

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-011**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-011, BZ, BB                      Submission Date: February 28, and April 11, 2000  
Drug : Roxicodone™ (Oxycodone Hydrochloride) Immediate Release Tablets 15 mg, 30 mg  
Sponsor: Roxane Laboratories, Inc., Columbus, Ohio  
Type of Submission: Bioequivalence study      Reviewers: Shinja R. Kim, Ph.D.

**SYNOPSIS:** Roxane Laboratories, Inc. has developed two new dosage strengths, 15 and 30-mg of immediate release oxycodone hydrochloride tablets, and submitted the NDA. Upon review, the agency found deficiencies in this NDA, and subsequently sent out an Approvable letter (dated 23 September 1999) to the sponsor: The 5 mg tablet that was used as reference was not considered to be appropriate (as a reference). The present submission is in accordance to this letter to amend the deficiency, using a bioequivalence (BE) study. This study is to assess the dose-adjusted bioavailability of oxycodone between an immediate release oxycodone HCl 15-mg tablet compared with three-tablets of Percodan® (XIR0299).

The section six of this submission consists of a single BE study, protocol XIR0299. The results showed that 90% confidence intervals around the log transformed and dose normalized ratios (treatment A/B), excluding subjects who vomited after dose administration, for AUC<sub>t</sub>, AUC<sub>∞</sub>, and C<sub>max</sub> were 93.1-104%, 93.1-104%, and 87.8-104.8%, respectively (i.e., all were within the BE criteria of 80-125%). Corresponding values in all subjects (i.e., ANOVA including patients who vomited post dose) were 90.4-101.4%, 90.3-101.3% and 91.6-104.2%, respectively. Therefore, it can be concluded that 15 mg oxycodone HCl immediate release tablet formulation (Roxane Laboratories) and 3 tablets of Percodan®, reference formulation, are bioequivalent with respect to oxycodone. Note: There is no change in labeling between the current and original NDA (i.e., no addition/modification due to the results of this study).

**Recommendation:** The amendment to the NDA 21-011 is acceptable from the Clinical Pharmacology and Biopharmaceutics perspective.

[ /S/ ]  
Shinja R. Kim, Ph.D.  
Division of Pharmaceutical Evaluation II

RD/F1 [ /S/ ] 2/20/00  
Kamana Uppoor, Ph.D.

cc:

NDA (21-011), HFD-170 (Divisional File; Milstein), HFD-850 (Lesko), HFD-870 (Kim, Uppoor, HuangS), CDR (Barbara Murphy)

APPEARS THIS WAY  
ON ORIGINAL

## Protocol XIR0299

This protocol was submitted as an IND 46,618 SNo.023, and reviewed by this reviewer (see review dated October 14, 1999). Therefore, the protocol will be outlined here briefly followed by the study results.

**Title:** A pharmacokinetic study to assess the bioavailability of oxycodone following a single dose of an oxycodone hydrochloride 15 mg immediate release tablet compared to a three-tablet dose of Percodan.

**Study site and Investigator:** \_\_\_\_\_

**Objective:** To assess the bioavailability (BA) of oxycodone in an immediate release oxycodone HCl 15 mg tablet compared with a three tablet dose of Percodan®.

**Study design:** The study had a single dose, randomized, open-label, two-way crossover design.

**Treatments:** Drugs are taken under the fasted state (i.e., overnight fast).

A: 1 x 15mg, Oxycodone HCl tablet ( → mg oxycodone free base). Manufactured by Roxane, Lot No. 979023.

B: 3 x Percodan® tablets (each tablet contains oxycodone HCl 4.5 mg, oxycodone terephthalate 0.38 mg and aspirin USP 325 mg) ( → mg oxycodone free base in 3 tablets), Manufactured by Endo Pharmaceuticals, INC., Lot No. ENB095A.

**Pharmacokinetic analysis:** The PK of oxycodone were assessed by measuring serial plasma concentrations of oxycodone following the administration of the test and reference formulations. BE was shown, by analysis of variance (ANOVA) using the appropriate model for this study design, if the 90% confidence intervals of the ratio of product means for the dose-normalized  $\text{LN}(C_{\text{max}})$ ,  $\text{LN}[AUC_{0-t}]$ , and  $\text{LN}[AUC_{0-\text{inf}}]$  were within the range of 80 to 125%. The parameter values of  $K_{\text{el}}$ ,  $t_{1/2}$ , and  $t_{\text{max}}$  were also compared between treatments.

## RESULTS

### Analytical Performance:

Assay Method: HPLC/MS/MS

Assay Sensitivity: The limit of quantification was \_\_\_\_\_ with linear range of \_\_\_\_\_

Assay Precision and Accuracy: The inter-day precision (and accuracy) values of the method at \_\_\_\_\_ ng/mL (all QC samples) were \_\_\_\_\_ and \_\_\_\_\_ respectively.

### Pharmacokinetic and statistical analyses:

Demographics: A total of 26 healthy subjects (13 per sex) participated and the number of subjects completed for the treatment A and B are 25 and 26, respectively. The mean (range) age, height and weight of subjects were 37 years (18-55), 67.3 inches (60-76.5) and 162 pounds (102-227), respectively. During the study period, vomiting occurred in 8 subjects (5 from A; 3 from B).

Oxycodone plasma concentrations: The arithmetic means and standard deviations (SD) of plasma oxycodone PK parameters and statistical comparisons following Treatments A and B are summarized in Table 1. Since vomiting occurred in some subjects, ANOVA was done without (left hand side of

the table) as well as with (right side of the table) these subjects. Figure 1 presents the mean  $\pm$  SD plasma oxycodone concentration versus time curves for treatment A and B.

Table 1. Summary of the PK parameters of oxycodone for Treatments A and B

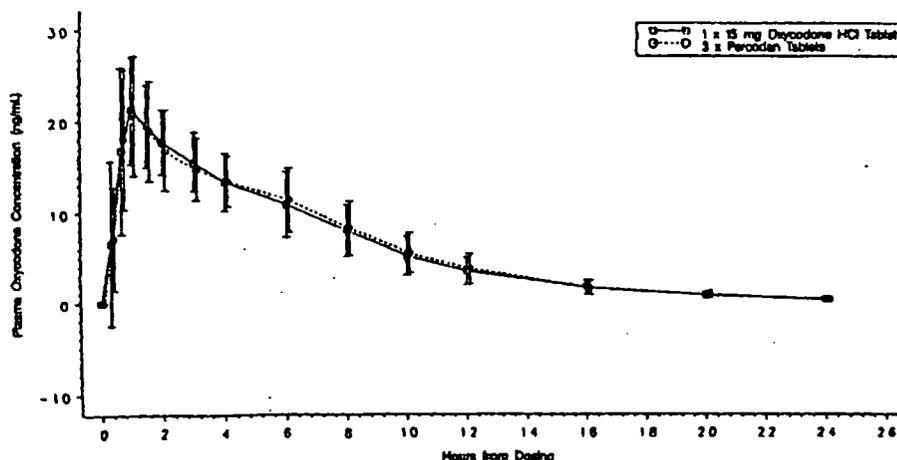
Pharmacokinetic Parameters	Plasma Oxycodone <sup>a</sup>			Plasma Oxycodone <sup>b</sup>		
	Treatment A Mean $\pm$ SD	Treatment B Mean $\pm$ SD	90% CI	Treatment A Mean $\pm$ SD	Treatment B Mean $\pm$ SD	90% CI
C <sub>max</sub> (ng/mL)	22.08 $\pm$ 6.4	20.93 $\pm$ 4.7		22.97 $\pm$ 6.2	22.28 $\pm$ 6.2	
C <sub>max</sub> N <sup>c</sup> (ng/mL)	1.64 $\pm$ 0.48	1.61 $\pm$ 0.36		1.71 $\pm$ 0.46	1.71 $\pm$ 0.48	
T <sub>max</sub> (hr)	1.49 $\pm$ 0.98	1.64 $\pm$ 1.51		1.38 $\pm$ 0.88	1.56 $\pm$ 1.40	
AUC <sub>0-t</sub> (ng•h/mL)	146.1 $\pm$ 33	144.3 $\pm$ 33		145.4 $\pm$ 32	145.9 $\pm$ 35	
AUC <sub>0-t</sub> N <sup>c</sup> (ng•h/mL)	10.86 $\pm$ 2.5	11.1 $\pm$ 2.6		10.81 $\pm$ 2.4	11.2 $\pm$ 2.7	
AUC <sub>∞</sub> (ng•h/mL)	148.9 $\pm$ 34	148.1 $\pm$ 33		148.0 $\pm$ 32	149.5 $\pm$ 35	
AUC <sub>∞</sub> N <sup>c</sup> (ng•h/mL)	11.1 $\pm$ 2.5	11.4 $\pm$ 2.6		11.0 $\pm$ 2.40	11.5 $\pm$ 2.7	
t <sub>1/2</sub> (h)	3.86 $\pm$ 0.62	3.76 $\pm$ 0.59		3.77 $\pm$ 0.58	3.73 $\pm$ 0.56	
K <sub>el</sub> (hr <sup>-1</sup> )	0.18 $\pm$ 0.03	0.19 $\pm$ 0.03		0.19 $\pm$ 0.03	0.19 $\pm$ 0.03	
Ln (C <sub>max</sub> )	3.06 $\pm$ 0.27	3.02 $\pm$ 0.22		3.10 $\pm$ 0.26	3.1 $\pm$ 0.26	
Ln (C <sub>max</sub> ) <sup>c</sup>	0.46 $\pm$ 0.27	0.45 $\pm$ 0.22	87.8-104.8	0.50 $\pm$ 0.26	0.50 $\pm$ 0.26	91.5-104.2
Ln (AUC <sub>0-t</sub> )	4.96 $\pm$ 0.23	4.95 $\pm$ 0.22		4.96 $\pm$ 0.22	4.96 $\pm$ 0.24	
Ln (AUC <sub>0-t</sub> ) <sup>c</sup>	2.36 $\pm$ 0.23	2.38 $\pm$ 0.23	93.1-104	2.36 $\pm$ 0.22	2.39 $\pm$ 0.24	90.4-101.4
Ln (AUC <sub>∞</sub> )	4.98 $\pm$ 0.23	4.97 $\pm$ 0.23		4.97 $\pm$ 0.23	4.98 $\pm$ 0.23	
Ln (AUC <sub>∞</sub> ) <sup>c</sup>	2.38 $\pm$ 0.23	2.41 $\pm$ 0.23	93.1-104	2.38 $\pm$ 0.23	2.42 $\pm$ 0.23	90.3-101.3

<sup>a</sup> ANOVA without subjects who vomited after the dose administration.

<sup>b</sup> Analyses including all subjects (i.e., included subjects who vomited post dose).

<sup>c</sup> Dose was normalized by the amount of oxycodone in Roxicodone ( ———— per 15 mg tablet) or Percodan ( ———— in 3 tablets).

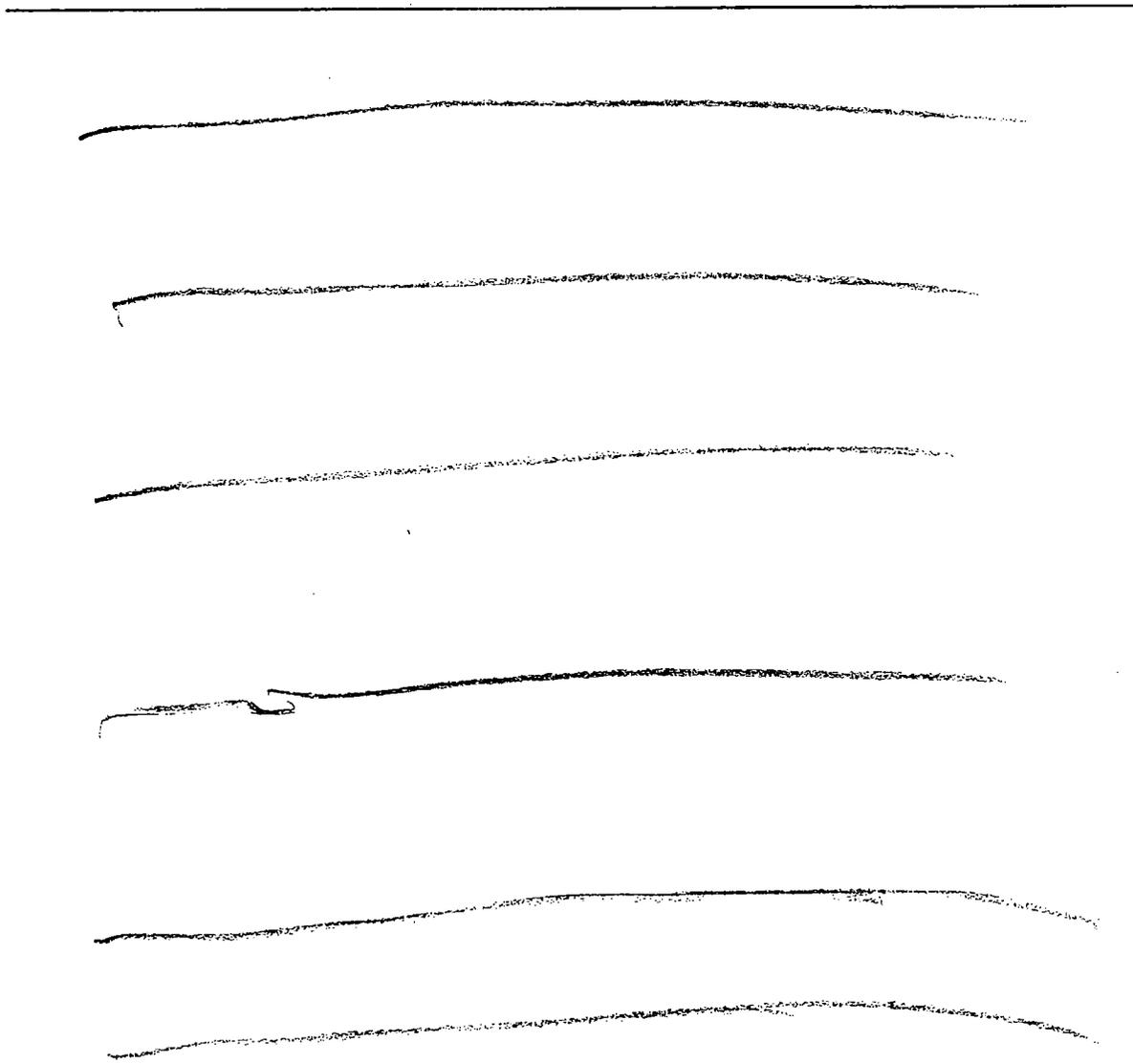
Figure 1. Mean (SD) plasma oxycodone concentrations versus time.



The results showed that 90% confidence intervals around the log transformed and dose normalized ratios (treatment A/B), excluding subjects who vomited after dose administration, for  $AUC_t$ ,  $AUC_{\infty}$ , and  $C_{max}$  were 93.1-104%, 93.1-104%, and 87.8-104.8%, respectively. Corresponding values in all subjects who completed the study were 90.4-101.4%, 90.3-101.3% and 91.5-104.2%, respectively (Table 1).

**Conclusion:** PK of oxycodone following the administration of 15 mg oxycodone HCl immediate release tablet formulation (Roxane Laboratories) and 3 x 4.50 oxycodone HCl/0.38mg oxycodone terephthalate/325 mg aspirin (Percodan®) reference formulation indicate that these two formulations are bioequivalent with respect to oxycodone.

**Package Insert:** The results from this study were not incorporated in the labeling (*i.e.*, same as the original NDA recommendation). Original recommendation (*i.e.*, current labeling) is shown below (limited to PK portion).



3 Draft Labeling Page(s) Withheld

Change

JUN 27 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-011  
 Submission Date: September 29, 1998 & January 13, 1999  
 Drug Name, Dose and Formulation: Roxicodone™ (Oxycodone Hydrochloride) Tablets 15 mg, 30 mg  
 Sponsor: Roxane Laboratories, Inc., Columbus, Ohio  
 Type of Submission: New Drug application, 3S  
 Reviewers: Shinja R. Kim, Ph.D.

**SYNOPSIS:** Roxane Laboratories, Inc. has developed two new dosage strengths (15 and 30-mg) of an immediate release oxycodone hydrochloride tablet for the convenience of patients who are taking high oral doses of oxycodone. Oxycodone HCl is currently marketed as 5-mg tablets, as a 5 mg/5 mL oral solution, and as a 20 mg/mL concentrated oral solution (Intensol™). The usual adult dose, currently, is 10 mg to 30 mg every 4 hours as needed; more severe pain may require 30 mg or more every 4 hours. The proposed labeling for the new strengths has the same dosing range as the 5-mg strength. Therefore, oxycodone IR 15- and 30-mg tablets are expected to have a safety and efficacy profile similar to that of the current products on the market.

The eight clinical/biopharm studies conducted in healthy volunteers, which are presented in this section of the NDA, consist of four single-dose bioavailability/bioequivalency (BA/BE) studies, two steady-state BA/BE studies, one food effect study, and one dose proportionality study. Only three studies (XIR0296, XIR0396 and XIR0596) used the to-be-marketed formulation, and all other studies used the currently marketed oxycodone IR tablet formulations or solutions. The 10-mg sustained-release oxycodone tablet formulation was compared with the currently marketed 5 mg/5 mL oxycodone oral solution in the steady-state BA/BE and the food effect studies. Although the oxycodone IR tablet formulations were not used in these studies, these studies have been included to illustrate the general effect of repeated dosing and the effect of food following administration with an oral solution of oxycodone. Population-based pharmacokinetics of oxycodone was characterized from patients with moderate-to-severe chronic pain. The overall conclusions from pharmacokinetic studies and population pharmacokinetic analysis support the approval of the two new dosage strengths.

**Recommendation:** The NDA 21-011 is acceptable from the Clinical Pharmacology and the Biopharmaceutics perspective provided the sponsor agrees to the labeling changes proposed by the Agency. Please forward the recommended modified labeling to the sponsor.

[ /S/ ]

Shinja R. Kim, Ph.D.  
 Division of Pharmaceutical Evaluation II

RD/FT [ |S| ] 7/27/99  
 Ramana Uppoor, Ph.D.

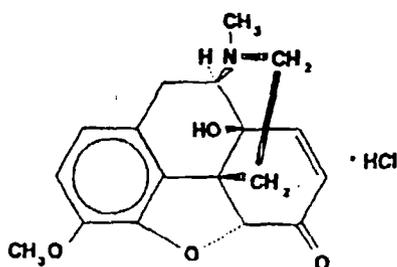
## TABLE OF CONTENTS

Background.....	3
Summary of Bio/PK characteristics.....	3
Proposed labeling.....	7
Comments (to the medical officer).....	11
 <u>Appendix I (Study summaries)</u>	
315-05      A Single-Dose, Two-Way Crossover Study to Compare the Relative Bioavailability of Oxycodone HCl 5 mg Immediate Release Tablets with Oxycodone HCl Oral Solution 5 mg/5 mL.....	13
315-07      A Single dose, Two-way Crossover Study to Compare the Relative Bioavailability of Oxycodone HCl 30 mg IR Tablet with Oxycodone HCl Oral Solution 5 mg/5 mL.....	15
XIR0296    A Randomized, Open-Label, Crossover study Comparing the Bioequivalence of Oxycodone Formulations of 3 x 5 mg Tablets, 1 x 15mg Tablet, and 0.75 mL of a 20 mg/mL Oral Solution.....	17
XIR0396    A Randomized, Open-Label, Crossover Study Comparing the Bioequivalence of Oxycodone Formulations of 6 x 5 mg Tablets, and 1x 30 mg Tablet.....	19
315-04      A Bioequivalence Study to Compare Two Formulations of Sustained-Release Oxycodone HCl Tablets (10 mg) to Immediate-Release Oxycodone HCl Oral Solution (Multiple-Dose, Three-Way Crossover).....	21
315-09      A Bioavailability Study to Compare Sustained-Release Oxycodone HCl 10 mg Tablet Formulation to Immediate-Release Oxycodone HCl Oral Solution (Multiple-Dose, Two-Way Crossover).....	24
315-10      A Single-Dose, Four-Way Crossover, Food Effect Study of the 10 mg Formulation of Oxycodone Sustained-Release Tablets and Oxycodone Immediate Release Oral Solution.....	27
XIR0196    A Single dose, Randomized, Double-Blind, Three-Way Crossover Study Comparing the Dose Proportionality of 5 mg, 15 mg, and 30 mg Doses of Oxycodone Administered Orally to Healthy Volunteers Under Fasting Conditions.....	30
Population Pharmacokinetics (XIR 0596 and XIR 0196).....	34
Dissolution .....	43

BACKGROUND

Oxycodone IR is a semi-synthetic narcotic, which is derived from the opium alkaloid, thebaine. Oxycodone is a pure agonist opioid and has multiple actions qualitatively similar to those of morphine. The principal therapeutic action of oxycodone is analgesia and this drug has been in clinical use since 1917. Oxycodone IR tablets are intended to be used for the management of moderate-to-severe chronic pain (cancer and non-cancer pain).

Chemically, oxycodone hydrochloride is 4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride and has the following structural formula.



C<sub>18</sub>H<sub>21</sub>NO<sub>4</sub>·HCl

MW 351.83

- I. FORMULATION: The formulation composition, on a per tablet basis, is provided below.

Ingredient	Tablet Strength		
	15mg	30mg	
		Formulation A	Formulation B
Oxycodone HCl	15.0	30.0	30.0
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
Lactose, NF	_____	_____	_____
Water, Purified, USP	_____	_____	_____
Stearic Acid, NF	_____	_____	_____
D&C Yellow #10, _____	_____	_____	_____
FD&C Blue #2, _____	_____	_____	_____

KEY: USP = United States Pharmacopeia; NF = National Formulary  
Formulation B = to-be-marketed formulation

II. BIOAVAILABILITY/BIOEQUIVALANCE

Bioavailability/bioequivalence: Study 315-05 was conducted to establish the bioequivalency of the currently marketed 5 mg/5 mL oral solution to the currently marketed 5-mg IR tablet.

Comparison of AUC indicated that the 5mg IR tablet was approximately 97% bioavailable compared to the 5 mg/5 mL oral oxycodone solution following 10 mg oral doses. The ratios and confidence intervals of the ratios for AUC and  $C_{max}$  met the bioequivalence criteria. The average  $T_{max}$  for the tablet was 1.27 hours compared with 1.06 hours for the oral solution (statistically different at  $p < 0.05$ ), but,  $K_{elim}$  and  $T_{1/2}$  of oxycodone were similar between the two formulations.

**Study 315-07** compared the 30-mg IR tablet to the 5 mg/5 mL oral solution. The 30-mg IR formulation used in this study was the earliest IR formulation and differed slightly from the to-be-marketed 30-mg IR tablet formulation used in the XIR0396 study. The results indicated that the 30 mg oxycodone IR tablet was approximately 96% bioavailable compared to an equivalent dose of the 5 mg/5 mL oral oxycodone solution. The ratios and confidence intervals of the ratios for AUC and  $C_{max}$  met the bioequivalence criteria. There was no statistically significant difference between the two dosage forms except for  $T_{max}$ .

In **study XIR0296**, the to-be-marketed 15-mg tablet formulation and the currently marketed 20 mg/mL (Intensol™) solution were compared to the currently marketed 5-mg IR tablet. The results indicated that the three oxycodone formulations were bioequivalent, determined by 90% CI.  $T_{max}$ ,  $K_{elim}$ , and  $T_{1/2}$  of oxycodone were also similar for the three formulations.

**Study XIR0396** compared the to-be-marketed 30-mg tablet formulation and the currently marketed 5-mg IR tablet. The results showed that the to-be-marketed oxycodone 30 mg IR tablet is bioequivalent to currently marketed 5-mg oxycodone IR tablet (6 x 5 mg). Also,  $T_{max}$ ,  $K_{elim}$ , and  $T_{1/2}$  of oxycodone were similar between the two formulations.

The two supportive Phase-1 studies conducted in healthy volunteers to evaluate steady-state bioavailability/bioequivalency, used the SR formulation. **Study 315-04** was to compare 10 mg oxycodone HCl SR tablets, Formulation A and B (one tablet every 12 hours for 7 doses) with 5 mg/5 mL oral solution (3.33 mL every 4 hours for 21 doses). The results showed that both SR formulations were equivalent to the oral solution with respect to  $AUC_{0-\infty}$ . The accumulation of oxycodone in plasma following repeated dosing was reasonably predictable from single dose information (study 315-07); in study 315-07, the mean  $k_e$  of 0.156/h suggests an accumulation factor of 2.15 for q4h dosing regimen. The mean observed values were underpredicted by 20-30%, however, the values illustrate that oxycodone plasma levels at steady state will be approximately 2-fold higher than those of a single dose which is consistent with its half-life. **Study 315-09** was to evaluate the bioavailability of an oxycodone SR 10 mg tablet given every 12 hours for 7 doses and an IR oxycodone oral solution given every 6 hours for 14 doses. The results revealed that the SR formulations had a relative bioavailability of 108% compared to the solution (based on  $AUC_{72-84}$ ), and the two formulations were bioequivalent with respect to  $C_{max}$  and  $AUC_{72-84}$ . The mean observed values of  $C_{max}$  at steady state and  $AUC_{72-84}$  following administration of oxycodone oral solution were under estimated by 32% and 20%, respectively (based on study 315-07).

**Food Effect:** Study 315-10 was conducted to evaluate the effect of food on the

pharmacokinetic characteristics of a sustained release (SR) oxycodone tablet formulation and an immediate release (IR) oxycodone oral solution. The study was designed as a single-dose, open-label, 4-way crossover study in fourteen healthy male volunteers. The four treatments include; (1) a single dose of 10 mg oxycodone SR tablet under fasting state, (2) a single dose of 10 mg oxycodone SR tablet following administration of a FDA high-fat breakfast, (3) 10 ml of 5 mg/5 mL oxycodone IR solution under fasting, and (4) 10 ml of 5 mg/5 mL oxycodone IR solution following administration of a FDA high-fat breakfast. The results of this study show that food increased the extent ( $AUC_{0-\infty}$ ) of absorption (26% increase), but not the rate ( $C_{max}$ ) of oxycodone absorption from the IR solution.  $T_{max}$  was delayed by 203% when IR solution was given with high fat meal compared to that under fasting condition. The oral solution was bioequivalent under fed and fasting conditions with respect to  $C_{max}$  but not for  $AUC_{0-\infty}$ . The to-be-marketed 15 or 30 mg IR tablet formulations have not been used in food effect study. However, the 15 and 30 mg IR tablet formulations have been compared to the currently marketed 5 mg IR tablet formulation and to the currently marketed 5 mg/5 mL and 20 mg/mL oral solutions in bioequivalence studies, and the tablet formulations have been shown to be bioequivalent to the oral solution in fasted state (XIR0296, XIR 0396, 315-07). Thus, the food effect seen on oral solution can be considered to be due to the drug substance. Therefore, the food effect for the to-be-marketed formulation tablets can be extrapolated from the food effects on IR solution.

### III. DOSE PROPORTIONALITY

**Study XIR0196** was conducted to determine (a) the **dose proportionality** of oxycodone tablets at doses of 5 mg, 15 mg, and 30 mg in healthy subjects and (b) whether there is an **efficacy dose response** in the cold pressor test after a single dose of the study medication. The study was designed as a single-dose, randomized, open-label, 3-way crossover study in 25 healthy male/female volunteers. The three treatments include; (1) 5mg IR tablet plus 5 placebo tablets (2) 3 x 5 mg IR tablet plus 3 placebo tablets (3) 6 x 5 mg IR tablets. The results show that pharmacokinetic dose proportionality was achieved with respect to AUC following single 5mg, 15 mg, and 30 mg doses of oxycodone.  $C_{max}$  was proportional to dose between the 5 mg and 15 mg doses and between the 15 and 30 mg doses, but not between the 5 mg and 30 mg doses. Pharmacodynamic dose proportionality analysis showed that the mean pain intensity/pain bothersomeness reported 1 hour postdose appeared to decrease as the dose increased, however, not linearly; the dose-response curves were shallow and the most significant effect (visually) was following 15 mg compared to that of 5 mg.

### IV. POPULATION PHARMACOKINETICS

Population PK Analysis was performed using the NONMEM software (version V). An initial data set, containing data from the patient safety study only (XIR0596, 62 patients, 122 PK samples) was constructed which resulted in poor model fits and parameter estimates (due to minimal blood samples at later times). In order to obtain the entire plasma drug concentration-time curve, data from Study XIR0196 in healthy volunteers (28 subjects, 967 total PK samples) was incorporated. The combined data set (90 subjects, 1089 PK samples)

was used for all subsequent model building. The steps to build the model involved the following; (1) defining a base model as a one-compartment model with first-order absorption and an absorption lag time, (2) generating empirical Bayesian estimates of individual model parameters using the POSTHOC subroutine in NONMEM, (3) generalized additive model (GAM) analysis to explore the relationships between covariate factors and individual estimates of model parameters. Results of the GAM analysis were used to build the "Full" model, and (4) the "Final" model was obtained by a stepwise deletion method, at the  $p < 0.005$  level.

Blood samples were collected, from the study XIR0596, approximately 0.5 to 2 hours after a dose. The second sample was to be collected within the 2 hours prior to the next dose. If this was not possible, the two blood samples may have been drawn after different doses or even on different days, anytime after stabilization (recorded the precise time of the blood collection and time of last dosing). From study XIR0196, blood samples were drawn from pre-dose (0 hour) to 36 hours post-dose with extensive time points.

The results of the analysis with respect to the PK parameters for Protocol-1 (patients) and Protocol-0 (healthy volunteers) are shown below (based on Final Model)

	CL/F (L/hr)		V/F (L)		$k_a$ (hr <sup>-1</sup> )	
	Protocol-1	Protocol-0	Protocol-1	Protocol-0	Protocol-1	Protocol-0
<b>Mean</b>	77.9	108	572	566	3.92	5.64
<b>Median</b>	73.6	102	564	574	4.00	3.99
<b>Minimum</b>	14.8	45.9	204	313	1.17	1.13
<b>Maximum</b>	223	180	1090	880	5.62	22.3
<b>SD</b>	37.4	33.2	189	123	0.670	5.23

An explanation for the significant difference in CL/F between patients and healthy volunteers was not evident from these data, except that data was obtained from two different populations with different protocols. Any covariate effect identified in this analysis is likely to be minor, as evidenced by the lack of a decrease in the random interindividual error estimates for CL/F and V/F (however, it is expected since covariates were within normal range, except LDH and AST values in a few patients). In this analysis, no gender differences in oxycodone pharmacokinetics were identified. The effect of race on oxycodone pharmacokinetics or effects of opioid use history were not examined, since numbers of patients who belong to these categories were small. No apparent explanation for the significant relationship between serum creatinine and V/F was evident and this may have simply been a correlated, but not explanatory, covariate factor. The model is a simple representation of some of the factors that influence oxycodone pharmacokinetics in patients/healthy volunteers. Fixed effects parameters as well as most random effect terms were estimated with precision and model predictions were without systematic bias. However, this analysis does not explain CL/F difference between patients and healthy volunteers; many 'laboratory test values' were incorporated as Covariates in the model for CL/F. However, the model indicated that only 'Protocol' had significant influence for the CL/F difference

between patients and healthy volunteers. This suggests that (not identified) factor(s), such as disease-state/sampling time/concomitant medication/rescue medication, other than 'laboratory test values' may be influencing the CL/F difference between patients and healthy volunteers. Nevertheless, predictions for steady state  $C_{max}$  and AUC are comparable for each other. Predictions based on single dose study (315-07), multiple dose study (315-09) or population pharmacokinetic analysis is shown below;

Parameter	Single Dose		Steady State		Steady State	
	Study 315-07		Study 315-09 (q6h)		Population PK (q6h)	
	Mean Observed	Dose Adjusted <sup>a</sup>	Predicted <sup>b</sup>	Mean Observed	Predicted <sup>c</sup> Patients <sup>e</sup>	Predicted <sup>d</sup> HV <sup>f</sup>
$C_{max}$	39.08	1.30	10.73	15.69	14.15	11.63
AUC	330.7	11.02	90.92	113.25	128.36	92.59

<sup>a</sup>Expressed per 1 mg dose. <sup>b</sup>Mean  $K_e = 0.156/h$  (Study 315-07); Accumulation factor =  $1/(1-e^{-k_e\tau}) = 1.65$  (q6h); Predicted = dose adjusted Accumulation factor x study dose.

<sup>c</sup>Based on mean values of CL/F = 77.9 L/hr, VL/F = 572 L,  $K_a = 3.92 \text{ hr}^{-1}$  and ALAG = 0.271  $\text{hr}^{-1}$

<sup>d</sup>Based on mean values of CL/F = 108 L/hr, VL/F = 566 L,  $K_a = 5.64 \text{ hr}^{-1}$  and ALAG = 0.271  $\text{hr}^{-1}$

<sup>e</sup>Patients = Protocol-1.

<sup>f</sup>HV (healthy volunteers) = Protocol-0

## V. DISSOLUTION

Drug release from Roxicodone™ Tablets, 15 and 30 mg, was found to be independent of pH, rotation speed and storage conditions, with all of the tested lots releasing  $\text{---}$  of oxycodone HCl at 45 minutes. The USP compendial method for Oxycodone HCl tablets, (USP) was found to be appropriate for evaluating the *in vitro* oxycodone HCl release from Roxicodone™ Tablets, 15 mg and 30 mg. The sponsor proposed a dissolution specification of Q =  $\text{---}$  in 45 minutes.

## VI. ANALYTICAL METHODOLOGY

Plasma samples from all subjects were assayed using HPLC/MS/MS procedure. The sensitivity and the linear range was  $\text{---}$  and  $\text{---}$  respectively for studies XIR-0396, -0296, -0196, and 315-10. Similarly, the sensitivity and the linear range were  $\text{---}$  and  $\text{---}$  respectively for studies XIR0596, 315-04, -05, -07 and -09. Assay precision (% CV) was approximately less than 15% both for Inter-assay and Intra-assay. Similarly, accuracy (% Error) was less than  $\text{---}$  for both Inter-assay and Intra-assay. Overall the analytical methodology was acceptable.

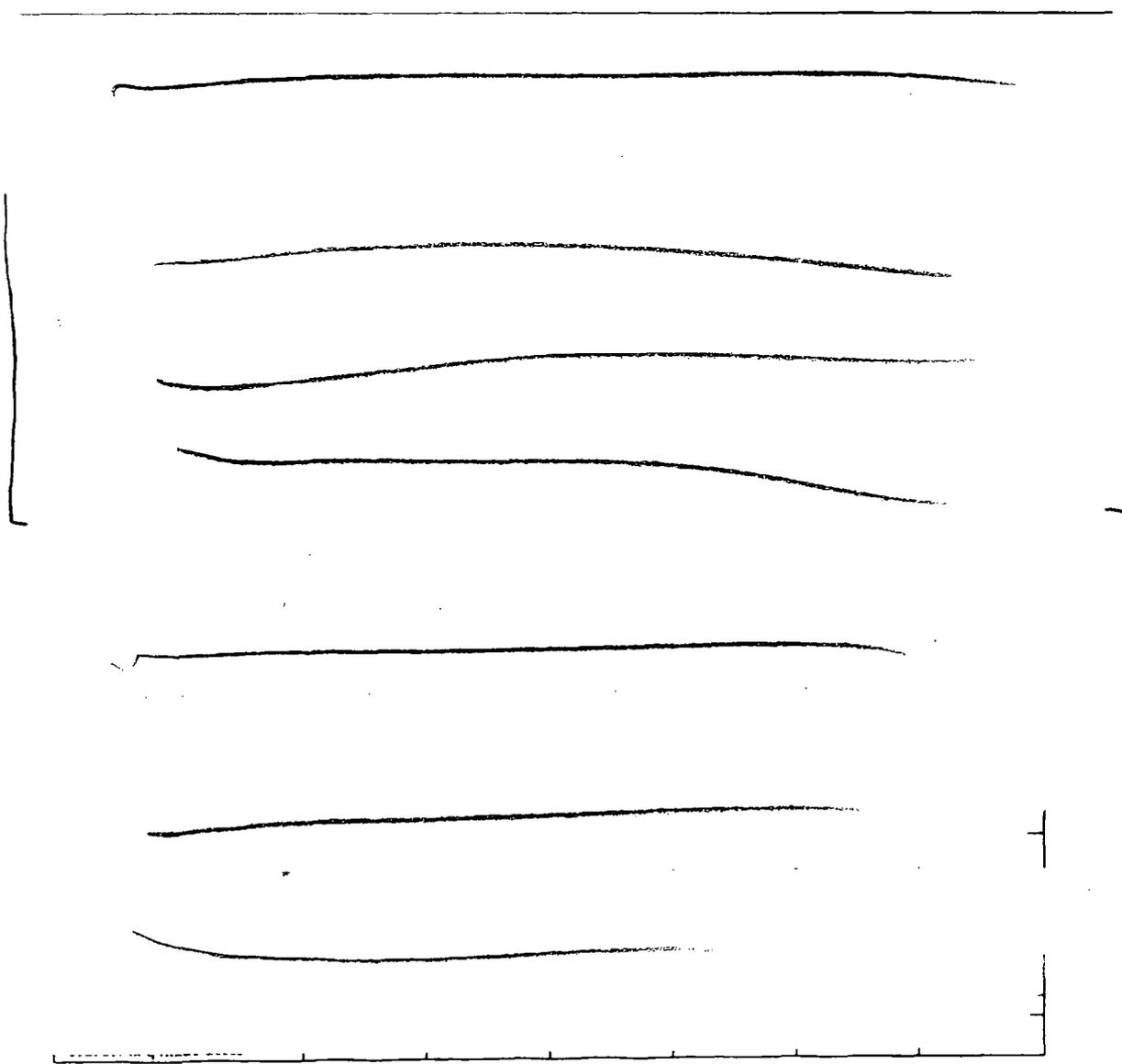
## VII. CONCLUSIONS

- The sponsor demonstrated that new 15 and 30 mg Roxicodone tablets are bioequivalent to the 5 mg tablets and oral solution.
- High fat meal caused an increase in AUC by 26% with no significant change in  $C_{max}$  following an oral solution of Roxicodone.

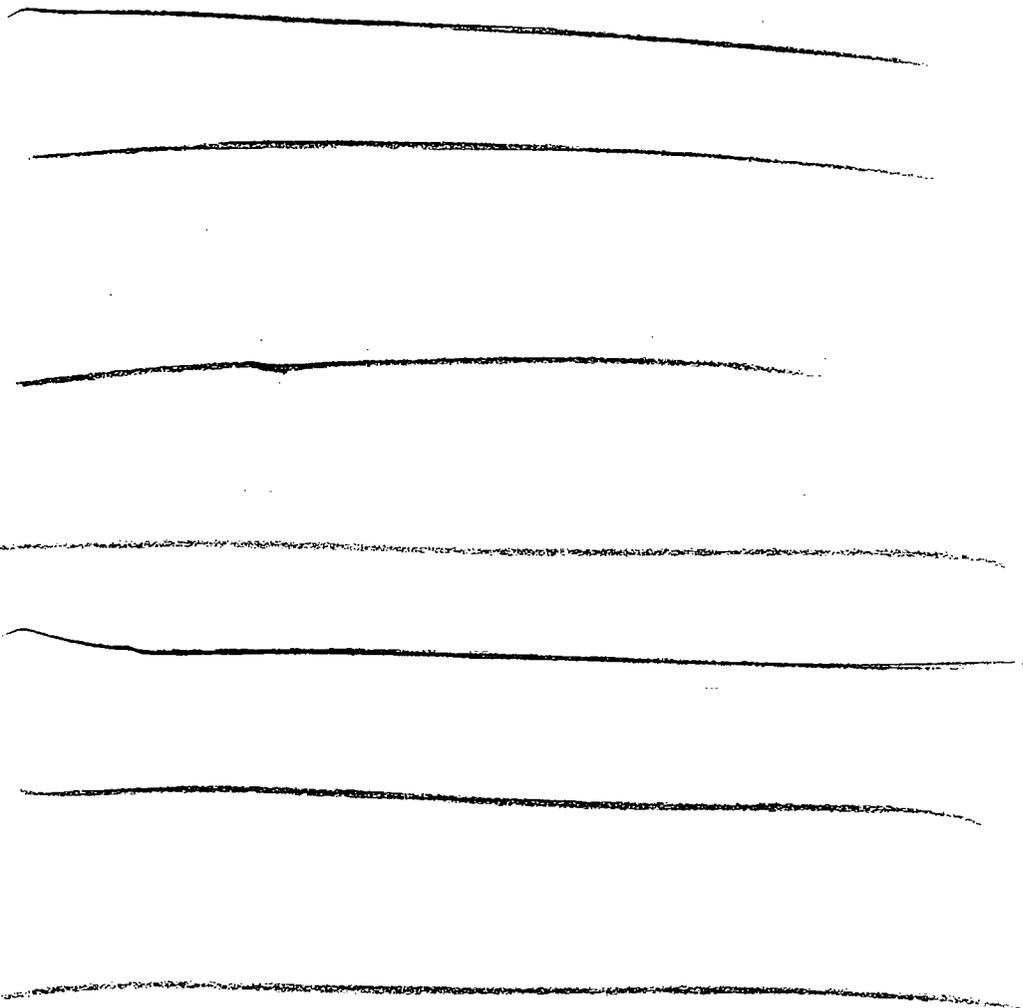
- Dose-proportionality for the dose range of 5 to 30 mg using currently marketed 5-mg tablet has been investigated and it maintained dose-proportionality within the dose investigated.
- Population-based pharmacokinetic analysis was performed which shows no gender differences in oxycodone pharmacokinetics.
- There was a consensus on modification of *Nursing Mothers* subsection in the package insert, under precaution section, by deleting words 'Low concentrations' in the Team meeting, DPE-II (No further action is needed).

VIII. PROPOSED PACKAGE INSERT

Note: Strikeouts and underlined text indicate this reviewer's suggested deletions and additions respectively.



2 Draft Labeling Page(s) Withheld



---

IX. COMMENT TO THE MEDICAL OFFICER:

1. The 15 mg and 30 mg Roxicodone tablets are bioequivalent to the currently marketed 5 mg tablets.
2. Co-administration of Roxicodone with food resulted in a 26% increase in oxycodone AUC with no significant effect on  $C_{max}$ . The  $T_{max}$  was delayed by about 1 hour ( $T_{max}$  almost doubled when taken with high fat meal).

*NDA 21,011*  
*Roxicodone™ Tablets*

*Pharmacokinetic Section, 12*  
*Submission Date: 09/30/98*

**APPENDIX**

**APPEARS THIS WAY  
ON ORIGINAL**

**Study 315-05:** A Single-Dose, Two-Way Crossover Study to Compare the Relative Bioavailability of Oxycodone HCl 5 mg Immediate Release Tablets with Oxycodone HCl Oral Solution 5 mg/5 mL.

Reference: Volume 14 -15

Investigators:

Study Location:

[ \_\_\_\_\_ ]

**Formulation:**

Treatment	Dosage Form	Dose	Lot #	Lot Size
A	Roxicodone™ tablets	2 x 5 mg	941086	_____
B	Roxicodone™ solution	10 mL of 5 mg/5mL	940729	_____

**Objective:**

To evaluate the relative bioavailability of Roxicodone™ 5-mg IR tablets with the Roxicodone™ oral solution 5 mg/5 mL

**Study Design:**

The study was designed as a single-dose, randomized, open-label, two-way crossover study with 7-day washout between treatments in 26 healthy male volunteers, mean age of 32.5 years (range, 19-51 years). All subjects will receive one dose of each treatment, shown above, under fasted conditions in a random order.

**Analytical Methodology:**

*Plasma Sampling Times:* pre-dose (0 hour), 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 3, 4, 6, 8, 12, 16, and 24 hours.

*Assay Method:* HPLC/MS/MS

*Assay Sensitivity:* The limit of quantitation was \_\_\_\_\_ with linear range of \_\_\_\_\_

*Assay Precision and Accuracy:* The inter-day precision and accuracy values of the method at \_\_\_\_\_ (all QC samples) were less than \_\_\_\_\_

**Results:**

Summary of pharmacokinetic data and profile of mean plasma concentrations over time following each treatment is shown in the following Table and Figure, respectively.

**Study 315-07:** A Single dose, Two-way Crossover Study to Compare the Relative Bioavailability of Oxycodone HCl 30 mg IR Tablet with Oxycodone HCl Oral Solution 5 mg/5 mL.

Reference: Volume 12 - 13

Investigators: [ \_\_\_\_\_ ]

Study Location [ \_\_\_\_\_ ]

**Formulation:**

Treatment	Dosage Form	Dose	Lot #	Lot Size
A	Roxicodone™ solution	30 mL of 5 mg/5mL	940729	_____
B	Oxycodone IR tablet	30 mg	949081	_____

**Objective:**

To evaluate the relative bioavailability of an oxycodone HCl 30-mg IR tablet with the oxycodone oral solution 5 mg/5 mL.

**Study Design:**

The study was designed as a single-dose, randomized, open-label, two-way crossover study with 7-day washout between treatments in 25 healthy male (19-53 years age) volunteers. All subjects will receive one dose of each treatment, shown above, under fasted conditions in a random order.

**Analytical Methodology**

*Plasma Sampling Times:* pre-dose (0 hour), 0.33, 0.67, 1, 1.33, 1.67, 2, 3, 4, 6, 8, 12, 16, and 24 hours.

*Assay Method:* HPLC/MS/MS

*Assay Sensitivity:* The limit of quantitation was \_\_\_\_\_ with linear range of \_\_\_\_\_

*Assay Precision and Accuracy:* The inter-day and intra-day precision and accuracy values of the method at \_\_\_\_\_ were less than: \_\_\_\_\_

**Results:**

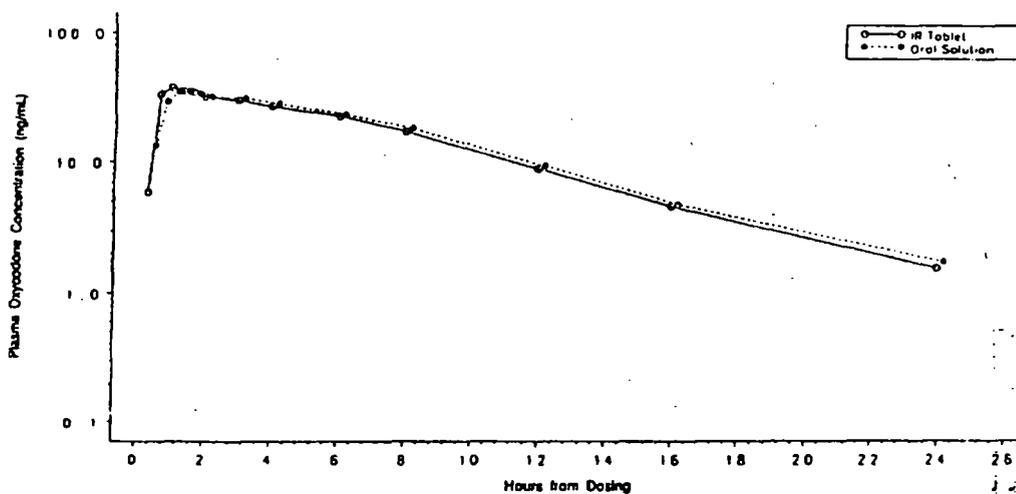
Summary of pharmacokinetic data and profile of mean plasma concentrations over time following each treatment is shown in the following Table and Figure, respectively. The 30 mg tablet formulation used in this study was slightly different (quantity of inactive ingredients) than the to-be-marketed 30 mg tablet formulation.

Table: Summary of Pharmacokinetic Data

Parameter	Mean ±SD (N=25)		Treatment Comparison		
	30-mg Oxycodone Tablet	30 mL of 5 mg/5 mL Solution	Percent Difference	p-value*	90% Confidence Intervals
$C_{max}$ (ng/mL)	40.25 ± 12.43	39.08 ± 10.95	2.99	0.5377	94.8 - 111.2
$T_{max}$ (h)	1.79 ± 1.54	2.00 ± 1.42	-10.39	0.6394	52.1 - 127.1
$AUC_{0-24}$ (ng•h/mL)	306.18 ± 71.49	318.23 ± 78.62	-3.79	0.2125	91.2 - 101.3
$AUC_{0-16}$ (ng•h/mL)	316.89 ± 78.31	330.69 ± 86.96	-4.17	0.1833	90.6 - 101.0
$k_p$ (1/h)	0.160 ± 0.023	0.156 ± 0.023	2.39	0.2167	99.2 - 105.6
$t_{1/2}$ (h)	4.44 ± 0.72	4.55 ± 0.77	-2.55	0.1988	94.2 - 100.8
$LN C_{max}$	3.65 ± 0.33	3.63 ± 0.29	0.51	0.6946	94.0 - 110.4
$LN AUC_{0-24}$	5.70 ± 0.22	5.73 ± 0.25	-0.57	0.2652	92.1 - 101.7
$LN AUC_{0-16}$	5.73 ± 0.23	5.77 ± 0.26	-0.63	0.2390	91.6 - 101.5

\* ANOVA test for significant differences between treatments

Figure: Mean Plasma Concentrations over time



**Conclusion:**

The results indicated that the 30 mg oxycodone IR tablet was approximately 96% bioavailable compared to an equivalent dose of the 5 mg/5 mL oral oxycodone solution. The ratios and confidence intervals of the ratios for AUC and  $C_{max}$  met the bioequivalence criteria. There was no statistically significant difference for all pharmacokinetic parameters between two dosage forms.

**BEST POSSIBLE COPY**

**Study XIR0296:** A Randomized, Open-Label, Crossover Study Comparing the Bioequivalence of Oxycodone Formulations of 3 x 5 mg Tablets, 1 x 15 mg Tablet, and 0.75 mL of a 20 mg/mL Oral Solution in Healthy Volunteers.

Reference: Volume 8 - 9

Investigators:

Study Location:

[ \_\_\_\_\_ ]

**Formulation:**

Treatment	Dosage Form	Dose	Lot #	Lot Size
A	Roxicodone® tablets	3 x 5 mg	961562	_____
B	Oxycodone IR tablet	15 mg	969032	_____
C	Intensol® oral solution	0.75 mL of 20 mg/mL	961635	_____

**Objective:**

To demonstrate the bioequivalence of three formulations of oxycodone given as a single oral dose to healthy male and female volunteers: three 5 mg tablets; one 15 mg to-be-marketed tablet; 0.75 mL of a 20 mg/mL solution (15 mg solution).

**Study Design:**

The study was designed as a single-dose, randomized, open-label, 3-way crossover study with at least 7-day washout between treatments in 24 healthy male/female volunteers, mean age of 28 years (range, 20-45 years). All subjects will receive one dose of each treatment, shown above, under fasted conditions in a random order.

**Analytical Methodology:**

Plasma Sampling Times: pre-dose (0 hour), 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours

Assay Method: HPLC/MS/MS

Assay Sensitivity: The limit of quantitation was \_\_\_\_\_ with linear range of \_\_\_\_\_

Assay Precision and Accuracy: For precision the inter-day and intra-day were \_\_\_\_\_ and that for accuracy were \_\_\_\_\_ at concentrations of \_\_\_\_\_ (all QC samples).

**Results and Discussion:**

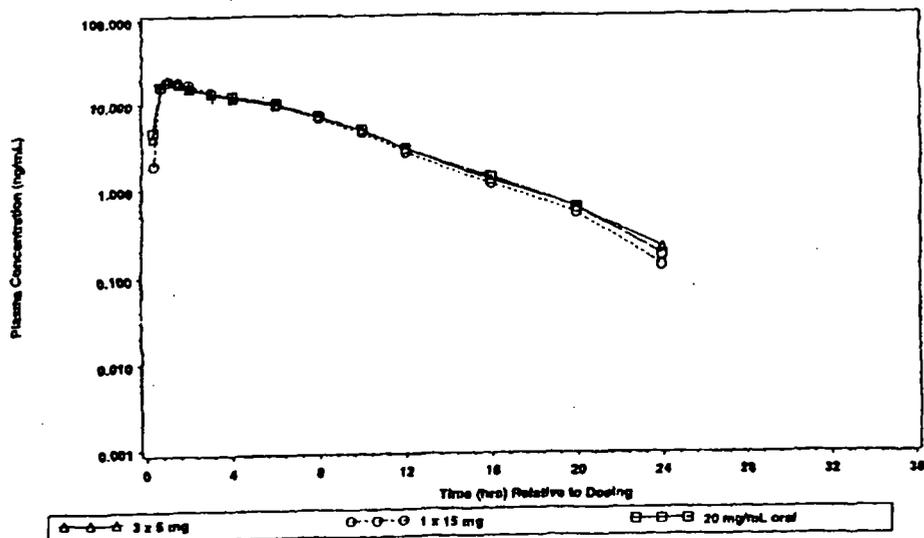
The results indicated that the 15 mg tablet and the solution are bioequivalent to the 5 mg tablets, based on 90% CI.  $T_{max}$ ,  $K_{elim}$ , and  $T_{1/2}$  of oxycodone were also similar for the three formulations. Summary of pharmacokinetic data and profile of mean plasma concentrations over time following each treatment is shown in the following Table and Figure, respectively.

Table: Summary of Pharmacokinetic Data

Parameter	Mean ± SD (N=24)			Comparison of Treatment		
	Treatment A 3 x 5 mg Tablet	Treatment B 1 x 15 mg Tablets	Treatment C 0.75mL of 20mg/mL Solution	Treatment	Ratio	90% Confidence Intervals
AUC <sub>0-24</sub> (ng•h/mL)	129.35 ± 32.69	124.23 ± 34.96	126.89 ± 34.51	B vs A C vs A	95.81% 98.35%	90.16% - 101.46% 92.70% - 104.00%
AUC <sub>0-∞</sub> (ng•h/mL)	133.23 ± 33.04	128.22 ± 35.13	130.58 ± 34.66	B vs A C vs A	96.01% 98.26%	90.52% - 101.51% 92.76% - 103.75%
C <sub>max</sub> (ng/mL)	22.28 ± 8.20	22.17 ± 7.62	21.11 ± 6.08	B vs A C vs A	99.63% 94.71%	92.42% - 106.83% 87.51% - 101.92%
k <sub>e</sub> (1/h)	0.19 ± 0.04	0.21 ± 0.05	0.20 ± 0.04	-	-	-
t <sub>1/2</sub> (h)	3.73 ± 0.90	3.55 ± 0.95	3.71 ± 0.76	-	-	-
T <sub>max</sub> (h)	1.80 ± 1.75	1.37 ± 0.74	1.89 ± 1.45	-	-	-
LN AUC <sub>0-24</sub>	125.14 ± 0.27	119.18 ± 0.30	121.59 ± 0.31	B vs A C vs A	94.97% 97.44%	87.42% - 103.18% 89.69% - 105.87%
LN AUC <sub>0-∞</sub>	129.08 ± 0.26	123.31 ± 0.29	125.41 ± 0.30	B vs A C vs A	95.25% 97.43%	87.91% - 103.22% 89.92% - 105.58%
LN C <sub>max</sub>	21.03 ± 0.34	21.02 ± 0.33	20.20 ± 0.31	B vs A C vs A	100.01% 96.01%	90.51% - 110.50% 86.89% - 106.08%

- Indicates these values were not calculated in the individual study report

Figure: Mean Plasma Concentrations over time



**REST POSSIBLE COPY**

**Study XIR0396:** A Randomized, Open-Label, Crossover Study Comparing the Bioequivalence of Oxycodone Formulations of 6 x 5 mg Tablets, and 1x 30 mg Tablet (to-be-marketed formulation) in Healthy Volunteers.

Reference: Volume 10 - 11

Investigators:

Study Location:

[ \_\_\_\_\_ ]  
[ \_\_\_\_\_ ]

**Formulation:**

Treatment	Dosage Form	Dose	Lot #	Lot Size
A	Roxicodone™ tablets	6 x 5 mg	961562	_____
B	Oxycodone IR tablet	30 mg	959069	_____

**Objective:**

To demonstrate the bioequivalence of two formulations of oxycodone given as a single oral dose to healthy male and female volunteers.

**Study Design:**

The study was designed as a single-dose, randomized, open-label, crossover study with 7-day washout between treatments in 17 healthy male and female volunteers. All subjects will receive one dose of each treatment, shown above, under fasted conditions in a random order.

**Analytical Methodology**

*Plasma Sampling Times:* pre-dose (0 hour), 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours

*Assay Method:* HPLC/MS/MS

*Assay Sensitivity:* The limit of quantitation was \_\_\_\_\_ with linear range of \_\_\_\_\_

*Assay Precision and Accuracy:* The within day precision ranged from \_\_\_\_\_ and for accuracy were \_\_\_\_\_ at concentrations of \_\_\_\_\_ (all QC samples).

**Results:**

Summary of pharmacokinetic data and profile of mean plasma concentrations over time following each treatment is shown in the following Table and Figure, respectively.

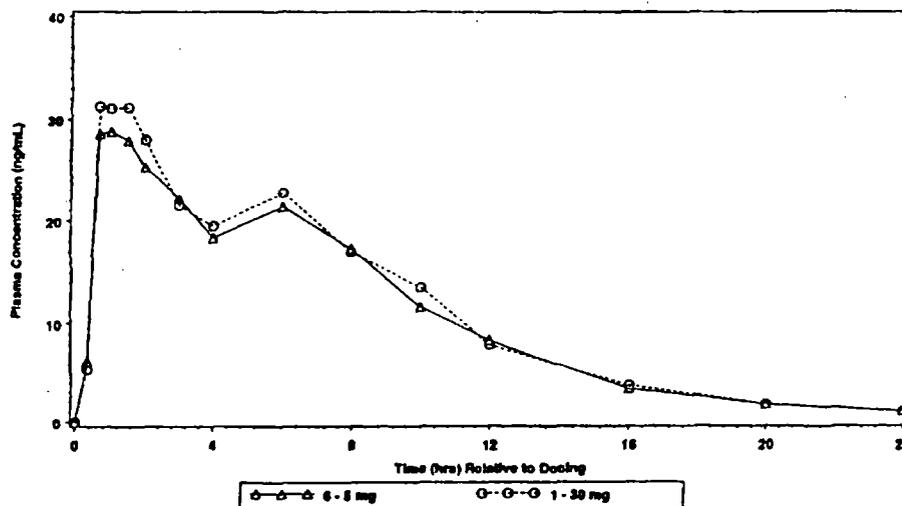
APPEARS THIS WAY  
ON ORIGINAL

Table: Summary of Pharmacokinetic Data

Parameter	Mean ± SD (N=17)		Comparison of Untransformed Data	
	1 x 30 mg Tablet	6 x 5 mg Tablets	Ratio (1 x 30 / 6 x 5)	90% Confidence Intervals of the Ratio
AUC <sub>0-24</sub> (ng•h/mL)	260.85 ± 56.06	256.07 ± 64.12	101.58%	93.74% - 109.42%
AUC <sub>0-∞</sub> (ng•h/mL)	268.19 ± 60.73	264.80 ± 67.89	100.87%	92.23% - 109.51%
C <sub>max</sub> (ng/mL)	39.34 ± 14.00	36.45 ± 12.49	107.65%	97.05% - 118.24%
k <sub>e</sub> (1/h)	0.19 ± 0.05	0.19 ± 0.05	--	--
t <sub>1/2</sub> (h)	3.85 ± 1.31	3.97 ± 1.61	--	--
T <sub>max</sub> (h)	2.63 ± 2.97	3.00 ± 2.66	--	--
LN AUC <sub>0-24</sub>	254.79 ± 0.23	248.12 ± 0.27	102.32%	94.86% - 110.36%
LN AUC <sub>0-∞</sub>	261.41 ± 0.24	256.11 ± 0.27	101.60%	93.51% - 110.38%
LN C <sub>max</sub>	37.24 ± 0.34	34.58 ± 0.33	107.32%	97.94% - 117.61%

-- Indicates these values were not calculated in the individual study report

Figure: Mean Plasma Concentrations over time



**Conclusion:**

The results indicated that the to-be-marketed oxycodone 30-mg IR tablet is bioequivalent to the currently marketed 5-mg oxycodone IR tablet (6 x 5 mg). Also, T<sub>max</sub>, K<sub>elim</sub>, and T<sub>1/2</sub> of oxycodone were similar between the two formulations.

Note: A double peak was observed in the plasma concentration profile in this study for both treatments.

**BEST POSSIBLE COPY**

**Study 315-04:** A Bioequivalence Study to Compare Two Formulations of Sustained-Release Oxycodone HCl Tablets (10 mg) to Immediate-Release Oxycodone HCl Oral Solution (Multiple-Dose, Three-Way Crossover).

Reference: Volume 18 - 22

Investigators: [

Study Location: \_\_\_\_\_ ]

**Formulation:**

Treatment	Dosage Form	Dose	Lot #	Lot Size
A	Oxycodone SR tablets	10 mg, Formulation A	939160	_____
B	Oxycodone SR tablet	10 mg, Formulation B	939161	_____
C	Roxicodone® solution	3.33 mL of 5 mg/5 mL	940048	_____

**Objective:**

To evaluate the bioequivalence of two oxycodone SR tablets and compare these results to an immediate release oxycodone solution (5 mg/5 mL).

**Study Design:**

The study was designed as a multiple-dose, open-label, 3-way crossover study with a washout period of 1 week between treatments in 30 healthy male volunteers. All subjects will receive each treatment, shown above, under fasted conditions in a random order. Formulation A and B were administered every 12 hours for 7 doses, while oral solution was administered every 4 hours for 21 doses.

**Analytical Methodology**

*Plasma Sampling Times:* pre-dose (0 hour), 12, 24, 36, 48, 60, 72 hour (trough concentrations) and at 72.5, 73, 74, 76, 76.5, 77, 78, 80, 80.5, 81, 82 and 84 hours (last dosing interval for the tablets and last three dosing intervals for the solution).

*Assay Method:* HPLC/MS/MS

*Assay Sensitivity:* The limit of quantitation was \_\_\_\_\_ with linear range of \_\_\_\_\_

*Assay Precision and Accuracy:* The inter-day and intra-day precision and accuracy values of the method at \_\_\_\_\_ (all QC samples) were less than \_\_\_\_\_

**Results:**

The two sets of (36/60 hour and 48/72 hour) trough concentration samples were compared to assess achievement of steady state. The analysis was done by linear regression of the concentrations over time using the SAS REG procedure. The means of the slopes and intercepts were tested against a nominal value of zero by the SAS MEANS procedure (steady state was achieved following 12 doses of the oral solution administered q4h, i.e., 48 hour). Summary of pharmacokinetic data is presented in Table 1. Observed and predicted (based on single-dose study, 315-07) mean values for  $C_{max}$  and AUC following doses of oral solution

are shown in Table 2. The mean plasma concentrations over time following each treatment is shown in Figure 1 (0-84 hour) and Figure 2 (72-84 hour).

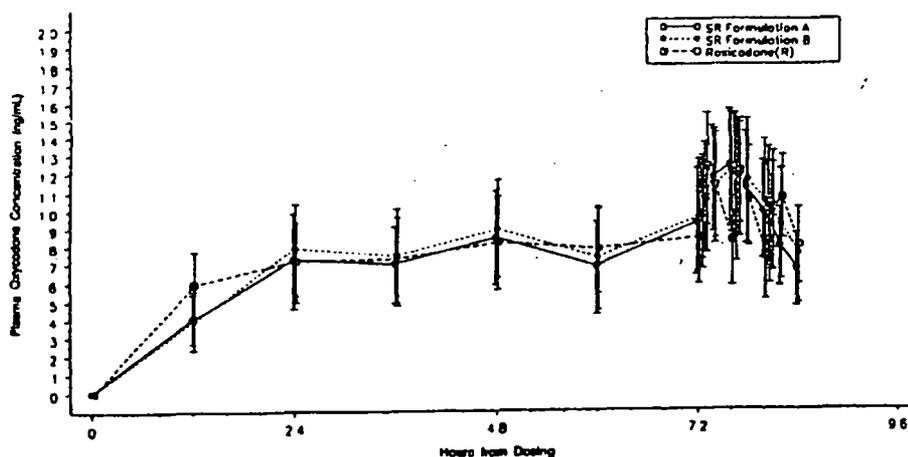
Table 1: Summary of Pharmacokinetic Data

Parameter	Formulation A	Formulation B	Solution	90% Confidence Interval	
				Formulation A/solution	Formulation B/solution
$C_{max}$ (ng/mL)	12.68 ± 3.28	12.78 ± 3.48	12.90 ± 3.05	94.4-102.2	95.1-103.0
$T_{max}$ (h)	3.70 ± 1.53	4.30 ± 1.83	1.04 ± 0.28	305.0-407.1	362.6-464.7
$AUC_{72-84}$ (h*ng/mL)	106.4 ± 27.9	108.3 ± 30.7	99.0 ± 24.8	103.4-111.5	105.3-113.4
$C_{avg}$ (ng/mL) <sup>a</sup>	10.02 ± 2.65	10.45 ± 2.92	9.73 ± 2.61	98.9-107.1	103.3-111.4
$C_{min}$ (ng/mL)	7.77 ± 2.19	8.44 ± 2.56	7.15 ± 2.28	103.2-114.3	112.5-123.6
Fluctuation Index <sup>b</sup>	0.557 ± 0.1	0.489 ± 1.13	0.718 ± 0.14	71.4-83.9	61.8-74.3

<sup>a</sup>  $C_{avg} = (C_{max} - C_{min}) / \ln(C_{max}/C_{min})$ .

<sup>b</sup> Fluctuation Index =  $(C_{max} - C_{min}) / C_{avg}$

Figure 1: Mean Plasma Concentrations over time (0-84 hour)



APPEARS THIS WAY  
ON ORIGINAL

Figure 2: Mean Plasma Concentrations over time (72-84 hour)

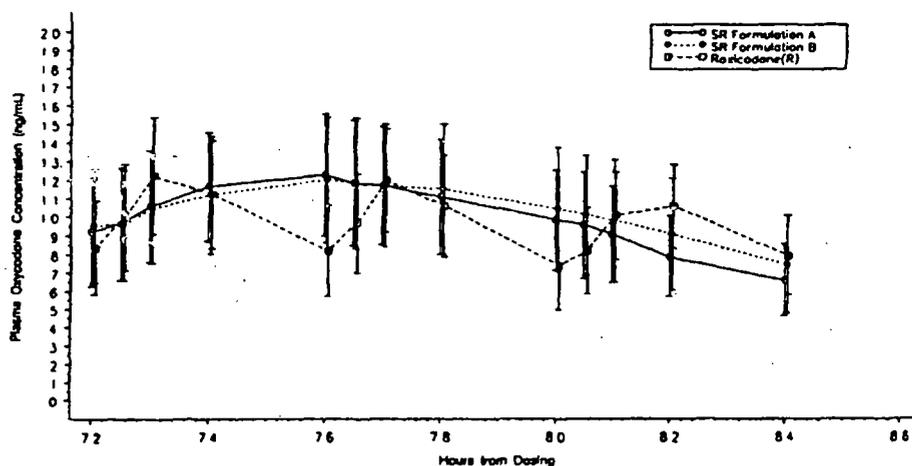


Table 2. Predictions of Steady State based on Single-Dose Data

Parameter	Single Dose		Steady State	
	Study 315-07		Study 315-04 (q4h)	
	Mean Observed	Dose Adjusted <sup>a</sup>	Predicted <sup>b</sup>	Mean Observed
C <sub>max</sub>	39.08	1.30	9.31	12.90
AUC	330.7	11.02	78.90	99.02

a Expressed per 1 mg dose.

b Mean K<sub>e</sub> = 0.156/h (Study 315-07)

Accumulation factor = 1/(1-e<sup>-k<sub>e</sub>t</sup>) = 2.15 (q4h).

Predicted = dose adjusted Accumulation factor x study dose

**Conclusion:**

Steady state was achieved following 4 doses (q12h dosing schedule) with the 10 mg SR formulation. There was less fluctuation of plasma levels with the SR formulation compared to that of the IR formulation. The data indicated that both SR formulations were bioequivalent to the oral solution with respect to the rate and extent of absorption (AUC<sub>72-84</sub>). The accumulation of oxycodone in plasma following repeated dosing was reasonably predictable from single dose information. In study 315-07, the mean k<sub>e</sub> of 0.156/h suggests an accumulation factor of 2.15 for q4h dose regimen. Although, the mean observed values were under-predicted by 20-30%, the values illustrate that oxycodone plasma levels at steady state will be approximately 2-fold higher than those of a single dose.

**BEST POSSIBLE COPY**

**Study 315-09:** A Bioavailability Study to Compare Sustained-Release Oxycodone HCl 10 mg Tablet Formulation to Immediate-Release Oxycodone HCl Oral Solution (Multiple-Dose, Two-Way Crossover).

Reference: Volume 23 - 24

Investigators: [

Study Location: ]

**Formulation:**

Treatment	Dosage Form	Dose	Lot #	Lot Size
A	Oxycodone SR tablet	10 mg, Formulation B	939161	_____
B	Roxicodone® solution	5 mL of 5 mg/5 mL	941548	_____

**Objective:** To evaluate the bioavailability of an oxycodone SR 10 mg tablet given every 12 hours for 7 doses and an IR oxycodone oral solution given every 6 hours for 14 doses.

**Study Design:** The study was designed as a multiple-dose, open-label, two-way crossover study between treatments (approximately a week apart) in 25 healthy male volunteers. All subjects will receive each treatment, shown above, under fasted conditions in a random order. SR tablet formulation was administered every 12 hours for 7 doses, while oral solution was administered every 6 hours for 14 doses.

**Analytical Methodology**

**SR Tablet** - predose (0 hour), 24, 36, 48, 60, 72, 72.5, 73, 74, 75, 75, 76, 77, 78, 80, 82, 84 hours.

**Oral Solution** - predose (0 hour), 24, 36, 48, 60, 72, 72.5, 73, 73.5, 74, 75, 76, 78, 78.5, 79, 79.5, 80, 81, 82, 84 hours.

**Assay Method:** HPLC/MS/MS

**Assay Sensitivity:** The limit of quantitation was \_\_\_\_\_ with linear range of \_\_\_\_\_

**Assay Precision and Accuracy:** The inter-day and intra-day precision and accuracy values of the method at \_\_\_\_\_ (all QC samples) were less than \_\_\_\_\_

**Results:** Steady state was determined using the trough concentration samples of 48, 60, 72 and 84 hours. The analysis was done by linear regression of the concentrations over time using the SAS REG procedure. The means of the slopes and intercepts were tested against a nominal value of zero by the SAS MEANS procedure. Summary of pharmacokinetic data is presented in Table 1. Observed and predicted (based on single-dose study, 315-07) mean values for C<sub>max</sub> and AUC following doses of oral solution are shown in Table 2. The mean plasma concentrations over time following each treatment is shown in Figure 1 (0-84 hour) and Figure 2 (72-84 hour).

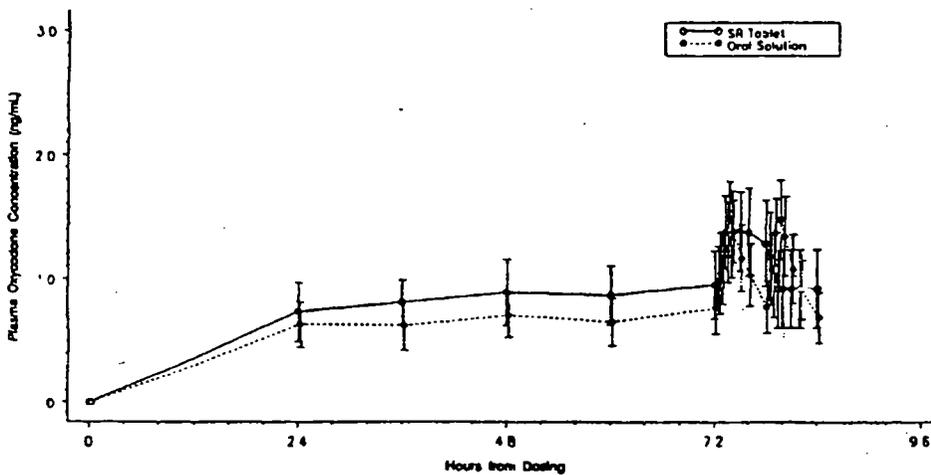
Table 1: Summary of Pharmacokinetic Data

Parameter	SR tablet	Solution	90% Confidence Interval SR tablet/solution
C <sub>max</sub> (ng/mL)	14.58 ± 3.63	15.69 ± 3.15	87.9-98.1
T <sub>max</sub> (h)	4.0 ± 1.6	1.3 ± 0.3	262.1-346.3
AUC <sub>72-84</sub> (h*ng/mL)	122.68 ± 31.5	113.25 ± 24.0	102.5-114.3
C <sub>avg</sub> (ng/mL) <sup>a</sup>	10.22 ± 2.63	9.44 ± 2.00	102.5-114.3
C <sub>min</sub> (ng/mL)	9.36 ± 2.66	7.42 ± 1.84	118.2-134.0
Fluctuation Index <sup>b</sup>	0.593 ± 0.216	1.149 ± 0.262	43.5-60.0

<sup>a</sup> C<sub>avg</sub> = (C<sub>max</sub> - C<sub>min</sub>)/ln(C<sub>max</sub>/C<sub>min</sub>).

<sup>b</sup> Fluctuation Index = (C<sub>max</sub> - C<sub>min</sub>) / C<sub>avg</sub>

Figure 1: Mean Plasma Concentrations over time (0-84 hour)



APPEARS THIS WAY  
 ON ORIGINAL

BEST POSSIBLE COPY

Figure 2: Mean Plasma Concentrations over time (72-84 hour)

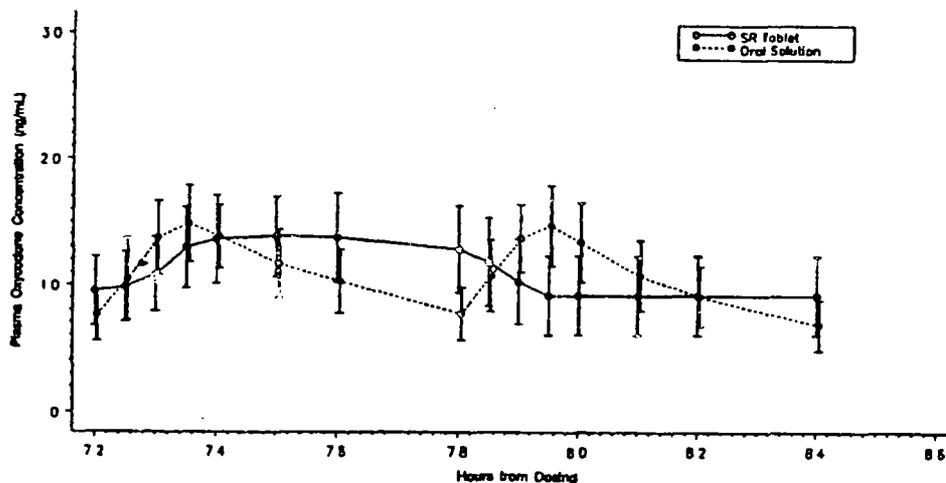


Table 2. Predictions of Steady State based on Single-Dose Data

Parameter	Single Dose		Steady State	
	Study 315-07		Study 315-09 (q6h)	
	Mean Observed	Dose Adjusted <sup>a</sup>	Predicted <sup>b</sup>	Mean Observed
C <sub>max</sub>	39.08	1.30	10.73	15.69
AUC	330.7	11.02	90.92	113.25

a Expressed per 1 mg dose.

b Mean K<sub>e</sub> = 0.156/h (Study 315-07)

Accumulation factor =  $1/(1-e^{-k_e\tau}) = 1.65$  (q6h).

Predicted = dose adjusted Accumulation factor x study dose

### Conclusion:

Steady state was achieved following 4 doses (dosed q12h) with the 10 mg SR formulation. There was less fluctuation of plasma levels with the SR formulation than the IR formulation. The SR formulations had a relative bioavailability of 108% compared to the solution (based on AUC<sub>72-84</sub>), and the two formulations were bioequivalent with respect to C<sub>max</sub> and AUC<sub>72-84</sub>. The accumulation of oxycodone in plasma following repeated dosing was reasonably predictable from single dose information. In study 315-07, the mean k<sub>e</sub> of 0.156/h suggests an accumulation factor of 1.65 for q6h dose regimen. Although, the mean observed values were under-predicted by 20-30%, the values illustrate that oxycodone plasma levels at steady state will be approximately 2-fold higher than those of a single dose.

**BEST POSSIBLE COPY**

**Study 315-10:** A Single-Dose, Four-Way Crossover, Food Effect Study of the 10 mg Formulation of Oxycodone Sustained-Release Tablets and Oxycodone Immediate Release Oral Solution in healthy volunteers.

Reference: Volume 25

Investigators:

Study Site:

[REDACTED]

**Formulation:**

Treatment	Dosage Form	Dose	Lot #	Lot Size
1	Oxycodone SR tablet	10 mg-fasted	939161	_____
2	Oxycodone SR tablet	10 mg-fed	939161	_____
3	Roxicodone® solution	10mL of 5mg/5mL-fasted	941548	_____
4	Roxicodone® solution	10 mL of 5 mg/5 mL-fed	941548	_____

**Objective:** To determine the effect of food on the pharmacokinetic characteristics of a sustained release (SR) oxycodone tablet formulation and an immediate release (IR) oxycodone oral solution following administration of a FDA high-fat breakfast and under fasting conditions.

**Study Design:** The study was designed as a single-dose, open-label, 4-way crossover study between treatments (approximately a week apart) in 14 healthy male volunteers. All subjects received one dose of each treatment, shown above, in a random order: subjects who were fed prior to dosing received a high-fat breakfast consisting of 2 fried eggs, 2 strips of bacon, 2 slices of toast with butter, 2-4 oz. servings of hash browned potatoes and 8 oz. (240 ml) of whole milk.

**Analytical Methodology**

**Plasma Sampling Times:** pre-dose (0 hour), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, and 48 hours following each dose.

**Assay Method:** HPLC/MS/MS

**Assay Sensitivity:** The limit of quantitation was \_\_\_\_\_ with linear range of \_\_\_\_\_

**Assay Precision and Accuracy:** The inter-day and intra-day precision and accuracy values of the method at \_\_\_\_\_ (all QC samples) \_\_\_\_\_

**Results:** Summary of pharmacokinetic data is presented in Table 1. Table 2 presents the ratios and CI for comparisons of the 10 mg/10 mL oral solution under fasting and fed conditions. The profile of mean plasma concentrations over time following each treatment is shown in Figure 1.

Table 1: Summary of Pharmacokinetic Data

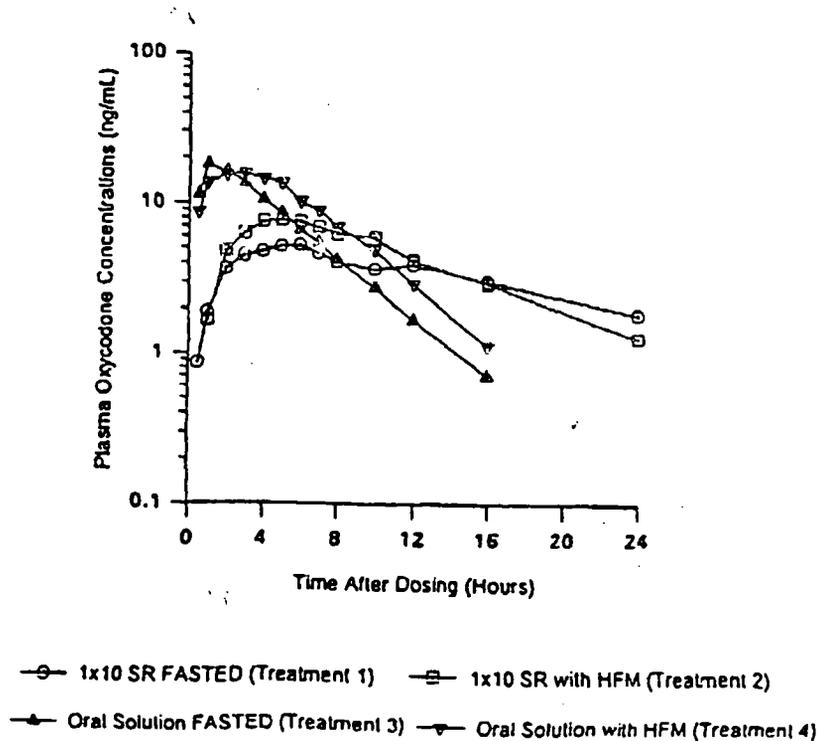
Parameter	SR Tablet 10 mg Fed	SR Tablet 10 mg Fasted	IR Oral Solution 10 mg Fed	IR Oral Solution 10 mg Fasted
$C_{max}$ (ng/mL)	8.92 ± 2.40	5.74 ± 0.94	17.7 ± 2.96	19.0 ± 3.67
$T_{max}$ (h)	4.79 ± 1.81	5.64 ± 1.55	2.54 ± 1.20	1.25 ± 0.51
$AUC_{0-24}$ (h•ng/mL)	130 ± 37.3	119 ± 20.7	133 ± 25.2	105 ± 16.2
$t_{1/2}$ (h)	9.13 ± 7.86	12.5 ± 7.43	3.26 ± 0.50	2.93 ± 0.36

Table 2: Comparison 10 mg/10 mL Fed versus Fasting

Parameter	IR Oral Solution 10 mg Fed	IR Oral Solution 10 mg Fasted	Ratio% (Fed/Fasting)	90% CI Original Data (%)	90% CI Log-Transformed Data (%)
$C_{max}$ (ng/mL)	17.7 ± 2.96	19.0 ± 3.67	94%	86% - 101%	87% - 101%
$T_{max}$ (h)	2.54 ± 1.20	1.25 ± 0.51	203%	163% - 244%	NR <sup>a</sup>
$AUC_{0-24}$ (h•ng/mL)	133 ± 25.2	105 ± 16.2	126%	118% - 134%	118% - 133%
$t_{1/2}$ (h)	3.26 ± 0.50	2.93 ± 0.36	111%	NR <sup>a</sup>	NR <sup>a</sup>

<sup>a</sup> Not required by the FDA bioequivalence guidelines

Figure 1: Mean Plasma Concentrations over time



**BEST POSSIBLE COPY**

**Conclusion:**

The results of this study show that food increased the extent ( $AUC_{0-\infty}$ ) of absorption (26% increase), but not the rate ( $C_{max}$ ) of oxycodone absorption from the IR solution.  $T_{max}$  was delayed by 203% when IR solution was given with high fat meal compared to that under fasting condition. The oral solution was bioequivalent under fed and fasting conditions with respect to  $C_{max}$  but not for  $AUC_{0-\infty}$ . A food effect study has not been conducted using the to-be-marketed 15 or 30 mg IR tablet formulations. However, the 15 and 30 mg IR tablet formulations have been compared to the currently marketed 5 mg IR tablet formulation and to the currently marketed 5 mg/5 mL and 20 mg/mL oral solutions in bioequivalence studies, and the tablet formulations have been shown to be bioequivalent to the oral solution in fasted state (XIR0296, XIR 0396, 315-07). Thus, the food effect seen on oral solution can be considered to be due to the drug substance. Therefore, the food effect for the to-be-marketed formulation tablets can be extrapolated from the food effects on IR solution.

**APPEARS THIS WAY  
ON ORIGINAL**

**Study XIR0196:** A Single dose, Randomized, Double-Blind, Three-Way Crossover Study Comparing the Dose Proportionality of 5 mg, 15 mg, and 30 mg Doses of Oxycodone Administered Orally to Healthy Volunteers Under Fasting Conditions

Reference: Volume 16 - 17

Investigators:

Study Location:

**Formulation:**

Treatment	Dosage Form	Dose	Lot #	Lot Size
A	Roxicodone™ tablet	1 x 5 mg and placebo	961562	_____
B	Roxicodone™ tablet	3 x 5 mg and placebo	961562	_____
C	Roxicodone™ tablet	6 x 5 mg	961562	_____

**Objective:**

To determine (a) the dose proportionality of oxycodone tablets at doses of 5 mg, 15 mg, and 30 mg in healthy subjects and (b) whether there is an efficacy dose response in the cold pressor test after a single dose of the study medication.

**Study Design:**

The study was designed as a single-dose, randomized, open-label, placebo-controlled, 3-way crossover study with at least 7-day washout between treatments in 25 healthy male and female volunteers, mean age of 26 years (range, 19-37 years). All subjects will receive one dose of each treatment, shown above, in a random order.

**Pharmacodynamic Analysis:** Each subject verbally reported 'pain' and 'pain bothersomeness' on a scale of 0 (not at all painful/pain bothersomeness) to 10 (extremely painful/pain bothersomeness) at 30, 70, 110 and 170 seconds after onset of the cold water immersion.

**Analytical Methodology**

**Plasma Sampling Times:** pre-dose (0 hour), 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, and 36 hours.

**Assay Method:** HPLC/MS/MS

**Assay Sensitivity:** The limit of quantitation was \_\_\_\_\_ with linear range of \_\_\_\_\_

**Assay Precision and Accuracy:** The inter-day and intra-day precision were \_\_\_\_\_ and for accuracy were \_\_\_\_\_ at concentrations of \_\_\_\_\_ (all QC samples).

**Results:**

Summary of pharmacokinetic data, profile of mean plasma concentrations over time, pain intensity dose response at 1 hour, pain bothersomeness dose response at 1 hour and adverse events with respect to dose following each treatment are shown in Table 1, Figures 1-4, respectively.

Figure 2: Oxycodone Dose Pain Intensity Response at 1 hour

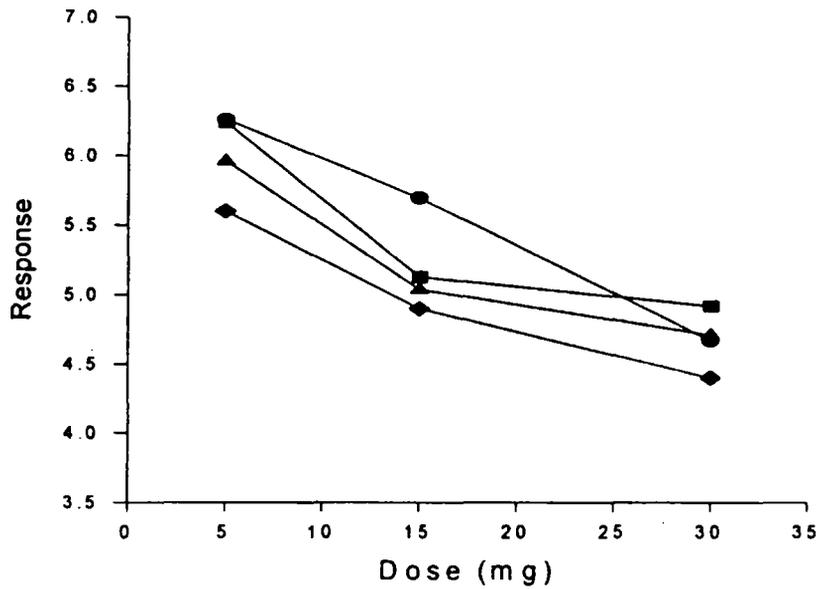
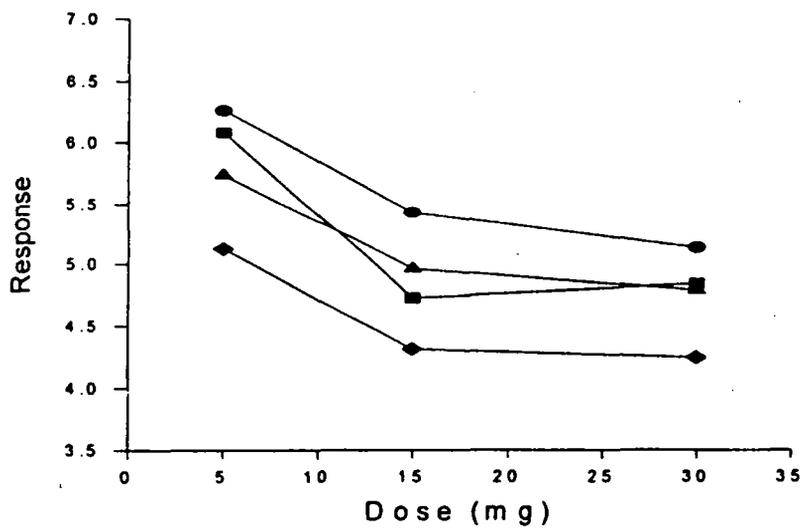
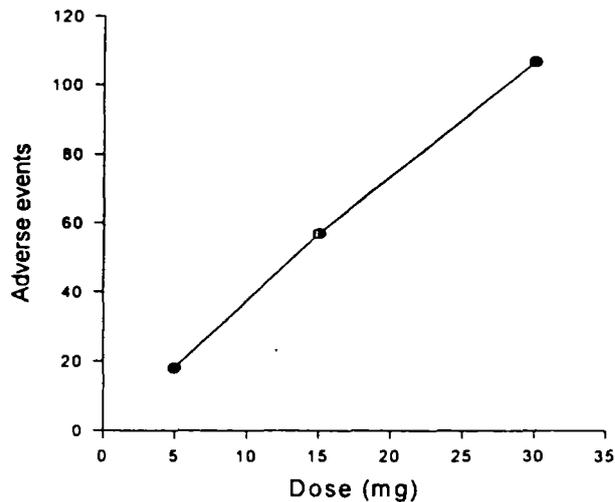


Figure 3: Oxycodone Dose Pain Botheredness Response at 1 hour



◆ 30 Seconds                      ▲ 110 Seconds  
■ 70 Seconds                      ● 170 Seconds

Figure 4: Adverse effects versus Dose: A total of 182 adverse events were reported during the study. Eighteen events were reported in the 5-mg dose group, 57 events were reported in the 15-mg dose group and 107 events were reported in the 30-mg dose group.



**Conclusion:**

Pharmacokinetic dose proportionality was achieved with respect to AUC following single 5mg, 15 mg, and 30 mg doses of oxycodone.  $C_{max}$  was proportional to dose between the 5 mg and 15 mg doses and between the 15 and 30 mg doses, but not between the 5 mg and 30 mg doses. Pharmacodynamic dose proportionality analysis showed that the mean pain intensity/pain bothersomeness reported 1 hour post-dose appeared to decrease as the dose increased, however, not linearly; the dose-response curves were shallow and the most significant effect (visually) was following 15 mg compared to that of 5 mg. In addition, adverse events increased nearly linearly as dose increased.

**APPEARS THIS WAY  
ON ORIGINAL**

POPULATION PHARMACOKINETIC ANALYSIS OF ROXICODONE™ IMMEDIATE-RELEASE TABLETS IN PATIENTS (STUDY XIR0596) AND HEALTHY VOLUNTEERS (STUDY XIR0196).

Reference: Volume 26

Reported by: \_\_\_\_\_

**Formulation:**

Clinical Study	Dosage Form	Lot No.	Lot Size
XIR0596	5-mg IR tablets	962810	[ _____ ]
	15-mg IR tablets	969032	
	30-mg IR tablets	959069	
XIR0196	5-mg IR tablets	961562	

**Objective:**

Objectives for this analysis were 1) to describe the dose-concentration relationship for immediate-release oxycodone tablets after multiple dosing in patients, 2) to identify any sub-populations of patients with altered oxycodone PK, and 3) to compare oxycodone PK parameters between patients and healthy volunteers.

**Study Design:**

Study XIR0596: This was a multicenter, open-label, Phase III study to assess the safety and efficacy of 15 and 30-mg tablets of IR oxycodone hydrochloride administered at regularly scheduled 4-6 hour intervals (approximately 4-6 doses/day) for the treatment of moderate-to-severe chronic pain. The study consisted of a 2-7 day stabilization period and a 7-day open-label treatment period. At the end of the 7-day study, patients could choose to participate in a 4-week extension study (XIR0696), with the approval of the investigator. Patients who required a dosage regimen of only the 15 mg tablet formulation were assigned to the 15 mg group. Patients who required a dosage regimen consisting of 30 mg tablets only or a combination of 15 mg and 30 tablets were assigned to the 30 mg group. Oxycodone 5 mg tablets were used as the rescue medication for breakthrough pain. Use of the rescue medication was not permitted within 1 hour of the scheduled dose of study medication. Only two doses of the rescue medication were allowed between doses of the study medication.

Study XIR0196: This was a single-dose, randomized, double-blind, three-way crossover study comparing the dose-proportionality of 5 mg, 15 mg (3 x 5 mg), and 30 mg (6 x 5 mg) doses of oxycodone administered orally to healthy volunteers (25 subjects) under fasting conditions.

**Analytical Methodology**

*Plasma Sampling Times:*

Study XIR0596 The first sample was to be collected approximately 0.5 to 2 hours after a dose. The second sample was to be collected within the 2 hours prior to the next dose. If this was not possible, the two blood samples may have been drawn after different doses or even on different days, anytime after stabilization (recorded the precise time of the blood collection and time of last dosing).

Study XIR0196 pre-dose (0 hour), 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, and 36 hours.

*Assay Method:* HPLC/MS/MS

*Assay Sensitivity:* The limit of quantitation was \_\_\_\_\_ with linear range of \_\_\_\_\_

*Assay Precision and Accuracy:* Within acceptable limits.

**Population Pharmacokinetic (PK) Analysis:**

Population PK Analysis was performed using the NONMEM software (version V). An initial data set, containing data from the patient safety study only (XIR0596, 62 patients, 122 PK samples) was constructed which resulted in poor model fits and parameter estimates. Further inspection of these data revealed that the majority of PK observations (79%) were obtained within the first three hours of dosing and minimal information (12% of samples) was obtained between 4 and 8 hours after dosing. In order to obtain the entire plasma drug concentration-time curve, data from Study XIR0196 in healthy volunteers (28 subjects, 967 total PK samples) was incorporated. The combined data set (90 subjects, 1089 PK samples) was used for all subsequent model building. The following briefly outlines the steps used to build the model:

1. Define a base model as a one-compartment model with first-order absorption and an absorption lag time, based on XIR0196.
2. Empirical Bayesian estimates of individual model parameters were generated using the POSTHOC subroutine in NONMEM.
3. Generalized additive model analysis, using S-PLUS software (Version 4.5) and Xpose (Version 2.003), to explore the relationships between covariate factors and individual estimates of model parameters. Results of the GAM analysis were used to eliminate insignificant covariates and guide the stepwise model building process; covariates from the patient data set, which were identified as those found significant in the GAM analysis, and all of the healthy volunteer covariates were included in the model building process since the number of different covariates in the healthy volunteer data set was small, and all healthy volunteer covariates were also present in the patient data.
4. "Final" model: after the full model was defined (the model resulting at the end of the building process is known as the "full" NONMEM model), the statistical significance of each covariate-parameter relationship was tested individually in a stepwise deletion method. The significance of a covariate was assessed at the  $p < 0.005$  level (increase in objective function value at least 7.88 units for 1 df).

Results and Discussion:

Summary of demographic factors: All of demographic factors, except LDH and ALT, were in normal range among patients in Study XIR0596 (opioid naive and race were not included due to lack of representation of these groups).

	XIR0596		XIR0196	
	Male	Female	Male	Female
Age (years)	45 ± 14	50 ± 11	29 ± 6	25 ± 3
Weight (lbs)	182 ± 35	167 ± 38	163 ± 14	129 ± 13
Height (in)	70 ± 3	64 ± 3	71 ± 2	65 ± 3
Total daily dose (mg)	129 ± 47	122 ± 88	NA	NA
Creatinine (mg/dL)	1.0 ± 0.2	0.8 ± 0.2	NA	NA
LDH (IU/L) <sup>1</sup>	190 ± 140	216 ± 137	NA	NA
ALT (IU/L) <sup>2</sup>	33 ± 33	17 ± 12	NA	NA
AST (IU/L)	28 ± 19	20 ± 7	NA	NA
Alkaline Phosphatase (IU/L)	80 ± 26	85 ± 42	NA	NA
Total Bilirubin (mg/dL)	0.6 ± 0.2	0.5 ± 0.2	NA	NA
Creatinine clearance ((L/hr)	7.1 ± 2.2	6.5 ± 2.6	NA	NA

<sup>1</sup>Normal range: 90 – 200 IU/L

<sup>2</sup>Normal range: 0 – 35 IU/L

Base Pharmacokinetic Model: Parameter estimates for the base PK model are listed in Table 1 and population mean predicted versus observed plasma oxycodone concentrations are shown in Figure 1. Estimates of all fixed effect parameters were precise. The estimated inter-individual variabilities in CL/F and  $k_a$  were large with CVs of 109% and 89.6%, respectively. Estimates of random effect parameters are less precise than fixed effect parameters. Figure 1 revealed a trend toward slight under-prediction at higher concentrations, but no significant systematic bias was evident (Figure 2).

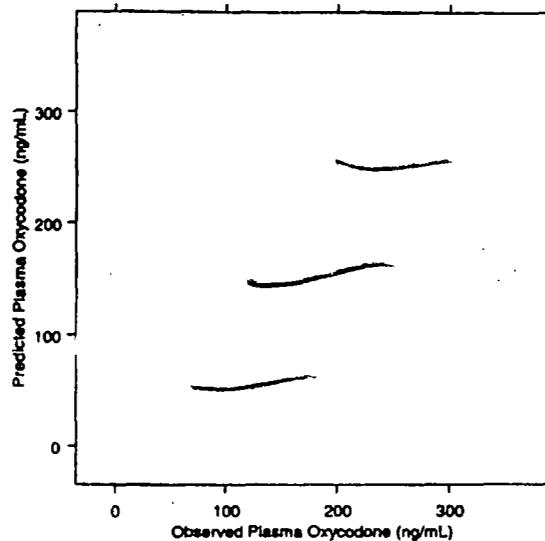
Table 1: Base Population PK Model Parameter Estimates

Structural Model and Interindividual Variance Parameters		
Parameter	Typical Value (%RSE*)	Interindividual CV% (%RSE*)
CL/F (L/hr)	79.4 (9.69%)	109% (54.8%)
V/F (L)	575 (6.73%)	32.1% (88.0%)
$k_a$ (hr <sup>-1</sup> )	5.36 (20.7%)	89.6% (35.0%)
ALAG (hr)	0.194 (24.2%)	NE**
Intraindividual, Residual Error		
Parameter	Estimate (%RSE*)	Interindividual CV% (%RSE*)
$\sigma^2_{1_{add}}$	SD=0.522 (55.5%)	-
$\sigma^2_{2_{prop}}$	CV%=35.5% (15.6%)	-

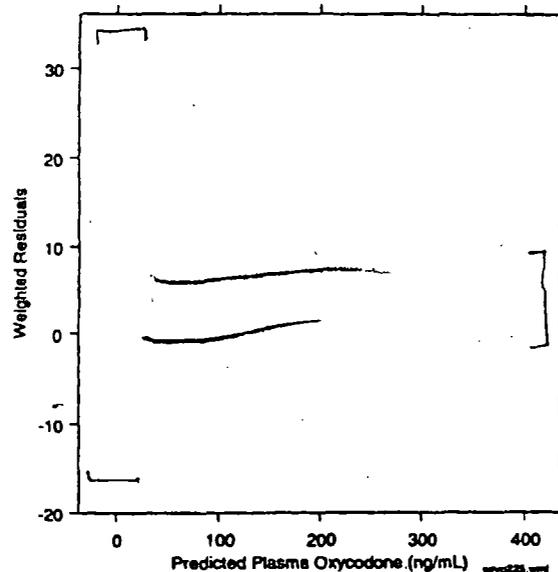
\* %RSE: percent relative standard error of the estimate = SE/parameter estimate \* 100

\*\* Not estimable

**Figure 1:** Population Mean Prediction vs. Observed Plasma Oxycodone Concentration (Base Model); plasma oxycodone concentrations are indicated by individual ID numbers and a loess (local regression method) smooth of the data (dotted line). The line of unity (solid) is included as a reference.



**Figure 2:** Weighted residuals vs. Predicted Plasma Oxycodone Concentrations (Base Model); notations are the same as figure 1.



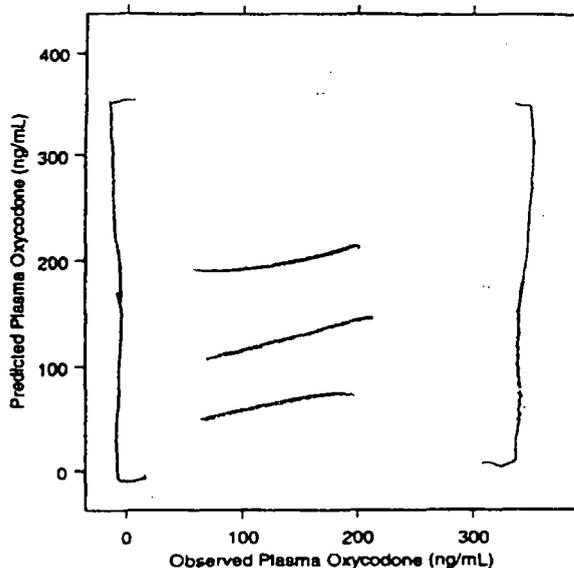
**Final Model:** The results revealed that the only significant covariates in the final model were PROT (protocol) on CL/F and CREA (creatinine) on V/F. Substitution of PROT for CREA on V/F resulted in a significant increase in the objective function value, indicating that interindividual variability in V/F was due to more than just protocol-dependent differences. Diagnostic scatterplot revealed a slight improvement in the model fit from the base model (Figure 3) with no significant systematic bias (Figure 4).

Table 5: Final Model Parameter Estimates

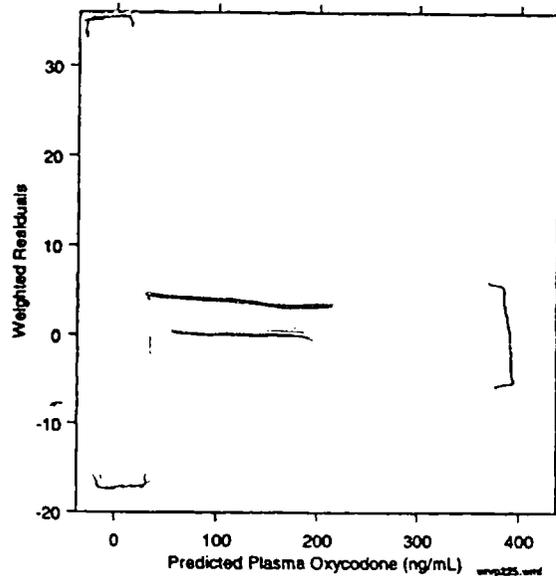
Structural Model and Interindividual Variance Parameters		
Parameter	Typical Value (%RSE*)	Interindividual CV% (%RSE*)
CL/F (L/hr)	~PROT	50.9% (24.3%)
$\theta_{1HV}$	104 (6.46%)	-
$\theta_{5PAT}$	71.9 (8.40%)	-
V/F (L)	~CREA	22.8% (38.4%)
$\theta_{2INT}$	563 (4.78%)	-
$\theta_{6CREA}$	881 (26.3%)	-
$k_a$ (hr <sup>-1</sup> )	No Covariates	79.3% (36.9%)
$\theta_3$	3.99 (17.5%)	-
ALAG (hr)	No Covariates	Not estimable
$\theta_4$	0.271 (3.25%)	-
Intraindividual, Residual Error		
Parameter	Estimate (%RSE*)	Interindividual CV% (%RSE*)
$\theta_{7add, HV}$	SD=0.047 (44.4%)	191% (73.6%)
$\theta_{8prop, HV}$	CV%=33.4% (6.47%)	27.2% (32.1%)
$\sigma^2_{3add, PAT}$	SD=21.4 (25.4%)	-

\*%RSE: percent relative standard error of the estimate = SE/parameter estimate \* 100

Figure 3: Population Mean Prediction vs. Observed Plasma Oxycodone Concentration (Final Model); notations are the same as figure 1.



**Figure 4:** Weighted residuals vs. Predicted Plasma Oxycodone Concentrations (Final Model); notations are the same as figure 1



Comparison of Oxycodone Pharmacokinetics in Patients and Healthy Volunteers: The frequency distribution of individual CL/F, V/F and  $K_a$  conditional estimates with the final model is displayed as a histogram (Figures 4-6); the top panel (PROT = 1.00) and bottom panel (PROT = 0.00) represent the distribution for patients and healthy volunteers, respectively. Additionally, comparison between patients and healthy volunteers with respect to PK parameters are listed in Table 6.

**Figure 5:** Distribution of Individual CL/F Estimates (Final Model)

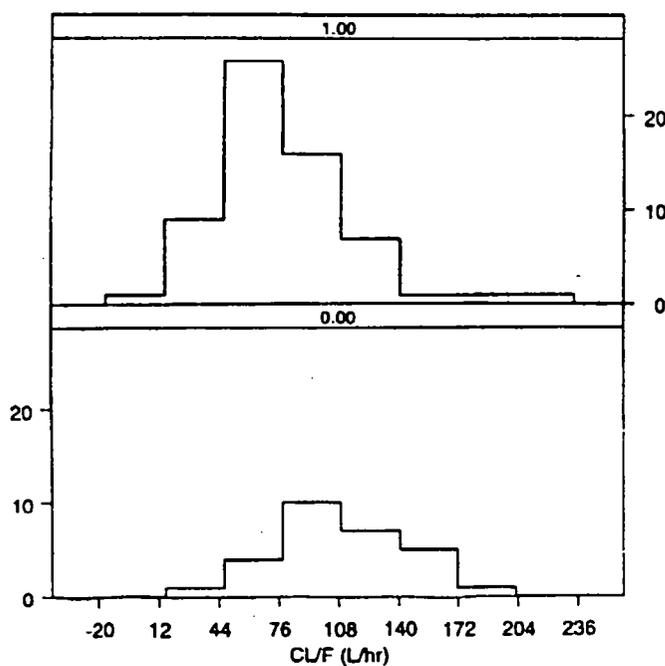


Figure 6: Distribution of Individual V/F Estimates (Final Model)

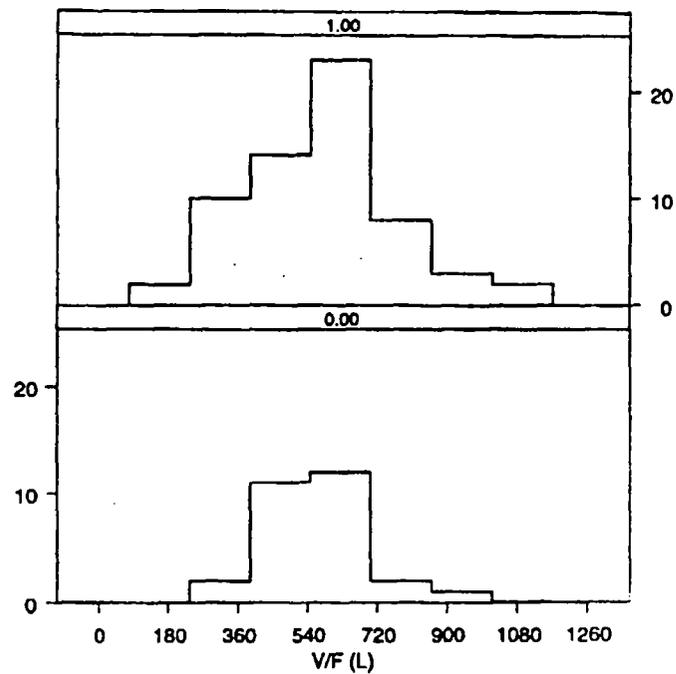
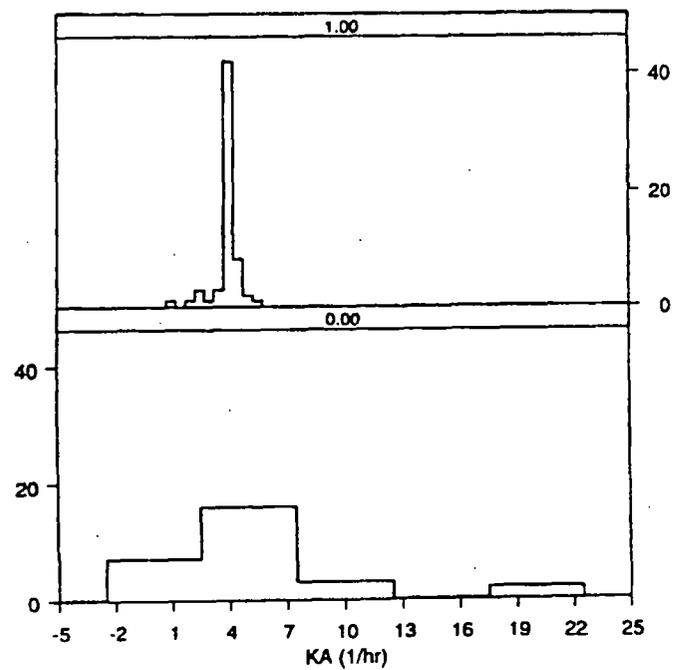


Figure 7: Distribution of Individual  $k_a$  Estimates (Final Model)



**Table 6:** Comparison of Conditional Estimates of Individual PK Parameters Between Patients and Healthy Volunteers.

	CL/F (L/hr)		V/F (L)		k <sub>a</sub> (hr <sup>-1</sup> )	
	Patients <sup>a</sup>	HV <sup>b</sup>	Patients <sup>a</sup>	HV <sup>b</sup>	Patients <sup>a</sup>	HV <sup>b</sup>
<b>Mean</b>	77.9	108	572	566	3.92	5.64
<b>Median</b>	73.6	102	564	574	4.00	3.99
<b>Minimum</b>	14.8	45.9	204	313	1.17	1.13
<b>Maximum</b>	223	180	1090	880	5.62	22.3
<b>SD</b>	37.4	33.2	189	123	0.670	5.23

<sup>a</sup>patients = protocol-1.

<sup>b</sup>HV = healthy volunteers (protocol-0).

The distributions of individual parameter estimates were different between patients and healthy volunteers. Variability in CL/F and V/F are greater for patients than healthy volunteers, while variability in k<sub>a</sub> was smaller.

**Conclusions:**

An explanation for the significant difference in CL/F between patients and healthy volunteers was not evident from these data, except that data came from two different populations with different protocols. This suggests that the model may need to include other factor(s), such as **disease-state/(different) sampling time/concomitant medication/rescue medication**, beside 'laboratory test values' to identify the factor(s) influencing the CL/F difference between patients and healthy volunteers.

Any covariate effect identified in this analysis is likely to be minor, as evidenced by the lack of a decrease in the random inter-individual error estimates for CL/F and V/F (however, it is expected since the chosen covariates were within normal range, except LDH and AST values in a few patients). In this analysis, no gender differences in oxycodone pharmacokinetics were identified. The effect of race on oxycodone pharmacokinetics or effects of opioid use history were not examined because of the poor representation of these groups, since the number of patients who belong to these categories were small. No apparent explanation for the significant relationship between serum creatinine and V/F was evident and this may have simply been a correlated, but not explanatory, covariate factor.

The model is a simple representation of some of the factors that influence oxycodone pharmacokinetics in patients/healthy volunteers. Fixed effects parameters as well as most random effect terms were estimated with precision and model predictions were without systematic bias. However, this analysis reveals that more experimentation and continued model development are required in terms of identifying the factor(s) influencing the CL/F difference between patients and healthy volunteers.

DISSOLUTION METHODOLOGY

Dissolution testing was done based on USP compendial method II using multiple media over a wide pH range, four NDA lots from each strength, stirring rate of 50 rpm; and storage conditions. Compendial-dissolution conditions and the four NDA lots of oxycodone 15 and 30 mg tablets were tested as shown in Table 1 and Table 2, respectively.

Table 1: Compendial dissolution conditions for Roxicodone™ Tablets 15 and 30 mg

Dissolution Medium	Deionized Water
Dissolution Volume	500 mL
Apparatus	USP Type II (paddle)
Rotation Speed	50 rpm
Temperature	37.0 ± 0.5 °C
Sample Time	45 minutes
Detection	UV @ 225 nm:

\* Method reference: Technical Report 0955-24, Roxane Laboratories, Inc.

Table 2: Roxicodone™ Tablets, 15 and 30 mg, NDA lots

NDA Lots	
15 mg Tablet	30 mg Tablet
969032	959069
969083	969081
969084	969082
979023	979024

1. TABLET DISSOLUTION AS A FUNCTION OF pH

Oxycodone release was evaluated over a pH range, 5.0 (deionized water) and 6.0 using the USP method II at 50 rpm. The dissolution profiles for 15 mg and 30 mg are shown in Figures 1 and 2, respectively.

Figure 1: Mean % release of oxycodone 15 mg as a function of pH; average of 6 tablets ± SD

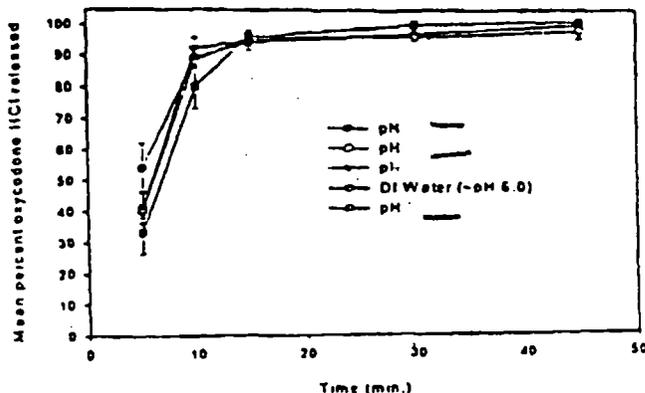
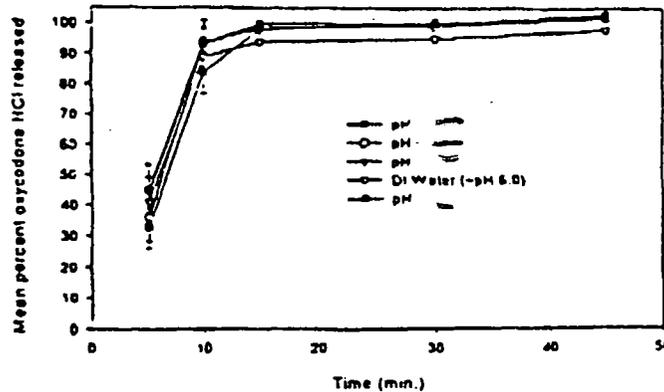


Figure 2: Mean % release of oxycodone 30 mg as a function of pH; average of 6 tablets ± SD



The results indicate that release of oxycodone Tablets, 15 mg and 30 mg, is independent of pH, with more than 90% of the drug released at 15 minutes.

## 2. DISSOLUTION PROFILES IN WATER: NDA LOTS

Dissolution testing of NDA lots from each tablet strength, 15 mg and 30 mg, was performed using the compendial method for oxycodone tablets. Dissolution was performed using 500 mL of deionized water at  $37.0 \pm 0.5^{\circ}\text{C}$ , 50 rpm, with additional samples withdrawn at 5 and 10 minutes. The results indicate that for all manufactured lots oxycodone HCl is released variably between 0 and 30 minutes, with a mean drug release greater than 90% in 30 minutes. The firm also investigated dissolution profiles on 12-tablets. The drug release profile was similar as 6-tablets. However, one NDA Lot, #969032 did not meet  $Q = 100\%$  in 30 minutes. Therefore, the sponsor proposed  $Q = 70\%$  in 45 minutes seems to be adequate. The graphical representations of the results for 15 and 30 mg (6-tablets) are shown in Figures 3 and 4, respectively.

Figure 3: Mean % release of oxycodone 15 mg (6 tablets ± SD)

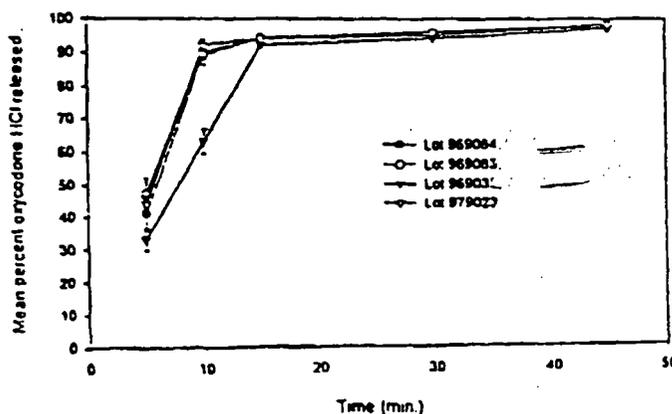
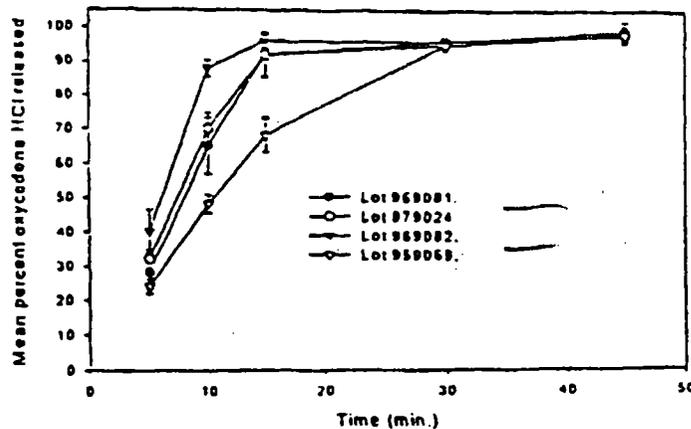


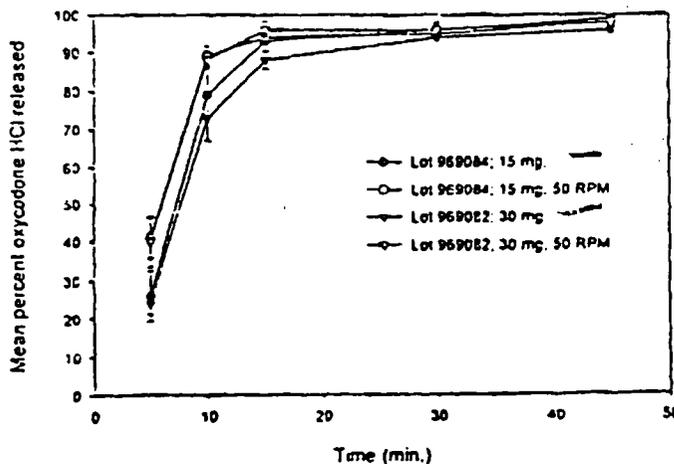
Figure 4: Mean % release of oxycodone 30 mg; average of 6 tablets ± SD



### 3. INFLUENCE OF PADDLE STIRRING RATE

Lots 969084 and 959082 for 15 mg and 30 mg, respectively, were selected to determine the influence of stirring rate. The USP dissolution method described in Table 1 was used with modification of the stir rate to  $\text{---}$  rpm. The results were compared to previous results obtained for these lots at 50 rpm. The graphical representation of the results for 15 and 30 mg is shown in Figure 5.

Figure 5: Mean % release of Roxicodone™ Tablets (6 tablets ± SD)

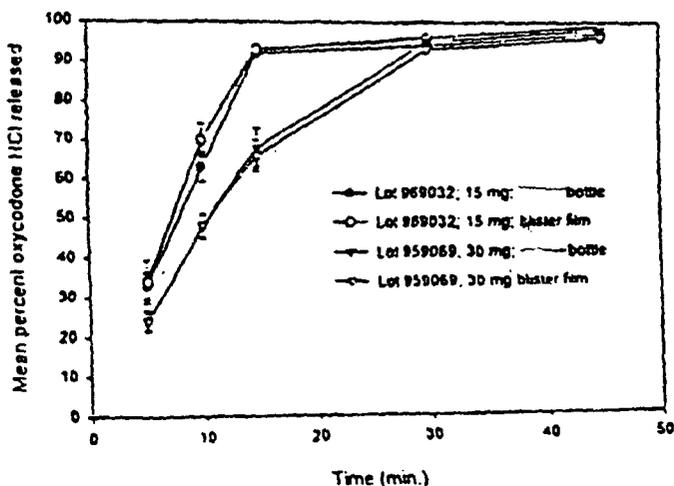


Oxycodone HCl release from Roxicodone™ tablets, 15 mg and 30 mg, is slower at 5 and 10 minutes when the stirring rate is  $\text{---}$  rpm. However, no differences in dissolution are apparent for either strength after 15 minutes at  $\text{---}$  rpm when compared to 50 rpm. It may be concluded that oxycodone release from Roxicodone™ tablets is independent of stir rate.

### 4. INFLUENCE OF PACKAGING MATERIAL

One NDA lot from each tablet strength was evaluated by comparing dissolution of tablets that were stored for \_\_\_\_\_ in either \_\_\_\_\_ bottles or unit dose blister film packages. Mean tablet hardness was \_\_\_\_\_ for lot 969032 and \_\_\_\_\_ for lot 959059. The graphical representation of the results for 15 and 30 mg is shown in Figure 6.

Figure 6: Mean % release of Roxicodone™ Tablets (6 tablets ± SD)



The results show that oxycodone release was rapid from lot 969032, with a mean > 90% after 15 minutes. The release rate of lot 959069 is relatively slow compared to other lots for the first 15 minutes, but after 30 minutes, mean dissolution is > 90% of the labeled drug amount. These data suggest that the oxycodone release rate is not significantly influenced by the selected storage containers at room temperature after \_\_\_\_\_ and exceeds dissolution specifications for Oxycodone HCl Tablets, USP, which is Q = 70% of the labeled amount dissolved in 45 minutes.

Assessment of 6-tablet dissolution at 45 minutes for stability (up to \_\_\_\_\_ lots of Roxicodone™ Tablets, 15 and 30 mg was done using the USP method outlined in Table 1. The results indicated that regardless of storage condition or packaging, mean dissolution of Roxicodone™ Tablets exceeded 75% in 45 minutes.

#### SUMMARY:

Drug release from Roxicodone™ tablets, 15 and 30 mg, was found to be independent of pH, rotation speed and storage conditions, with all of the tested lots releasing \_\_\_\_\_ of oxycodone HCl at 30 minutes. The USP compendial method for oxycodone HCl tablets, USP was found to be appropriate for evaluating the *in vitro* oxycodone HCl release from Roxicodone™ tablets, 15 mg and 30 mg. Since dissolution data on one NDA bio lot, #969032, did not meet Q = \_\_\_\_\_ in 30 minutes, the sponsor proposed a dissolution specification of Q = 70% in 45 minutes which is same as the USP specification. This seems to be adequate.

BEST POSSIBLE COPY