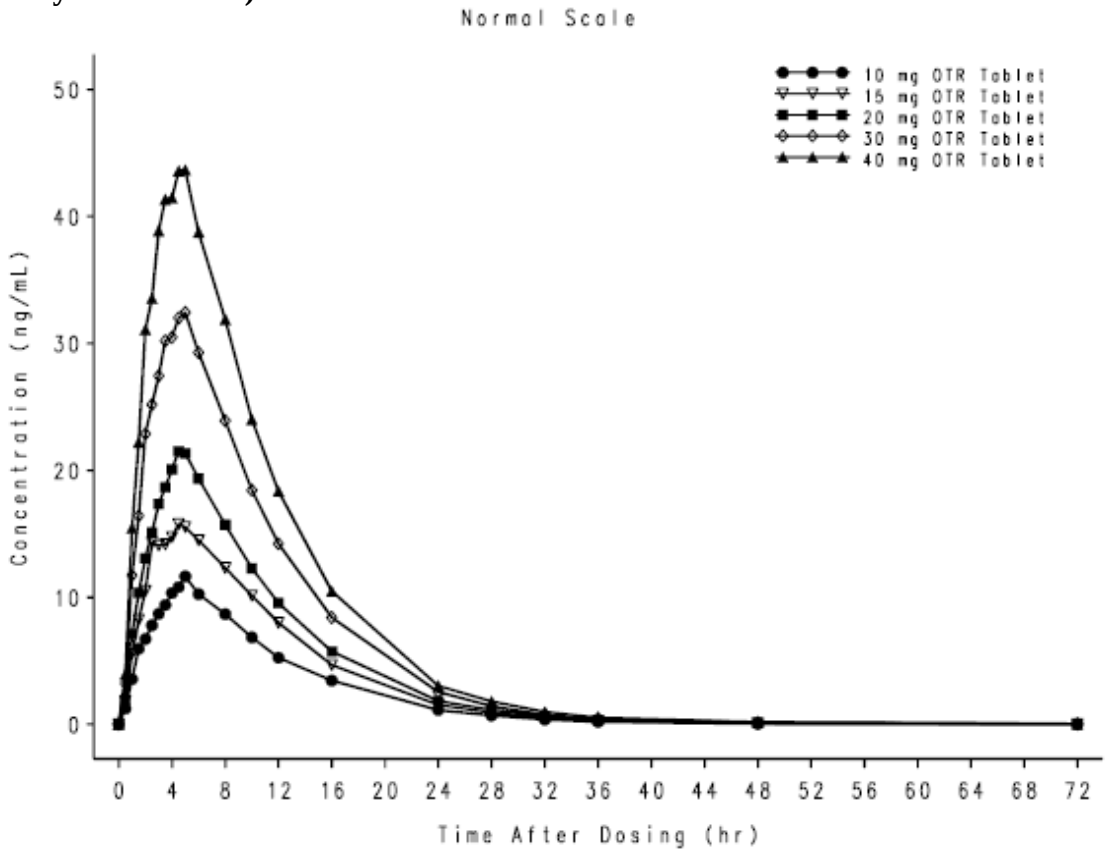
Single and Multiple dose PK data were previously obtained for the currently marketed formulation. Multiple dose PK studies were not needed for this product as bioequivalence was demonstrated between OTR and currently approved formulation.

2.2.4.2 Is the PK of Oxycodone dose-proportional?

The sponsor conducted one study to determine the dose proportionality among the five strengths; 10, 15, 20, 30, and 40 mg OTR tablet after a single dose in fasting state (Study # OTR-1006).

From this study the exposure between 10 to 40 mg was dose proportional with respect to both Cmax and AUC (**Figure 2.2.4.2.1)**.

Figure 2.2.4.2.1. Oxycodone Plasma-Concentration Time Profiles in Fasted State (Study # OTR-1006)



It should be noted that dose proportionality was established between 10 and 40 mg for the currently marketed formulation as well.

2.2.4.3 What is the Extent of Systemic Exposure After Oxycodone Administration?

No multiple dose study was conducted in this NDA.

2.3 Intrinsic factors

2.3.1 Does age, weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

No formal studies were conducted in special population in this NDA. However, based on known metabolic and excretion pathways of oxycodone and its metabolites, the current labeling for OxyContin® calls for dose titration in patients with hepatic impairment. The initial dose should be 1/3 to ½ of the usual dose.

2.4 Extrinsic factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, diet, smoking and alcohol on oxycodone use and pharmacodynamic effects were not evaluated in this NDA.

No specific studies were conducted to investigate the effect of extrinsic factors on the disposition of oxycodone in this NDA. However, based on the clinical experience other CNS depressant drugs such as alcohol, other opioids or illicit drugs may have additive effect on oxycodone.

However, the sponsor conducted specific study(s) to investigate the bioequivalence of OTR formulation in fed and fasted states. These studies will be discussed in the next sections below.

2.5 General Biopharmaceutics

DSI inspection was requested for study # OTR-1005. At that time of writing this review, DSI inspection report is not available. An addendum to the this review will be written capturing the implications of DSI findings once the DSI inspection report is available.

2.5.1 What is the BCS Class classification for Oxycodone?

This information was not provided by the sponsor in this NDA and it is not pertinent for this submission.

2.5.2 What is the effect of food on the BA of Oxycodone?

The sponsor conducted four studies to establish the bioequivalence between OTR 10 mg and 40mg strengths relative to the respective OxyContin® strengths in fasted and fed states (Studies OTR-1002, 1003, 10004, and 1005).

From these studies, there was no obvious effect of food on either OTR or OxyContin® plasma concentration time profiles for 10 mg (**Figures 2.5.2.1 and 2.5.2.2**) and 40 mg (**Figures 2.5.2.3 and 2.5.2.4**) strengths in fed and fasted conditions. The 90% CI for both Cmax and AUC were within 80% to 125% limits. Therefore, it can be concluded that OTR formulation is bioequivalent to Oxycontin® irrespective of presence or absence of food.

Figure 2.5.2.1. Oxycodone Plasma-Concentration Time Profiles of 10 mg Strength in Fed State (Study # OTR-1002)

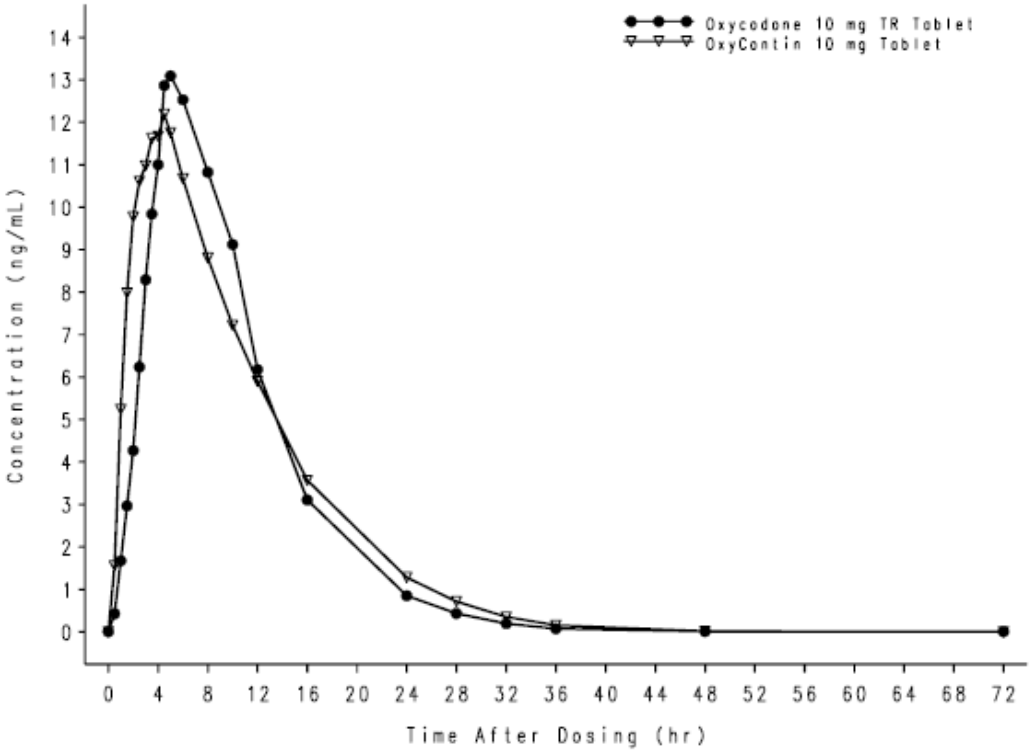


Figure 2.5.2.2. Oxycodone Plasma-Concentration Time Profiles of 10 mg Strength in Fasted State (Study # OTR-1003)

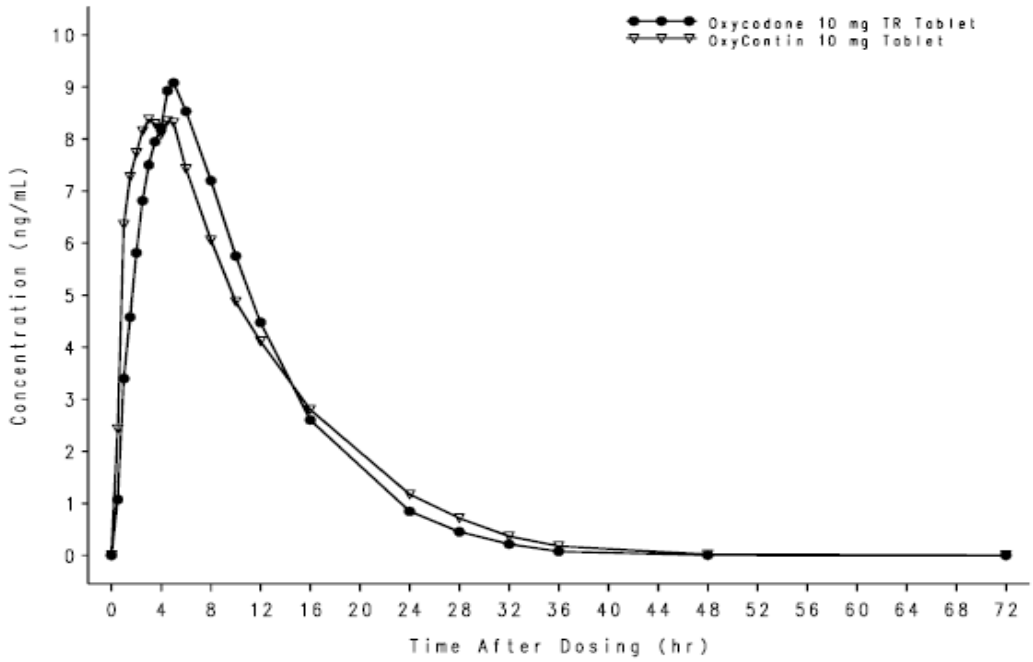


Figure 2.5.2.2. Oxycodone Plasma-Concentration Time Profiles of 40 mg Strength in Fed State (Study # OTR-1004)

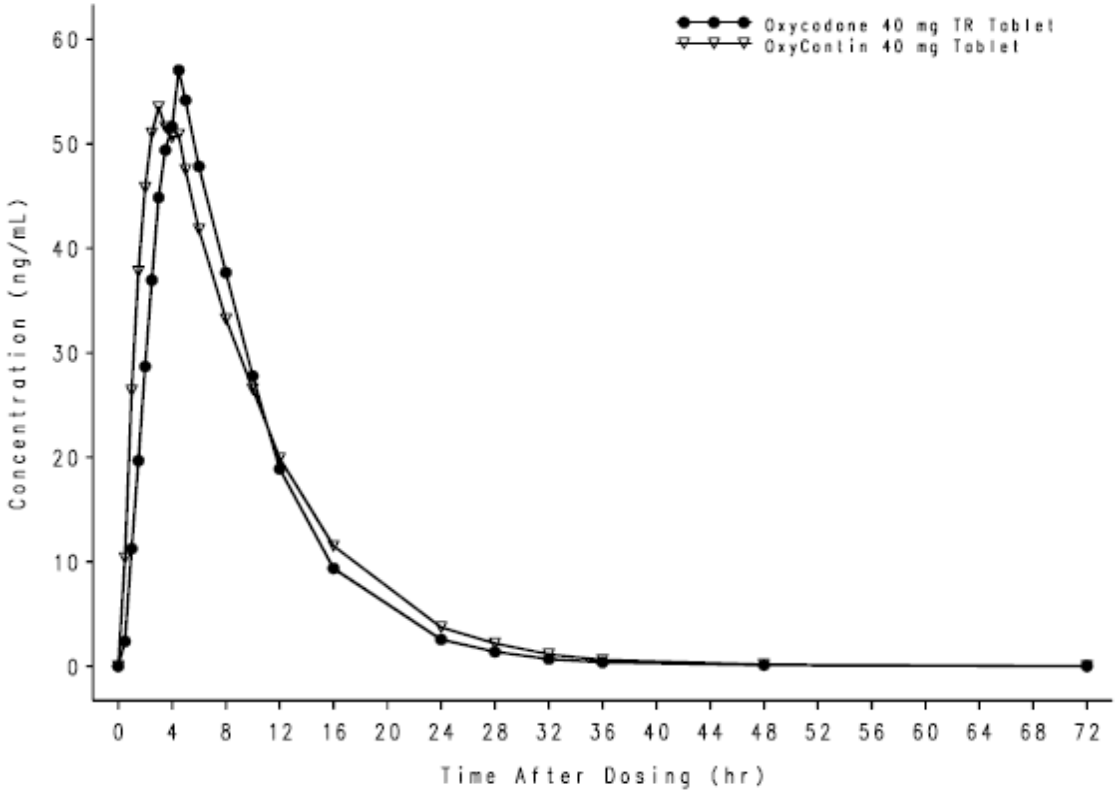
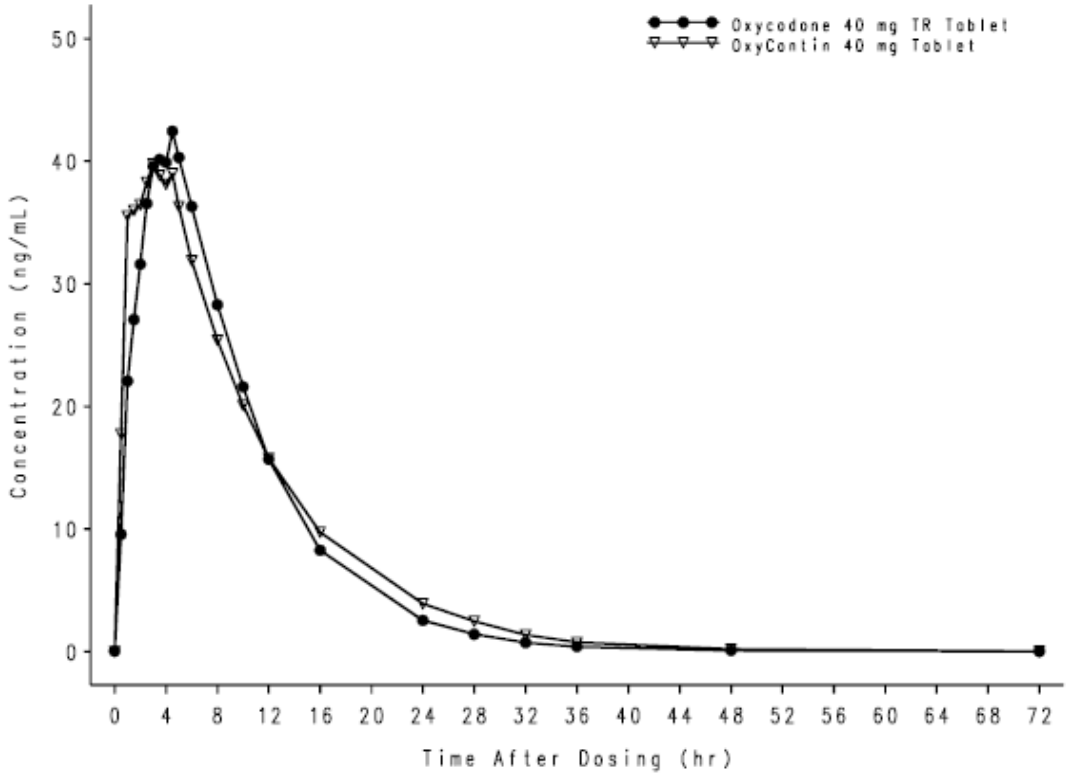


Figure 2.5.2.2. Oxycodone Plasma-Concentration Time Profiles of 40 mg Strength in Fasted State (Study # OTR-1005)



2.5.3 Was the to-be-marketed formulation used in the PK/Clinical trials?

The formulation used in the PK/BE studies is the final to-be-marketed formulation. No clinical (i.e., safety and efficacy) studies were conducted in support of the OTR formulation per the agreement reached between the Agency and the sponsor at the meeting dated October 26, 2006.

2.5.4 What are the Biopharmaceutical Characteristics of the Products?

OTR Tablets are an eroding matrix formulation of oxycodone hydrochloride where the release of drug is controlled by the polyethylene oxide matrix. The Description of the dosage form is provided in **Table 2.5.4.1**. However, for more details on the formulation composition see the ONDQA review.

Table 2.5.4.1. Description of Different Strengths of OTR Formulation

Tablet Strength	Tablet Description
Oxycodone HCl q12h 10mg TR Tablets	Round, (b) (4) white-colored, bi-convex tablets debossed with OP on one side and 10 on the other
Oxycodone HCl q12h 15 mg TR Tablets	Round, (b) (4) gray-colored, bi-convex tablets debossed with OP on one side and 15 on the other
Oxycodone HCl q12h 20 mg TR Tablets	Round, (b) (4) pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other
Oxycodone HCl q12h 30 mg TR Tablets	Round, (b) (4) brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other
Oxycodone HCl q12h 40mg TR Tablets	Round, (b) (4) yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other

It should be noted that the tablet cores have the same total weight and qualitative composition. The additional drug loading in the higher strengths is achieved by replacement of the (b) (4) with oxycodone. The tablet coatings applied for the purpose of differentiating the strengths of the oxycodone OTR tablets are the same as the currently used for OxyContin® Tablets, 10-40 mg (**NDA# 20-553**).

The tablets for all strengths are composed of a controlled-release core ((b) (4)) with a (b) (4) coat. The cores for all strengths have the same qualitative composition, (b) (4) . The cores of the 10 mg through 40 mg tablets have the same total weight. The sum of the (b) (4) and oxycodone hydrochloride weights for the 10 mg through 40 mg strengths is (b) (4) out of a total core weight of 150 mg. In terms of composition, the 10 mg and 40 mg strengths bracket the 15, 20, and 30 mg strengths.

Figure 2.5.4.2. Composition of 10 mg OTR Tablet

.

Oxycodone Hydrochloride 10 mg TR Tablets

Component	mg/tablet	Function	
(b) (4)			
Oxycodone HCl	10.0	Active Ingredient	USP
Polyethylene Oxide (b) (4)	(b) (4)	(b) (4)	NF
(b) (4)			
Magnesium Stearate			NF
			(b) (4)
Magnesium Stearate	(b) (4)		NF
			(b) (4)
Total	156.0		

(b) (4)

Figure 2.5.4.3. Composition of 15 mg OTR Tablet

Oxycodone Hydrochloride 15 mg TR Tablets

Component	mg/tablet	Function	
(b) (4)			
Oxycodone HCl	15.0	Active Ingredient	USP
Polyethylene Oxide (b) (4)		(b) (4)	NF
Magnesium Stearate			NF
			(b) (4)
Magnesium Stearate		(b) (4)	NF
			(b) (4)
Total	156.0		

(b) (4)

Figure 2.5.4.4. Composition of 20 mg OTR Tablet

Oxycodone Hydrochloride 20 mg TR Tablets

Component	mg/tablet	Function	
(b) (4)			
Oxycodone HCl	20.0	Active Ingredient	USP
Polyethylene Oxide (b) (4)	(b) (4)		NF
Magnesium Stearate			NF
(b) (4)			
Magnesium Stearate	(b) (4)		NF
(b) (4)			
Total	156.0		

(b) (4)

Figure 2.5.4.6. Composition of 40 mg OTR Tablet

Oxycodone Hydrochloride 30 mg TR Tablets

Component	mg/tablet	Function	
(b) (4)			
Oxycodone HCl	30.0	Active Ingredient	USP
Polyethylene Oxide (b) (4)	(b) (4)		NF
Magnesium Stearate			NF
(b) (4)			
Magnesium Stearate	(b) (4)		NF
(b) (4)			
Total	156.0		

(b) (4)

Figure 2.5.4.6. Composition of 40 mg OTR Tablet

Oxycodone Hydrochloride 40 mg TR Tablets

Component	mg/tablet	Function	
(b) (4)			
Oxycodone HCl	40.0	Active Ingredient	USP
Polyethylene Oxide (b) (4)	(b) (4)		NF
(b) (4)			
Magnesium Stearate			NF
(b) (4)			
Magnesium Stearate	(b) (4)		NF
(b) (4)			
Total	156.0		

(b) (4)

The (b) (4) coatings applied to the cores are cosmetic to differentiate the different strengths, and do not impact release or "tamper resistant" properties described above. The compositions of the coating materials used for the 10 mg through 40mg tablets are shown in **Table 2.5.4.7.**

Table 2.5.4.7. Composition of the Cosmetic Coating Used in OTR Formulation

%	10mg	15mg	20mg	30mg	40mg
Color	White	Grey	Pink	Brown	Yellow
(b) (4)					
Total	100	100	100	100	100

It should be noted that the polyethylene oxide used as the major excipient in OTR formulation. Its main function is to provide controlled release and tamper resistance characteristics of the formulation.

Alcohol and Dose Dumping

The sponsor conducted a specific *in vitro* study to investigate the effect of alcohol on dose dumping on the OTR formulation. This study is summarized briefly here.

The study was conducted using the NDA dissolution method (Apparatus 1 at a speed of 100 RPM and Sampling time points of 1,2, 4, 6, 8, 10, and 12 hours) in a medium containing simulated gastric fluid (SGF) without enzymes with 0%, 4%, 20%, and 40% v/v ethanol, respectively.

The data clearly show inverse relationship between percent release and ethanol concentration. The higher the ethanol concentration the lower the oxycodone release from the 10 mg and 40 mg tablet strengths (**Figure 2.5.4.1 and 2.5.4.2**).

Figure 2.5.4.1

Figure 4A. Dissolution Curves for OTR 10 mg in SGF and Ethanolic Media

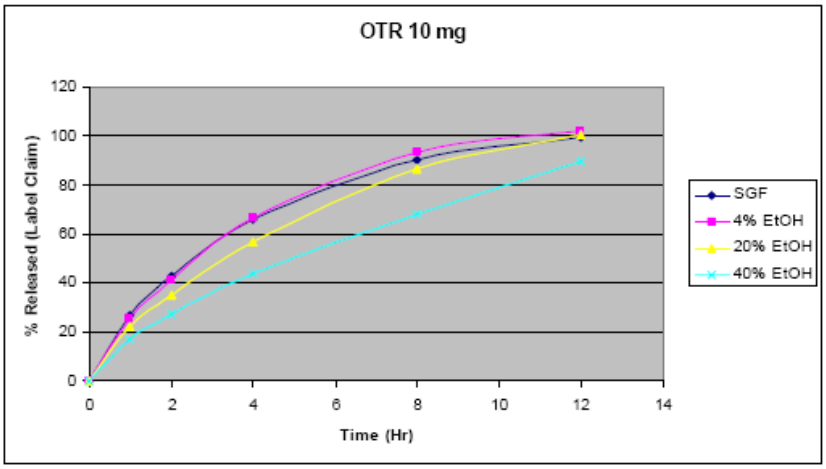
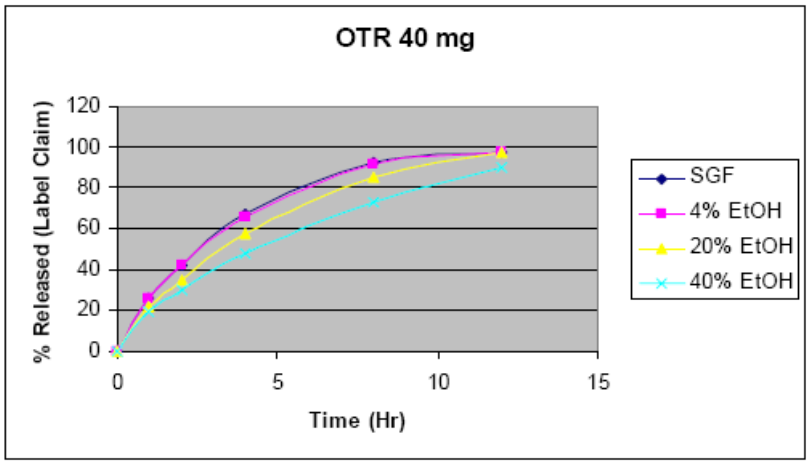


Figure. 2.5.4.1

Figure 4E. Dissolution Curves for OTR 40 mg in SGF and Ethanolic Media



Based on this *in vitro* data, it can be concluded that there is no evidence to show that the release of oxycodone was accelerated with alcohol. Conversely, the release was slower in the presence of alcohol. Therefore, no *in vivo* dose dumping can be expected with this formulation. As such, an *in vivo* study is not necessary to further investigate the alcohol interaction potential.

Support for the Intermediate Strengths, 15 mg, 20 mg, and 30 mg:

At the meeting held with the sponsor on October 26, 2006 the sponsor was advised to conduct a dose proportionality study across all proposed OTR dosage strengths due to the lack of proportionality of ingredients between different dose strengths and also to establish bioequivalence with the reference product, OxyContin®, at 10 mg and 40 mg strengths.

Based on the Agency's recommendation the sponsor conducted dose proportionality study (# OTR-006) and bioequivalence studies (# OTR-002 to 005) in fasted and fed states relative to OxyContin®. In addition, the sponsor conducted *in vitro* dissolution studies in three different media for all strengths.

The data from the human PK studies show dose proportionality among all strengths and also bioequivalence of the 10 and the 40 mg strengths to the approved formulation of OxyContin®, at fed and fasted states. Furthermore, based on the historical data for OxyContin®, the exposure of oxycodone (Cmax and AUC) is also dose proportional up to 80 mg (OxyContin® current approved label) with the current formulation. For *in vitro* data, the similarity factor (f2) was above 50 (ranging from 71 to 98) for all strengths and in all media. This indicates that there is no difference in the *in vitro* dissolution among all strengths.

Therefore, based on the above information, the sponsor was informed that no formal biowaiver request for the immediate strengths is necessary (letter dated August 10, 2007).

2.5.5 Are the method and dissolution specifications supported by the data provided by the sponsor?

The final method and proposed specifications for *in vitro* dissolution for all tablet strengths is summarized below:

Apparatus: 1 (Basket)
Medium: SGF (Application Media, without enzyme, pH 1.2)
Speed: 100 RPM
Sampling Time Points : 1, 2, 4, 6, 8, 10, and 12 hours.
Proposed Specifications: The following dissolution specs were submitted on March 13, 2008 (Serial Number 0013).

Strength	Time Points	Specs Range)
10 mg	1 hour 4 hour 12 hour	(b) (4)
15 mg	1 hour 4 hour 12 hour	
20 mg	1 hour 4 hour 12 hour	
30 mg	1 hour 4 hour 12 hour	
40 mg	1 hour 4 hour 12 hour	

The *in vitro* dissolution profiles in the four media, SGF without enzymes, USP Buffer pH 4.5, USP Buffer pH 6.8 Media 4, and USP Buffer pH 7.5 are shown in **Figures 2.5.5.1-4.**

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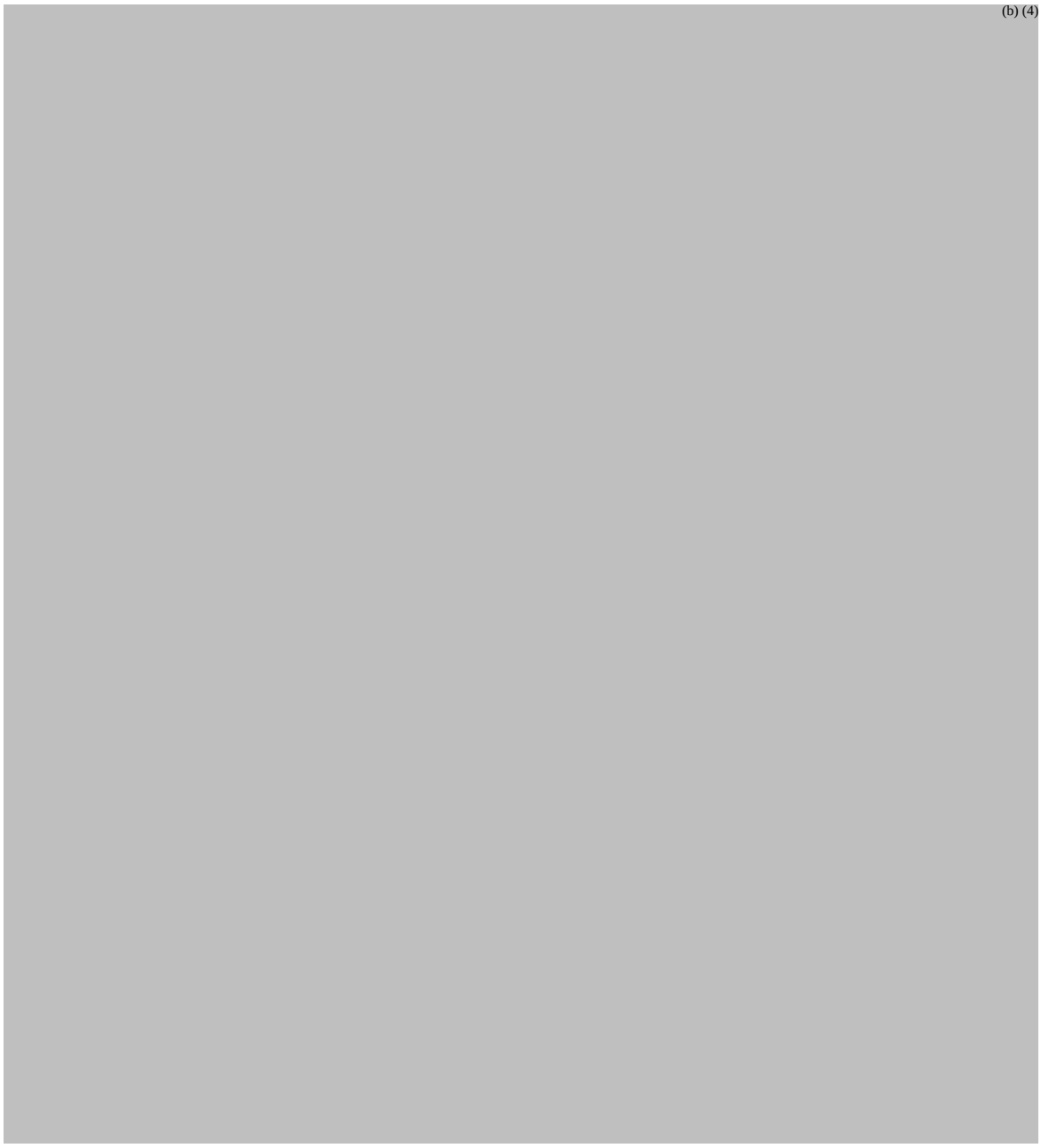

It should also be noted that the similarity factor (f2) values were all within 50 to 100 acceptance criteria indicating the dissolution profiles of all strengths are similar. For detail discussion and recommendation related to dissolution specifications and method acceptability, see ONDQA review.

2.6 Analytical Section

The plasma concentrations of oxycodone were determined by a validated LC-MS method. The limit of quantitation of the assay is 0.1 ng/mL. Overall, the assay validation data are satisfactory. The inter- and intra-day assay %CV is <10%.

3.0 Labeling Comments

An addendum to this review will be written separately summarizing the proposed labeling changes.

4.0 Appendices.

4.1 Sponsor's Proposed Label
(Original Label Submitted on November 29, 2007)

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4.2.2. Study # OTR-1002 (10 mg in Fed State)

Objective:

The primary objective of this study is to establish the BE of OTR 10 mg tablet relative to 10 mg OxyContin® in fed state.

Study Design:

This was a single dose, 2 periods, 2 treatments, crossover design in 82 healthy subjects as follows:

Treatment A (OTR, Test): 10 mg OTR tablets in fed state

Treatment B (OxyContin, Reference): 10 mg OTR tablet at fed state

Products Administration:

In both treatments each subject received 25 mg oral dose of naltrexone (opioid antagonist) to counteract the effect of oxycodone at -12 hours, 0, and 12 relative to the time of oxycodone administration.

Blood samples were collected at appropriate time points over 72 hours for the determination of oxycodone.

Results:

- There was no major difference in any of the PK parameters or profiles in both treatments (**Table 4.2.2.1 and Figure 4.2.2.1)**. The Tmax was slightly longer for OTR compared to oxyContin® (**Table 4.2.2.1).**

- The 90% CLs were within 80% to 125% under fed conditions (**Table 4.2.2.2).**

Table 4.2.2.1 PK Parameters in Fed State (Study # OTR1002).

PK Metric	Units		OxyContin® 10 mg tablet Treatment OC (Reference)	Oxycodone 10 mg TR tablet Treatment TR (Test)
AUC_t	(ng*hr/mL)	Mean	149	142
		SD	36.6	33.4
		N	81	79
AUC_{inf}	(ng*hr/mL)	Mean	150	143
		SD	36.7	33.5
		N	81	79
C_{max}	(ng/mL)	Mean	13.6	14.2
		SD	2.75	2.99
		N	81	79
t_{max} [a]	(hr)	Mean	3.50	5.00
		SD	1.50, 12.0	3.50, 10.0
		N	81	79
λ_z	(1/hr)	Mean	0.170	0.178
		SD	0.0283	0.0234
		N	81	79
$t_{½z}$	(hr)	Mean	4.21	3.96
		SD	0.861	0.593
		N	81	79
t_{lag}	(hr)	Mean	0.118	0.297
		SD	0.214	0.380
		N	81	79

Source: Table 14.2.2-1 (sequence = All).
[a] Median (min, max) shown for t_{max}.

Figure 4.2.2.1. Oxycodone Plasma-Concentration Time Profiles in Fed State (Study # OTR-1002)

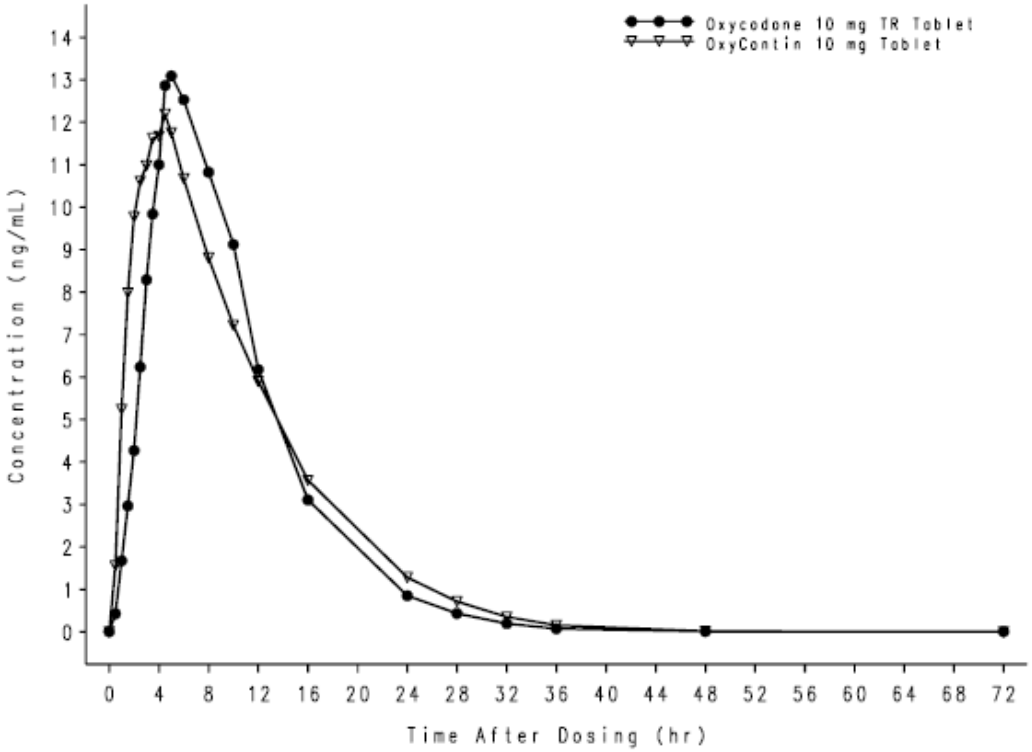


Table 4.2.2.2 Statistical Analysis of PK Parameters in Fed State (Study # OTR1002).

Metric	Units	LS Mean[a]				Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
		N	(Test)	N	(Reference)					
C_{max}	ng/mL	79	13.9	81	13.3	105	(101.06 , 108.51)	0.0243	0.0180	13
AUC_t	ng*hr/mL	79	138	81	145	95.7	(93.85 , 97.68)	0.0460	0.00562	8
AUC_{inf}	ng*hr/mL	79	139	81	146	95.6	(93.73 , 97.53)	0.0456	0.00557	7

Population: Full Analysis

Note: Test = Oxycodone 10 mg TR tablet; Reference = OxyContin® 10 mg tablet.

[a] Least squares mean from ANOVA. Natural log (ln) metric means calculated by transforming the ln means back to the linear scale, i.e., geometric means.

[b] Ratio of metric means for ln-transformed metric (expressed as a percent). Ln-transformed ratio transformed back to linear scale.

[c] 90% confidence interval for ratio of metric means (expressed as a percent). Ln-transformed confidence limits transformed back to linear scale.

[d] Intersubject variability, intrasubject variability, and intrasubject coefficient of variation (expressed as a percent) for ln-transformed metric from ANOVA.

Reviewer's Comments:

- This study provides information on the bioavailability of OTR 10 mg tablets relative to Oxycontin® 10 mg tablet in fed state.
- The two formulations are bioequivalent to each other under fed condition.
- There was slight delay in Tmax after OTR tablet compared to OxyContin®.

Conclusions:

From this study it can be concluded that the OTR 10 mg tablet is bioequivalent to 10 mg OxyContin® at fed condition.

4.2.3. Study # OTR-1003 (10 mg in Fasting State)

Objective:

The primary objective of this study is to establish the BE of OTR 10 mg tablet relative to 10 mg OxyContin® in fasted state.

Study Design:

This was a single dose, 2 periods, 2 treatments, crossover design in 83 healthy subjects as follows:

Treatment A (OTR, Test): 10 mg OTR tablets in fasted state

Treatment B (OxyContin, Reference): 10 mg OTR tablet at fasted state

Products Administration:

In both treatments each subject received 25 mg oral dose of naltrexone (opioid antagonist) to counteract the effect of oxycodone at -12 hours, 0, and 12 relative to the time of oxycodone administration.

Blood samples were collected at appropriate time points over 72 hours for the determination of oxycodone.

Results:

- There was no major difference in any of the PK parameter or profiles in both treatments (**Table 4.2.3.1 and Figure 4.2.3.1)**. The Tmax was lightly longer for OTR compared to oxyContin® (**Table 4.2.3.1).**

- The 90% CI was within 80% to 125% for the primary PK parameters (**Table 4.2.3.2).**

Table 4.2.3.1 PK Parameters in Fasted State (Study # OTR1003).

PK Metric	Units		OxyContin® 10 mg tablet Treatment OC (Reference)	Oxycodone 10 mg TR tablet Treatment TR (Test)
AUC_t	(ng*hr/mL)	Mean	113	110
		SD	28.3	25.0
		N	81	81
AUC_{inf}	(ng*hr/mL)	Mean	114	110
		SD	28.6	25.0
		N	81	81
C_{max}	(ng/mL)	Mean	9.38	9.60
		SD	1.92	2.49
		N	81	81
t_{max}[a]	(hr)	Median	3.00	5.00
		(Min, Max)	(1.00, 5.03)	(1.00, 12.0)
		N	81	81
λ_z	(1/hr)	Mean	0.158	0.172
		SD	0.0358	0.0239
		N	81	81
$t_{½z}$	(hr)	Mean	4.69	4.10
		SD	1.41	0.597
		N	81	81
t_{lag}	(hr)	Mean	0.0123	0.0247
		SD	0.111	0.109
		N	81	81

Source: Table 14.2.2-1 (sequence = All).
[a] Median (min, max) shown for t_{max}.

Figure 4.2.3.1. Oxycodone Plasma-Concentration Time Profiles in Fasted State (Study # OTR-1003)

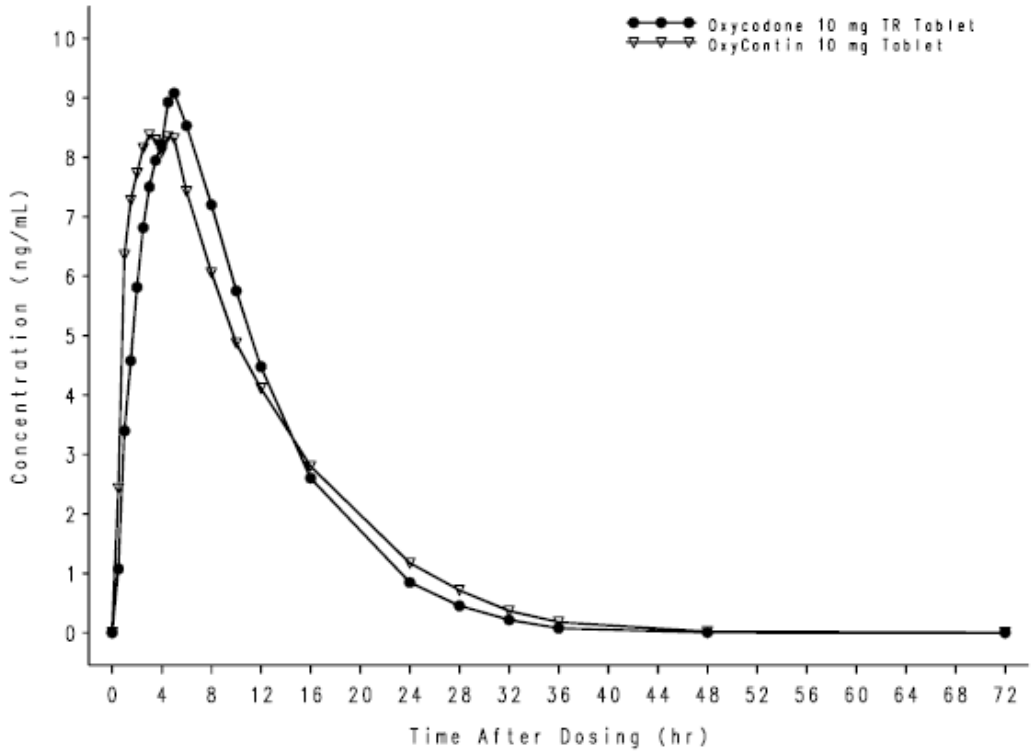


Table 4.2.3.2 Statistical Analysis of PK Parameters in Fasted State (Study # OTR1003).

Metric	Units	LS Mean[a] N	LS Mean[a] (Test)	LS Mean[a] N	LS Mean[a] (Reference)	Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
C_{max}	ng/mL	81	9.36	81	9.15	102	(99.35 , 105.42)	0.0423	0.0126	11
AUC_t	ng*hr/mL	81	107	81	109	98.3	(95.20 , 101.48)	0.0432	0.0146	12
AUC_{inf}	ng*hr/mL	81	108	81	110	98.0	(94.94 , 101.19)	0.0427	0.0146	12

Source: Table 14.2.3-1.

Note: Test = OTR 10 mg tablet; Reference = OxyContin® 10 mg tablet.

[a] Least squares mean from ANOVA. Natural log (ln) metric means calculated by transforming the ln means back to the linear scale, i.e., geometric means.

[b] Ratio of metric means for ln-transformed metric (expressed as a percent). Ln-transformed ratio transformed back to linear scale.

[c] 90% confidence interval for ratio of metric means (expressed as a percent). Ln-transformed confidence limits transformed back to linear scale.

[d] Intersubject variability, intrasubject variability, and intrasubject coefficient of variation (expressed as a percent) for ln-transformed metric from ANOVA.

Reviewer's Comments:

- This study provides information on the bioavailability of OTR 10 mg tablets relative to Oxycontin® 10 mg tablet in fasted state.

- The two formulations are bioequivalent to each other under fasted condition.

- There was slight delay in Tmax after OTR tablet compared to OxyContin®.

Conclusions:

From this study it can be concluded that the OTR 10 mg tablet is bioequivalent to 10 mg OxyContin® at fasted condition.

4.2.4. Study # OTR-1004 (40 mg in Fed State)

Objective:

The primary objective of this study is to establish the BE of OTR 40 mg tablet relative to 40 mg OxyContin® in fed state.

Study Design:

This was a single dose, 2 periods, 2 treatments, crossover design in 74 healthy subjects as follows:

Treatment A (OTR, Test): 40 mg OTR tablets in fed state

Treatment B (OxyContin, Reference): 40 mg OTR tablet at fed state

Products Administration:

In both treatments each subject received 50 mg oral dose of naltrexone (opioid antagonist) to counteract the effect of oxycodone at -12 hours, 0, 12,24, and 36 hours relative to the time of oxycodone administration.

Blood samples were collected at appropriate time points over 72 hours for the determination of oxycodone.

Results:

- There was no major difference in any of the PK parameter or profiles in both treatments (**Table 4.2.4.1 and Figure 4.2.4.1)**. The Tmax was lightly longer for OTR compared to OxyContin® (**Table 4.2.4.1).**

- The 90% CI was within 80% to 125% for the primary PK parameters (**Table 4.2.4.2).**

Table 4.2.4.1 PK Parameters in Fed State (Study # OTR1004).

PK Metric	Units		OxyContin® 40 mg tablet Treatment OC (Reference)	Oxycodone 40 mg TR tablet Treatment TR (Test)
AUC_t	(ng*hr/mL)	Mean	577	535
		SD	115	134
		N	80	76
AUC_{inf}	(ng*hr/mL)	Mean	579	537
		SD	115	135
		N	80	76
C_{max}	(ng/mL)	Mean	61.5	62.0
		SD	12.3	16.5
		N	80	76
t_{max} [a]	(hr)	Median	3.00	4.50
		(Min, Max)	1, 8	(1.50, 8.00)
		N	80	76
λ_z	(1/hr)	Mean	0.136	0.138
		SD	0.0503	0.0600
		N	80	76
$t_{½z}$	(hr)	Mean	6.53	6.92
		SD	4.58	5.16
		N	80	76
t_{lag}	(hr)	Mean	0.0563	0.0921
		SD	0.178	0.212
		N	80	76

Source: Table 14.2.2-1 (sequence = All)

[a] Median (min, max) shown for t_{max}.

Figure 4.2.4.1. Oxycodone Plasma-Concentration Time Profiles in Fed State (Study # OTR-1004)

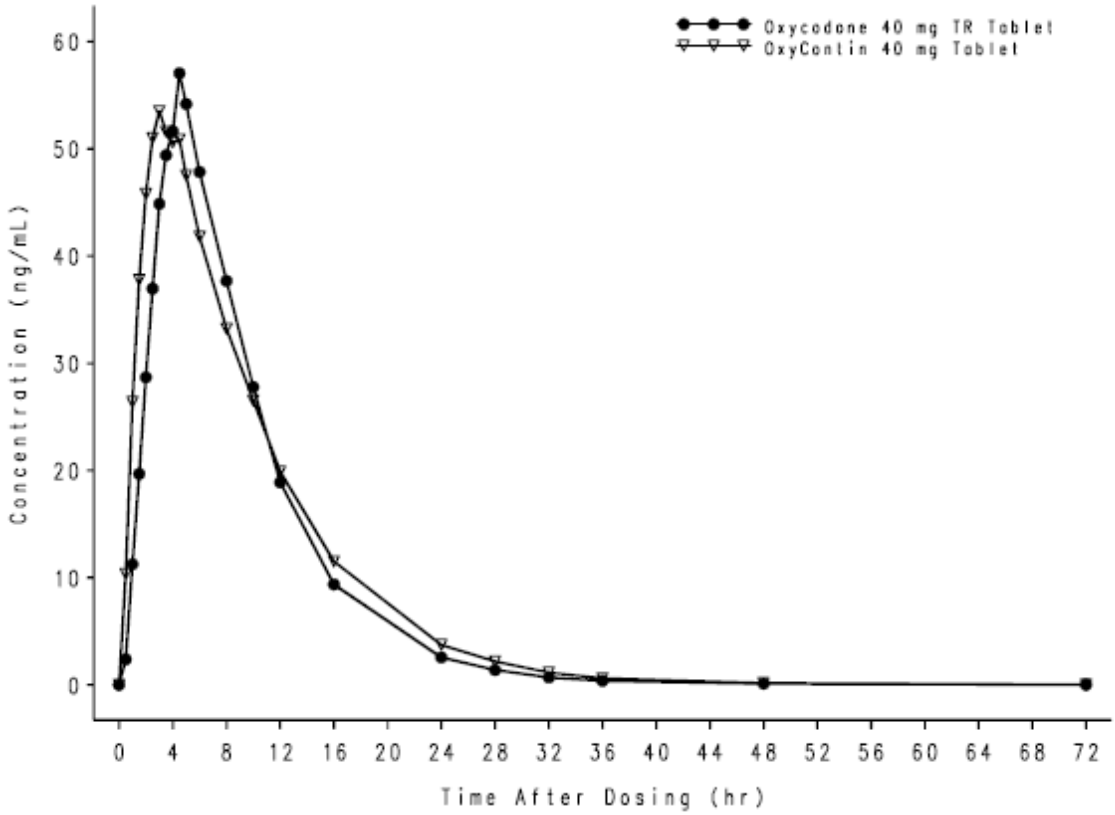


Table 4.2.4.2 Statistical Analysis of PK Parameters in Fed State (Study # OTR1004).

Metric	Units	LS Mean[a] N	LS Mean[a] (Test)	LS Mean[a] N	LS Mean[a] (Reference)	Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
C_{max}	ng/mL	76	59.8	80	59.9	99.9	(95.40 , 104.52)	0.0356	0.0274	17
AUC_t	ng*hr/mL	76	517	80	558	92.6	(90.13 , 95.13)	0.0606	0.00928	10
AUC_{inf}	ng*hr/mL	76	519	80	560	92.6	(90.11 , 95.09)	0.0605	0.00922	10

Population: Full Analysis

Note: Test = Oxycodone 40 mg TR tablet; Reference = OxyContin® 40 mg tablet.

[a] Least squares mean from ANOVA. Natural log (ln) metric means calculated by transforming the ln means back to the linear scale, i.e., geometric means.

[b] Ratio of metric means for ln-transformed metric (expressed as a percent). Ln-transformed ratio transformed back to linear scale.

[c] 90% confidence interval for ratio of metric means (expressed as a percent). Ln-transformed confidence limits transformed back to linear scale.

[d] Intersubject variability, intrasubject variability, and intrasubject coefficient of variation (expressed as a percent) for ln-transformed metric from ANOVA.

Reviewer's Comments:

- This study provides information on the bioavailability of OTR 40 mg tablets relative to Oxycontin® 40 mg tablet in fed state.

- The two formulations are bioequivalent to each other under fed condition.

Conclusions:

From this study it can be concluded that the OTR 40 mg tablet is bioequivalent to 40 mg OxyContin® at fed condition.

4.2.5. Study # OTR-1005 (40 mg in Fasted State)

Objective:

The primary objective of this study is to establish the BE of OTR 40 mg tablet relative to 40 mg OxyContin® in fasted state.

Study Design:

This was a single dose, 2 periods, 2 treatments, crossover design in 80 healthy subjects as follows:

Treatment A (OTR, Test): 40 mg OTR tablets in fasted state

Treatment B (OxyContin, Reference): 40 mg OTR tablet at fasted state

Products Administration:

In both treatments, each subject received 50 mg oral dose of naltrexone (opioid antagonist) to counteract the effect of oxycodone at -12 hours, 0, 12,24, and 36 hours relative to the time of oxycodone administration.

Blood samples were collected at appropriate time points over 72 hours for the determination of oxycodone.

Results:

- There was no major difference in any of the PK parameter or profiles in both treatments (**Table 4.2.5.1 and Figure 4.2.5.1)**. The Tmax was lightly longer for OTR compared to oxyContin® (**Table 4.2.5.1).**

- The 90% CI was within 80% to 125% for the primary PK parameters (**Table 4.2.5.2).**

Table 4.2.5.1 PK Parameters in Fasted State (Study # OTR1005).

PK Metric	Units		OxyContin® 40 mg tablet Treatment OC (Reference)	Oxycodone 40 mg TR tablet Treatment TR (Test)
AUC_t	(ng*hr/mL)	Mean	477	453
		SD	119	116
		N	82	85
AUC_{inf}	(ng*hr/mL)	Mean	480	454
		SD	120	116
		N	82	85
C_{max}	(ng/mL)	Mean	48.4	47.4
		SD	10.9	12.9
		N	83	85
t_{max}[a]	(hr)	Median	2.50	4.00
		(Min, Max)	(0.500, 5.00)	(1.50, 6.00)
		N	83	85
λ_z	(1/hr)	Mean	0.138	0.151
		SD	0.0510	0.0522
		N	82	85
$t_{½z}$	(hr)	Mean	6.12	5.79
		SD	3.45	4.00
		N	82	85
t_{lag}	(hr)	Mean	0.00610	0
		SD	0.0552	0
		N	82	85

Source: Table 14.2.2-1 (sequence = All)
[a] Median (min, max) shown for t_{max}.

Figure 4.2.5.1. Oxycodone Plasma-Concentration Time Profiles in Fasted (Study # OTR-1005)

Metric	Units	LS Mean[a] N	(Test)	N	(Reference)	Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
C_{max}	ng/mL	85	46.1	83	47.7	96.6	(92.80 , 100.56)	0.0411	0.0232	15
AUC_t	ng*hr/mL	85	442	83	463	95.5	(92.93 , 98.18)	0.0585	0.0107	10
AUC_{inf}	ng*hr/mL	85	444	82	468	94.8	(92.42 , 97.24)	0.0568	0.00901	10

Population: Full Analysis

Note: Test = Oxycodone 40 mg TR tablet; Reference = OxyContin® 40 mg tablet.

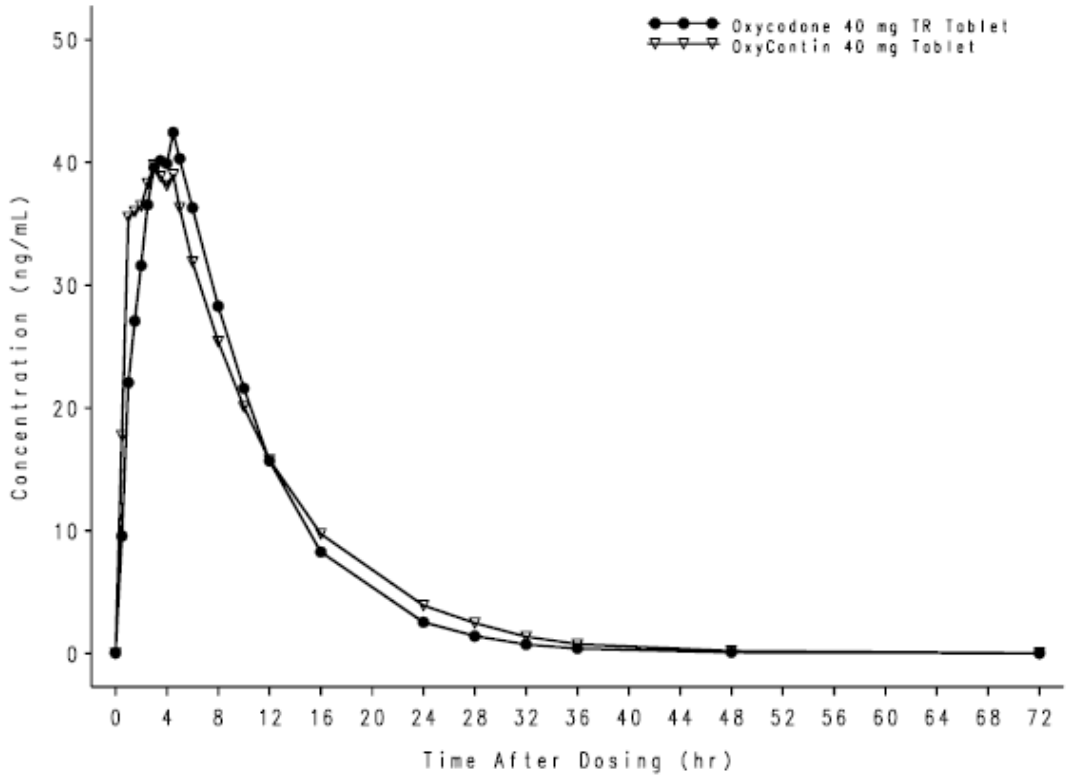
[a] Least squares mean from ANOVA. Natural log (ln) metric means calculated by transforming the ln means back to the linear scale, i.e., geometric means.

[b] Ratio of metric means for ln-transformed metric (expressed as a percent). Ln-transformed ratio transformed back to linear scale.

[c] 90% confidence interval for ratio of metric means (expressed as a percent). Ln-transformed confidence limits transformed back to linear scale.

[d] Intersubject variability, intrasubject variability, and intrasubject coefficient of variation (expressed as a percent) for ln-transformed metric from ANOVA.

Figure 4.2.4.2. Oxycodone Plasma-Concentration Time Profiles in Fasted State (Study # OTR-1005)



Reviewer's Comments:

- This study provides information on the bioavailability of OTR 40 mg tablets relative to Oxycontin® 40 mg tablet in fasted state.

- The two formulations are bioequivalent to each other under fasted condition.

Conclusions:

From this study it can be concluded that the OTR 40 mg tablet is bioequivalent to 40 mg OxyContin® under fasted condition.

4.2.6. Study # OTR-1006 (Dose Proportionality Study at Fasted State)

Objective:

The primary objective of this study is to establish the dose proportionality for the five strengths 10, 15, 20, 30, and 40 mg OTR in fasted state.

Study Design:

This was a single dose, 5 treatment, crossover design in 52 healthy subjects as follows:

Treatment A (10 mg OTR): 10 mg OTR tablets in fasted state

Treatment B (15 mg OTR): 15 mg OTR tablets in fasted state

Treatment C (20 mg OTR): 12 mg OTR tablets in fasted state

Treatment D (30 mg OTR): 30 mg OTR tablets in fasted state

Treatment E (40 mg OTR): 40 mg OTR tablets in fasted state

Products Administration:

In both treatments, each subject received 50 mg oral dose of naltrexone (opioid antagonist) to counteract the effect of oxycodone at -12 hours, 0, 12, 24, and 36 hours relative to the time of oxycodone administration.

Blood samples were collected at appropriate time points over 72 hours for the determination of oxycodone.

Results:

- There was proportional increase in both Cmax and AUC of oxycodone with increasing the dose from 10 to 40 mg (**Table 4.2.6.1 and Figure 4.2.6.1)**. In addition, the dose normalized values of Cmax and AUC are constant across strengths.

Table 4.2.6.1 PK Parameters in Fasted State (Study # OTR1006).

PK Metric	Units		10 mg OTR Tablet	15 mg OTR Tablet	20 mg OTR Tablet	30 mg OTR Tablet	40 mg OTR Tablet
AUC_t	(ng*hr/mL)	Mean	135	194	247	375	495
		SD	37.1	54.3	60.4	90.9	132
		N	44	44	45	42	47
DN AUC_t[a]	(ng*hr/mL)	Mean	135	129	123	125	124
		SD	37.1	36.2	30.2	30.3	33.0
		N	44	44	45	42	47
AUC_{inf}	(ng*hr/mL)	Mean	136	196	248	377	497
		SD	37.3	54.9	61.1	91.2	133
		N	44	44	45	42	47
DN AUC_{inf}[a]	(ng*hr/mL)	Mean	136	130	124	126	124
		SD	37.3	36.6	30.5	30.4	33.1
		N	44	44	45	42	47
C_{max}	(ng/mL)	Mean	11.5	16.8	22.7	34.6	47.4
		SD	3.06	4.91	5.73	7.43	14.0
		N	44	44	45	42	47
DN C_{max}[a]	(ng/mL)	Mean	11.5	11.2	11.4	11.5	11.9
		SD	3.06	3.27	2.87	2.48	3.50
		N	44	44	45	42	47

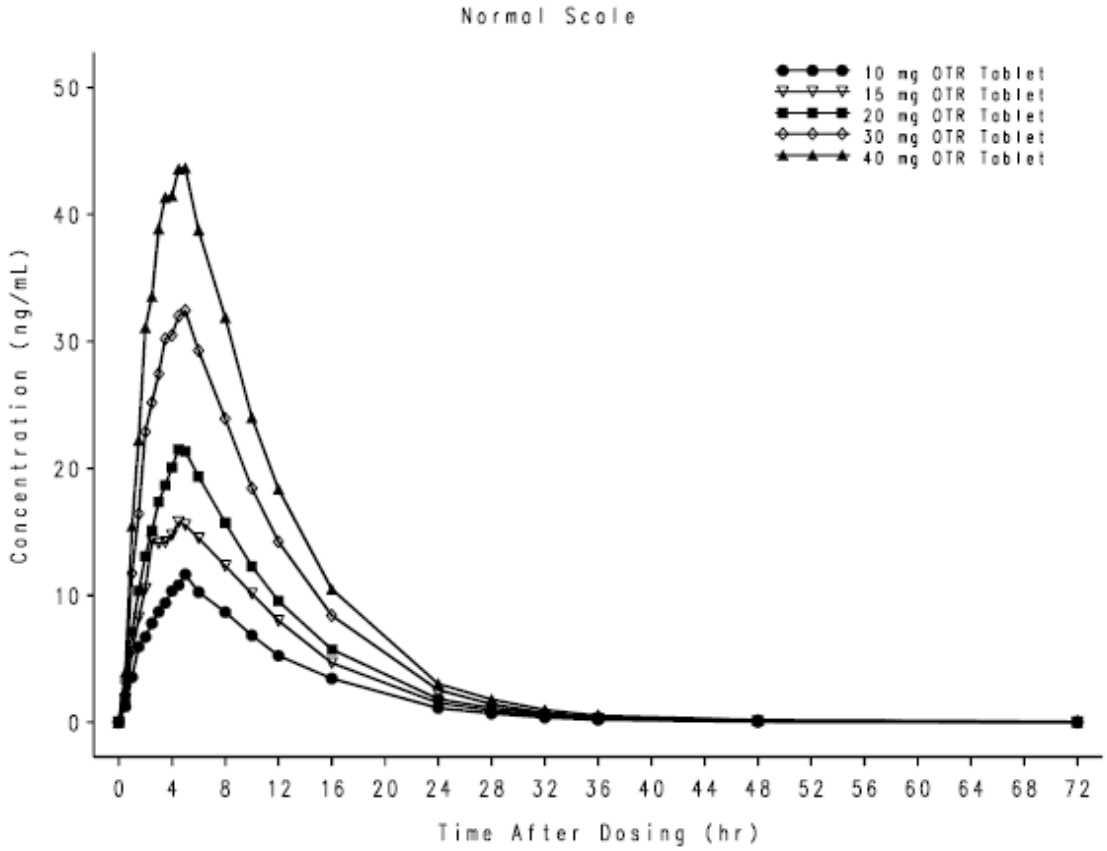
Source: Tables 14.2.2-1a and 14.2.2-2a.
[a] DN indicates a dose-normalized metric, where the metric has been normalized to a dose of 10 mg where applicable.

Table 4.2.6.1 (Continued, Study # OTR1006)

PK Metric	Units		10 mg OTR Tablet	15 mg OTR Tablet	20 mg OTR Tablet	30 mg OTR Tablet	40 mg OTR Tablet
t_{max}[b]	(hr)	Median	5.00	4.50	4.50	4.50	4.50
		(Min, Max)	(2.50, 8.00)	(2.50, 6.00)	(2.00, 8.00)	(2.50, 8.00)	(2.50, 8.00)
		N	44	44	45	42	47
λ_z	(1/hr)	Mean	0.153	0.145	0.137	0.127	0.128
		SD	0.0380	0.0438	0.0465	0.0519	0.0555
		N	44	44	45	42	47
$t_{½z}$	(hr)	Mean	5.13	5.43	5.87	7.08	7.10
		SD	2.82	2.65	2.76	4.64	4.35
		N	44	44	45	42	47
t_{lag}	(hr)	Mean	0	0.0227	0.0111	0.0119	0.0106
		SD	0	0.105	0.0745	0.0772	0.0729
		N	44	44	45	42	47

Source: Tables 14.2.2-1a and 14.2.2-2a.
[b] Median (min, max) show for t_{max}.

Figure 4.2.6.1. Oxycodone Plasma-Concentration Time Profiles (Study # OTR-1006)



Reviewer's Comments:

- This study provides information on the dose proportionality across the five strengths in fasted healthy subjects.

- The five strengths demonstrate dose proportionality in both Cmax and AUC.

Conclusions:

From this study, it can be concluded that the exposure after the five strengths, 10, 15, 20, 30, and 40 mg is dose proportional.

4.3 Consult Review (Pharmacometric Review)

No pharmacometric consult was needed for this NDA.

4.4 Filing Memo:

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-272	Brand Name	OxyContin®
OCP Division (I, II, III, IV, V)	II	Generic Name	Oxycodone
Medical Division	Anesthesia, Analgesia, and Rheumatology Products	Drug Class	Opioid Analgesic
OCP Reviewer	Sayed (Sam) Al-Habet, RP.h., Ph.D.	Indication(s)	Pain
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Tablet
		Dosing Regimen	10-40 mg BID
Date of Submission	November 29, 2007	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	Purdue Pharma
PDUFA Due Date		Priority Classification	Priority
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				

Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**x**	**5**		
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**		***In vitro* alcohol interaction**
Dissolution:	**x**	**ONDQA will review**		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**8**		
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	**X**	**Bioavailability/bioequivalent studies formulation and to be marketed formulation is the same**
Comments sent to firm ?	**X**	
QBR questions (key issues to be considered)	**1) Has the sponsor adequately characterized the PK of the drug product?** **The sponsor conducted adequate PK studies to establish the bio-equivalency between the currently marketed formulation and the proposed formulation.** **2) Is the new formulation bioequivalent to the currently marketed formulations under fasting and fed conditions?** **The sponsor conducted study to address this question.** **3) Does the timing of drug products administration need to be adjusted relative to meal consumption?** **The sponsor conducted study to investigate the effect of food on the bioavailability of the drug.** **4) Is the new formulation resistant to alcohol interaction and consequent dose dumping?** **The sponsor conducted *in vitro* study to address this question.**	
Other comments or information not included above	**DSI Inspection of study # OTR 1005 was requested.**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Slides

Clinical Pharmacology Review
Filing Meeting
(NDA 22-272 Oxycontin)
(January 8, 2008)

Sayed (Sam) Al Habet, R.Ph., Ph.D.
and
Suresh Doddapaneni, Ph.D.

1

Submission Summary

NDA #:	22,272
Date of Submission:	November 30, 2007
Generic Name:	Oxycodone
Trade Name:	Oxycontin®
Formulation:	Tablet (Oxycodone Tamper Resistant –PCR)
Route of Administration:	Oral
Indications:	Pain
Type of Submission:	Original NDA
Sponsor:	PURDUE
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D
Team Leader:	Suresh Doddapaneni, Ph.D.

2

Overview

General:

- 505(b)2 application
- Strengths: 10, 15, 20, 30, and 40 mg
- Six studies:
  - Pilot
  - BE (10 mg and 40 mg)
  - Dose proportionality (10, 15, 20, 30, and 40 mg)
  - Effect of food
- *In vitro* alcohol interaction
- Safety and efficacy: Cross reference of original NDA (#20-553)for OxyContin.

3

Listing of Studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	OTR1001	Pilot, PK, Relative BA	Randomized Cross-over	Tablet, 10 mg, single dose, oral	34	Healthy Subjects	Single dose	Ongoing; Synoptic
BE	OTR1002	Comparison of new formulation to marketed formulation	Randomized Cross-over	Tablet, 10 mg, single dose, oral	84	Healthy Subjects	Single dose	Ongoing; Full
	OTR1003	Comparison of new formulation to marketed formulation	Randomized Cross-over	Tablet, 10 mg, single dose, oral	84	Healthy Subjects	Single dose	Ongoing; Full
	OTR1004	Comparison of new formulation to marketed formulation	Randomized Cross-over	Tablet, 40 mg, single dose, oral	84	Healthy Subjects	Single dose	Ongoing; Full
	OTR1005	Comparison of new formulation to marketed formulation	Randomized Cross-over	Tablet, 40 mg, single dose, oral	84	Healthy Subjects	Single dose	Ongoing; Full
PK/ BA	OTR1006	Dose proportionality	Randomized Cross-over	Tablet, 10-40mg, single dose, oral	54	Healthy Subjects	Single dose	Ongoing; Full

4

Pivotal BE Studies (#1002-1005)

- Dose : 10 and 40 mg strengths
- Design: Single dose, crossover, fed/fasted
- N=84 healthy subjects

Table 5. Pivotal BE Studies: OTR1002 – OTR1005

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Target Number of Subjects	Age	Duration of Treatment	Blood sampling for PK
BE	OTR1002-1005	Comparisons of new formulation to marketed formulation	Randomized Cross-over, under fed/fasting conditions	Tablet, 10 and 40 mg, single dose, oral	84 Healthy Subjects	aged 18 to 50 years	Single dose 6-day washout separated dose administrations	At time points through 72 hours post study drug

5

Summary of PK Data (Pivotal BE Studies #1002-1005)

Table 6: Pharmacokinetic Results Following Oral Administration of OTR in the Fed and Fasted States

Study	Dose	Condition	Cmax		AUCt	
			LS Mean Ratio	90% CI	LS Mean Ratio	90% CI
OTR1002	10 mg	Fed	105.0	[101.06, 108.51]	95.7	[93.85, 97.68]
OTR1003	10 mg	Fasted	102.0	[99.35, 105.42]	98.3	[95.20, 101.48]
OTR1004	40 mg	Fed	99.9	[95.40, 104.52]	92.6	[90.13, 95.13]
OTR1005	40 mg	Fasted	96.6	[92.80, 100.56]	95.5	[92.93, 98.18]

6

Dose Proportionality (Study # 1006)

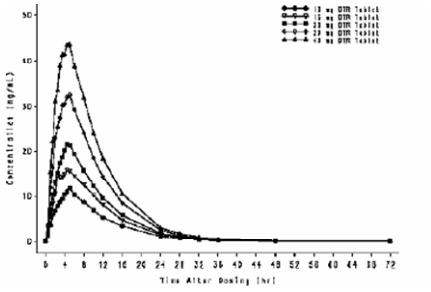
- Dose : 10, 15, 20, 30, and 40 mg strengths
- Design: Single dose, Four-way crossover
- N=52 healthy subjects

Table 7. OTR 1006 Pivotal Dose Proportionality Study

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Age	Duration of Treatment	Blood sampling for PK
PK/BA	OTR1006	Dose Proportionality	Randomized Cross-over, under fasting conditions	Tablet, 10, 15, 20, 30 and 40 mg, single dose, oral	54 Healthy Subjects	aged 18 to 50 years	Single dose 6-day washout separated dose administrations	At time points through 72 hours post study drug

7

PK Profiles
(Dose Proportionality Study # 1006)



8

Recommendation

From the clinical pharmacology perspective, the application is fileable.

9

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/s/

Sayed Al-Habet
4/7/2008 10:23:24 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
4/7/2008 12:17:26 PM
BIOPHARMACEUTICS

Appendix II
Addendum Dated May 23, 2008 to Original Review Dated April 7, 2008

Addendum to Primary Clinical Pharmacology Review

NDA: 22-272	**Dates of Submission:**	November 29, 2007

Generic Name	Oxycodone
Brand Name:	**Oxycontin®**
Formulation:	Extended Release Tablets
Strengths:	10, 15, 20, 30, 40, and 80 mg
OCP Division	Division of Clinical Pharmacology II
OND Division	Division of Anesthesia, Analgesia, and Rheumatology Products
Route of Administration:	Oral
Indication:	-Management of moderate to severe pain when a continuous, around-the clock analgesic is needed for an extended period of time. –Not for use as a prn analgesic or in the immediate post-operative period (the first 12 to 24 hours following surgery).
Dosage and Administration:	-Q12h (individualized) -Use low initial doses in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications. –For patients already receiving opioids, use standard conversion ratio estimates.
Type of Submission:	Original NDA; Priority
Sponsor:	Purdue Pharma Stamford, CT
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.

BACKGROUND:

This review is an addendum to the original Clinical Pharmacology review for NDA 22-272 dated April 7, 2008. At the time of completion of the original review, report of the Division of Scientific Investigations (DSI) inspection findings of study OTR-1005 was not available. The decision on the acceptability of the Clinical Pharmacology data submitted to the NDA was deferred until a review of the DSI inspection report is completed. In addition, review of the sponsor's proposed labeling changes was also deferred. This addendum will include a discussion of the DSI findings of study OTR-1005 as it relates to the acceptability of the data and preliminary labeling comments.

DISCUSSION:

1. **DSI Inspection findings:**

DSI's original memo dated May 7, 2008 identified two significant issues. Subsequent to this, DSI received a response from (b) (4). (The CRO for study OTR-1005) addressing the issues identified in form 483. DSI then amended the original memo with an addendum on May 14, 2008. The two issues as stated in the original memo are;

"

- *The oxycodone bioanalytical method was not evaluated for hemolyzed samples. Approximately 200 study samples (including 8 Cmax samples) collected in Study OTR1005 were hemolyzed. The sponsor should provide data to address accuracy of the assay in hemolyzed samples (item 1 above).*

- *Accuracy of period 1 oxycodone concentrations for subjects 5040-5042 in run 07307cga14a and subjects 5043, 5044, and 5046 in run 07307cgb14a cannot be assured (item 2 above)."*

In the addendum to the memo dated May 15, 2008, based on data submitted by (b) (4), DSI concluded that hemolysis had no impact on the accuracy of oxycodone bioanalytical method putting this issue to rest. However, with respect to the accuracy of period 1 oxycodone concentrations in runs 07307cga14a and 07307cgb14a, DSI concluded that (b) (4) in their response did not provide direct documentation clearing this issue and that the original recommendation regarding this remains unchanged.

As such, before data from study OTR1005 can be accepted, sponsor should reanalyze and submit the data from study OTR1005 demonstrating bioequivalence after completely excluding data from subjects 5040, 5041, 5042, 5043, 5044, and 5045. Alternatively, sponsor can reanalyze the plasma concentrations as identified and confirm the original values.

2. **Labeling Comments:**

Detailed labeling comments will be provided upon the submission of acceptable bioequivalence data as described above. However, this addendum will address one significant issue related to CYP3A metabolic pathway of oxycodone and the potential for drug-drug interactions involving inhibitors of CYP3A enzyme.

Based on two publications investigating the *in vitro* metabolism and *in vivo* pharmacokinetics of oxycodone and its metabolites, sponsor has proposed labeling changes identifying a major role of CYP3A4 isozyme in the metabolism of oxycodone. Previously, involvement of CYP2D6 in oxycodone's metabolism was known and is described in the package insert. Eventhough, the publications clearly identify the role of CYP3A4 as a major metabolizing isozyme, effect of CYP3A4 inhibitors on the levels of oxycodone is unknown and presents a knowledge gap at this time. Although, this can be handled in the label at the present time based on theoretical expectations, quantification of this effect is essential in the proper use of this product. As such, sponsor should study the effect of Ketoconazole on the pharmacokinetics of oxycodone. Effect of CYP3A inducers need not be studied as the overall metabolism of oxycodone is expected to be higher and the drug can be titrated up to the desired effect. Information on the effect of CYP2D6 inhibitor quinidine on oxycodone metabolism is already available and is already presented in the approved OxyContin package insert. It should be noted that sponsor submitted similar labeling changes to NDA 20-553 in labeling supplement 060 on December 13, 2007. Clinical Pharmacology review dated May 21, 2008 of this supplement contains an extensive discussion of this issue. In this supplement review a recommendation was made that the sponsor should conduct a study to investigate the interaction of ketoconazole with oxycodone as a post marketing requirement as follows;

Available data suggests a major role for CYP3A4 isozyme in the metabolism of oxycodone. However, the effect of coadministration of CYP3A4 inhibitors on the metabolism of oxycodone is unknown at this time. Since this is a critical piece of information needed to use OxyContin in a safe and effective manner, magnitude of the effect of ketoconazole on the pharmacokinetics of oxycodone and its known metabolites should be characterized. See "Guidance for Industry: In Vivo Drug Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling" for additional details on the design and conduct of the study.

COMMENTS TO THE SPONSOR:

(1) As noted during Division of Scientific Investigations inspection of study OTR1005, accuracy of period 1 oxycodone concentrations for subjects 5040-5042 in run 07307cga14a and subjects 5043, 5044, and 5046 in run 07307cgb14a cannot be assured. As such, before data from study OTR1005 can be accepted, you should reanalyze and submit the data from study OTR1005 demonstrating bioequivalence after completely excluding data from subjects 5040, 5041, 5042, 5043, 5044, and 5045. Alternatively, you can reanalyze the plasma concentrations as identified and confirm the original values.

(2) Available data suggests a major role for CYP3A4 isozyme in the metabolism of oxycodone. However, the effect of coadministration of CYP3A4 inhibitors on the metabolism of oxycodone is unknown at this time. Since this is a critical piece of information needed in the selection of appropriate OxyContin dose, magnitude of the effect of ketoconazole on the pharmacokinetics of oxycodone and its known metabolites should be characterized. See "Guidance for Industry: *In Vivo* Drug Metabolism/Drug

Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling" for additional details on the design and conduct of the study.

RECOMMENDATION:

Sponsor should satisfactorily address the deficiency identified in DSI inspection (comment 1 above) before Clinical Pharmacology data is deemed to be acceptable.

Sponsor should conduct the ketoconazole and oxycodone pharmacokinetic interaction study (comment 2 above) to quantify the effect of CYP3A inhibitors on the pharmacokinetics of oxycodone. Absence of this data at this time does not preclude acceptability of Clinical Pharmacology data in this NDA as the original formulation has been on the market since 1995. As discussed, this can be addressed in the label based on theoretical expectations while data quantifying the magnitude of the interaction is acquired. This study can be conducted pre-approval if there are significant approvability related deficiencies from other disciplines that the sponsor needs to resolve and that time frame would allow the sponsor to complete the study (generally 6 to 9 months). Otherwise, this study can be conducted as a post marketing requirement. Further, in labeling supplement SLR-060 to NDA 20-553, this same study was recommended to be performed as a post marketing requirement. Administratively, as appropriate, this study can be linked to either NDA 22-272 or 20-553/SLR-060, or both.

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/s/

Sayed Al-Habet
5/23/2008 09:02:30 AM
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Suresh Doddapaneni
5/23/2008 09:15:27 AM
BIOPHARMACEUTICS

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22272	ORIG 1	PURDUE PHARMA INC	OXYCONTIN
NDA 22272	ORIG 1	PURDUE PHARMA INC	OXYCONTIN
NDA 22272	ORIG 1	PURDUE PHARMA INC	OXYCONTIN

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