12.0. Comments

1) In the population pharmacokinetic analysis, it was stated by the study author that in these studies there is no relationship between plasma oxycodone concentration and VAS measurement. However, it is more accurate to say that no relationship was found in the present analysis (not that it does not exist).

2) It was stated in the population pharmacokinetic analysis that the population pharmacokinetic analysis and pharmacokinetic-pharmacodynamic models and simulation results helped to explain and lend support to the efficacy analysis results. Since the results obtained in this analysis were not correlated to the clinical efficacy results and since PK/PD modeling portion of the analysis was not successful, the above statement is not completely true. However, it is more accurate to say that since similar steady-state plasma concentrations are obtained with either dosage form similar clinical efficacy may result.

3) The proposed dissolution method and specifications are not acceptable to the Agency. Data on the pH dependence and effect of dissolution media and agitation speed were not provided. Clearly, it is not adequate to have only % drug release *in vitro* at the end of hours. The dissolution method and specifications proposed can be only be approved on an interim basis. Specifications more reflective of the *in vivo* delivery of the product should be developed and submitted to the Agency in a timely fashion. Dissolution should be carried out at until at least % of drug is dissolved or a plateau is reached.

4) In studies where % confidence intervals were used to evaluate t_{max} and $t_{1/2}$, a more appropriate approach would have been to use a non-parametric method.

APPENDIX

SINGLE DOSE RELATIVE BIOAVAILABILITY

Study Type: Relative bioavailability.
Study Title: A single-dose, three-way cross-over study to compare the relative bioavailability of two formulations of sustained release oxycodone HCL (10 mg) to immediate release oxycodone HCL (10 mg).
NDA: 20-932 **Submission Date:** December 29, 1997 **Volume:** 1.18-1.19 **Protocol:**315-03
Clinical Investigator: Analytical Investigator:

Single Dose: Yes Cross-over: Three-way Other Design: Open, randomized
Fasted: yes (10 hour overnight)

Subject Breakdown
Normal Yes Young Yes
Subject Type: Male Group Normal N= 30 M= 30
Weight Mean 78.7 Range kg
Age Mean 29 Range yrs
Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
Formulation A	20 mg	SR Tablet	10 mg	939160	
Formulation B	20 mg	SR Tablet	10 mg	939161	
Intensol™ Solution	20 mg	Solution	20mg/20mL	931800	Liters

Analytical Methodology

Objectives
To evaluate the relative bioavailability of two sustained release formulations of oxycodone with respect to oxycodone oral solution.
Study Features
This is a single dose, randomized, three treatment, three-way cross-over study in about 30 healthy adult males. The three treatments were;

Formulation A: 2 x 10 mg oxycodone SR tablets.
Formulation B: 2 x 10 mg oxycodone SR tablets.
Oral Solution: 1 mL of Intensol™ (20 mg/mL) solution.

Results And Discussion

Figure 1 and Table 1 show mean oxycodone plasma concentration-time profiles and pharmacokinetic parameters respectively. The comparison made in this study does not appear to be appropriate in that oxycodone is supposed to be administered every 4 hours or as directed by the physician. In which case, the 20 mg dose of oxycodone for the solution should have been administered as 6.66 mg every 4 hours to assess the sustained release properties of the oxycodone SR tablets. Between the two sustained release formulations, they seem to exhibit similar profiles with formulation B displaying slightly lower C_{max}. ANOVA analysis indicated statistically significant differences between formulation A and Intensol solution as well as formulation B and Intensol solution with respect to C_{max}, t_{max}, AUC_{∞}, K_{el}, and $t_{1/2}$. Between the two sustained release formulations, there were statistically significant differences with respect to t_{max} and $t_{1/2}$. The 90% confidence intervals were within the bioequivalence criteria with respect to the AUC_{∞} when the two formulations were separately compared to the Intensol™ solution. Between the two sustained release formulations, confidence intervals for the log transformed C_{max} and AUC_{∞} were within the bioequivalency limits. Comparison of the two sustained release formulations suggests that formulation B may provide a better sustained-release properties based on a lesser C_{max} together with comparable extent of absorption.

Conclusions

Both sustained release formulations were equivalent to oral solution with respect to the extent of absorption (AUC).

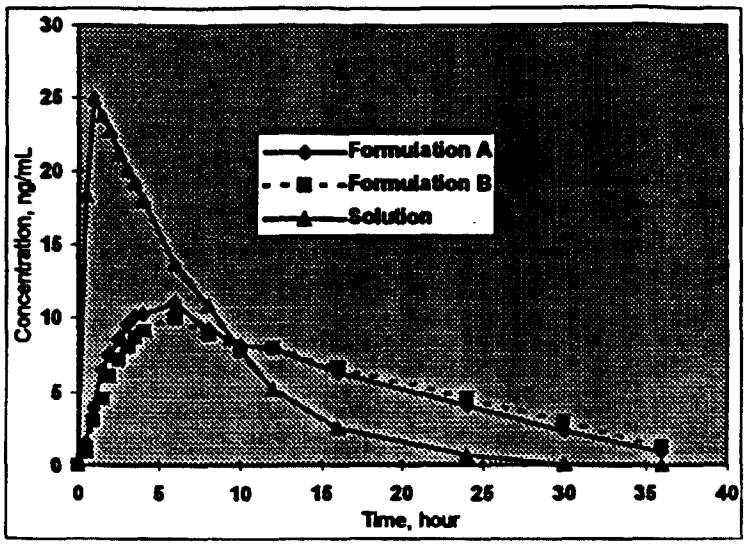


Figure 1. Mean plasma concentration Vs time profiles of oxycodone when administered single 20 mg equivalent doses of oxycodone solution and oxycodone 10 mg SR tablet-formulation A and formulation B.

Table 1. Oxycodone pharmacokinetic parameters when administered as oxycodone SR tablets (formulations A and B) and Intensol™ solution in equivalent doses of 20 mg (mean (% CV)).

Pharmacokinetic Parameter	Formulation A	Formulation B	Solution	90% Confidence Intervals	
				Formulation A/solution	Formulation B/solution
C_{max}, ng/mL	11.65 (25)	10.64 (21)	27.5 (27)	36.6-48.9	32.6-44.8
t_{max}, hour	5.2 (26)	6.4 (40)	1.4 (74)	306.3-414.2	395.4-503.3
$AUC_{0-\infty}$, ng hour/mL	219.0 (34)	228.7 (32)	207.0 (27)	98.9-112.7	103.6-117.3
$t_{1/2}$, hour	8.8 (33)	10.1 (32)	4.1 (16)	189.7-237.0	222.3-269.6

MULTIPLE DOSE-RELATIVE BIOAVAILABILITY

Study Type: Bioequivalence study
Study Title: 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)
NDA: 20-932 **Submission Date**: December 29, 1997 **Volume**: 1.23-124 **Protocol**: 315-04
Clinical Investigator: **Analytical Investigator:**

Multiple Dose: Yes, **Cross-over**: Three-way **Other Design**: Open, randomized
Fasted: yes (10 hour overnight)

Subject Breakdown
Normal Yes **Young** Yes
Subject Type: Male **Group** Normal N= 26 M= 26
Weight **Mean** 80 **Range** kg
Age **Mean** 32 **Range** yrs
Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
Formulation A	10 mg	SR Tablet	10 mg	939160	
Formulation B	10 mg	SR Tablet	10 mg	939161	
Roxicodone®	10 mg	Oral Solution	5mg/5mL	940048	Liters

Objective
The objective of this study was to evaluate the bioequivalence of two oxycodone sustained release tablets and compare these results to an immediate release oxycodone solution.

Study Design
This was a multiple dose, randomized, three-period, three-way cross-over design in thirty (30) adult male subjects. The three treatments were;

Formulation A: 10 mg oxycodone SR tablet administered every 12 hours for 7 doses.

Formulation B: 10 mg oxycodone SR tablet administered every 12 hours for 7 doses.
Oral Solution: 3.33 mg of 5 mg/5 mL solution administered every 4 hours for 21 doses.

C_{max} (last dosing interval), AUC_{72-84}, t_{max}, % fluctuation = $(C_{min}/C_{max})*100$, C_{avg1} (average concentration from 72 to 84 hours) = $(C_{max}-C_{min})/\ln(C_{max}/C_{min})$, C_{avg2} (average concentration from 72 to 84 hours) = AUC/12, Fluctuation index 1 = $(C_{max}-C_{min})/C_{avg}$, Fluctuation index 2 = $(C_{max}-C_{min})/C_{min}$ were the pharmacokinetic parameters that were evaluated.

Results And Discussion

This study differs from the previous study (protocol 315-03) in that this is a steady state evaluation at an equivalent dose of 10 mg every 12 hours. Steady state analysis revealed that trough concentrations in the morning at 24, 48, and 72 hours were higher than those in the evening at 36, 60, and 84 hours. The sponsor attributed this to possible circadian effects (literature survey did not yield any information on this aspect). Steady state was assessed separately for the morning and evening trough concentrations between 36-72 hours. At evening pre-dose samples of 36 and 60 hours, the slope for the oral solution was significantly different from zero. At morning pre-dose samples at 48 and 72 hours, the slope for formulation A was significantly different from zero. Based on the small values for the slopes across the trough samples, the sponsor concluded that steady state was achieved.

Pharmacokinetic parameters for all three treatments are given in Table 1. Both formulation A and formulation B, when compared to the oral solution separately, and between formulation A and formulation B, the 90% confidence intervals for both C_{max} and AUC_{72-84} were within the FDA bioequivalence limits. Between both formulations, ANOVA indicated statistically significant differences between the treatment means for C_{min} and the two measures of fluctuation. The differences between the treatment least square means were all less than 15%. Although, both formulation A and formulation B were bioequivalent to each other and have similar sustained release properties, formulation B appears to be better in this respect (the fluctuation indices are smaller, the C_{min} is higher). The fluctuation index values were about 76% and 63% for formulation A and formulation B, respectively, of that of the oral solution. The C_{min} values were about 108% and 118% for formulation A and formulation B, respectively, of that of the oral solution. From these data it is also clear that formulation B has better sustained release performance characteristics over formulation A.

Table 1. Oxycodone pharmacokinetic parameters (mean (% CV)) when administered 10 mg equivalent multiple doses of oxycodone solution (3.33 mg every 4 hours) and oxycodone 10 mg SR tablet (every 12 hours)- formulation A and formulation B.

Pharmacokinetic Parameter	Formulation A	Formulation B	Solution	90% Confidence Intervals	
				Formulation A/solution	Formulation B/solution
C_{max}, ng/mL	12.68 (26)	12.78 (27)	12.9 (24)	94.4-102.2	95.1-103.0
c_{min}, ng/mL	7.77 (28)	8.44 (30)	7.15 (32)	103.2-114.3	112.5-123.6
t_{max}, hour	3.7 (41)	4.3 (42)	1.04 (27)	305.0-407.1	362.6-464.7
AUC_{72-84}, ng hour/mL	106.41 (26)	108.26 (28)	99.02 (25)	103.1-111.9	103.9-112.8
% Fluctuation	61.2 (10)	65.9 (12)	54.7 (13)	-	-
Fluctuation Index 1	0.56 (18)	0.49 (26)	0.72 (20)	71.4-83.9	61.8-74.3
Fluctuation Index 2	0.65 (26)	0.54 (34)	0.86 (26)	67.4-84.1	54.3-71.0
c_{avg1}, ng/mL	10.02 (26)	10.45 (28)	9.73 (27)	98.9-107.1	103.3-111.4
c_{avg2}, ng/mL	8.87 (26)	9.02 (28)	8.25 (25)	103.4-111.5	105.3-113.4

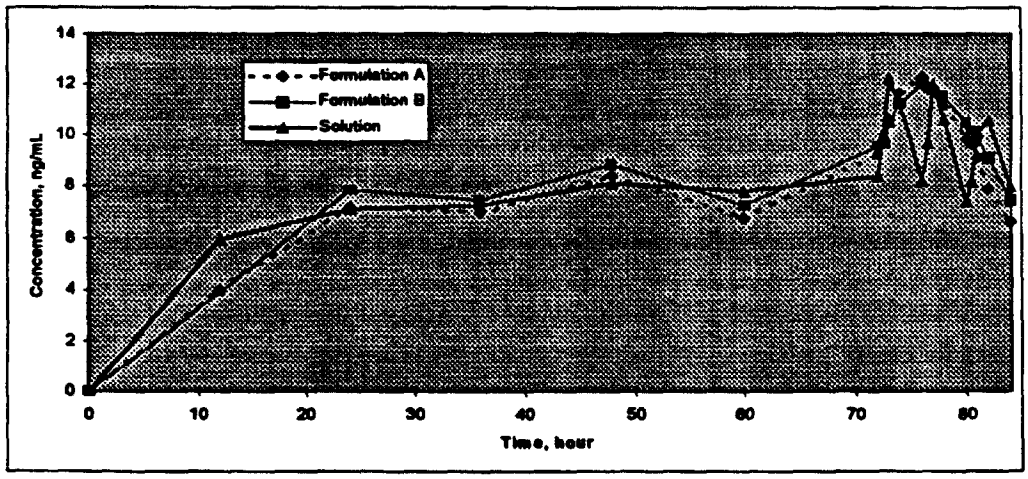


Figure 1. Mean plasma concentration Vs time profiles of oxycodone when administered 10 mg equivalent multiple doses of oxycodone solution (3.33 mg every 4 hours) and oxycodone 10 mg SR tablet (every 12 hours)- formulation A and formulation B.

DOSAGE FORM BIOEQUIVALENCE

Study Type: Relative bioavailability.
Study Title: A single-dose, two-way cross-over study to compare the relative bioavailability of oxycodone HCL 30 mg sustained release tablets with oxycodone HCL 10 mg sustained release tablets.
NDA: 20-932 Submission Date: December 29, 1997 Volume: 1.21-1.22 Protocol: 315-08
Clinical Investigator: Analytical Investigator:

Single Dose: Yes Cross-over: Two-way Other Design: Open, randomized
Fasted: yes (10 hour overnight)
Subject Breakdown
Normal Yes Young Yes
Subject Type: Male Group Normal N= 26 M= 26
Weight Mean 82 Range kg
Age Mean 31 Range yrs
Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
30 mg SR Tablet	30 mg	SR Tablet	30 mg	949085	
10 mg SR Tablet	30 mg	SR Tablet	10 mg	939161	

Assay Method:

Objective

To evaluate the dose equivalence of one 30 mg SR tablet with three 10 mg SR tablets, following single dose administration.

Study Design

This was a single-dose, randomized two period, two-way cross-over study conducted in 13 adult male volunteers after a 10 hour overnight fast.

C_{max}, t_{max}, AUC_{0-24}, $AUC_{0-\infty}$, k_{el}, and $t_{1/2}$ were the pharmacokinetic parameters that were evaluated. ANOVA with effects for sequence, treatment, period, and subjects (within sequence) was used to analyze the data. The two one-sided t-tests procedure was used to construct 90% and 95% confidence intervals for C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ with the 3x10 mg SR tablets as the reference treatment.

Results And Discussion

Analysis of variance indicated no statistically significant differences between the treatments for any of the pharmacokinetic parameters. The percentage differences between the treatments were less than 8% for all parameters. The 90% confidence intervals were within the bioequivalence limits for all parameters except t_{max} (Table 1).

Conclusion

- The 30 mg sustained release formulation was bioequivalent to the 10 mg sustained release formulation (reference formulation) when administered as 30 mg doses.

Table 1. Mean pharmacokinetic parameters of oxycodone after the administration of one 30 mg SR tablet and three 10 mg SR tablets.

Pharmacokinetic Parameter	30 mg SR Tablet	10 mg SR Tablet	90% confidence Intervals
C_{max}, ng/mL	14.69 (22)	15.44 (27)	89.0-101.1
t_{max}, hour	5.62 (62)	5.89 (52)	73.8-117.1
AUC_{0-48}, ng hour/mL	286.94 (24)	309.28 (27)	86.5-99.1
$AUC_{0-\infty}$, ng hour/mL	301.70 (25)	324.08 (27)	87.1-99.1
$t_{1/2}$, hour	9.84 (36)	9.59 (32)	88.5-116.9

MULTIPLE DOSE-RELATIVE BIOAVAILABILITY

Study Type: Relative bioavailability.
Study Title: A bioavailability study to compare a sustained release oxycodone HCL 10 mg tablet formulation to an immediate release oxycodone HCL oral solution.
NDA: 20-932 Submission Date: December 29, 1997 Volume: 1.27-1.28 Protocol: 315-09
Clinical Analytical
Investigator: Investigator:

Multiple Dose: Yes Cross-over: Two-way Other Design: Open, randomized
Fasted: yes Washout Period: at least 1 week

Subject Breakdown
Normal Yes Young Yes
Subject Type: Male Group Normal N= 26 M= 26
Weight Mean 81 Range kg
Age Mean 33 Range yrs
Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
SR Tablet	70 mg	SR Tablet	10 mg	939161	
Roxicodone™	70 mg	Oral Solution	5mg/5mL	941548	Liters

Objective

To evaluate the relative bioavailability of oxycodone sustained release 10 mg tablet in development given every 12 hours for seven doses and the currently marketed 5 mg/5mL oxycodone oral solution USP (Roxicodone™) given every six hours for 14 doses.

Study Design

This is an open label, randomized, multiple dose, two-way cross-over design in 26 adult male subjects with at least one week washout period between the two treatments.

C_{max}, C_{min}, C_{av} (average concentration during the final dosing period, $AUC_{72-84}/12$), t_{max}, AUC_{72-84} (AUC of the last dosing interval), Fluctuation index 1 $((C_{max}-C_{min})/C_{avg})$, Fluctuation index 2 $((C_{max}-C_{min})/C_{min})$, trough concentrations at 48, 60, 72, and 84 hours were the pharmacokinetic parameters that were evaluated. ANOVA with effects for sequence, treatment, period, and subjects (within sequence) was used to analyze the data. The two one-

sided t-tests procedure was used to construct 90% and 95% confidence intervals for the pharmacokinetic parameters.

Results And Discussion

Since the terminal half-lives of oxycodone given in solution and as sustained release formulation are about 3 and 10 hours respectively, steady state is expected to be achieved by end of day 2 of dosing. Linear regression of the trough oxycodone concentrations at 48, 60, 72, and 84 hours indicated mean slopes for both treatments which were not significantly different from zero indicating the attainment of steady state by the final dosing period. Analysis of variance indicated statistically significant differences between the treatments for all of the pharmacokinetic parameters evaluated. The 90% confidence intervals for both untransformed and log transformed C_{max}, C_{av} and AUC_{72-84} were within the FDA recommended bioequivalency limits. Based on comparison of the AUC_{72-84} values, the 10 mg sustained release tablets had a relative bioavailability of 108% compared to 10 mg of the oral solution. The SR tablet had satisfactory sustained release properties as evidenced by the small fluctuation index value, a high C_{min} value and a comparable C_{max} value with respect to the solution. The fluctuation index value was 51%, the C_{min} value was about 126%, and the C_{max} value was 93% of that of the solution, respectively.

Conclusions

Based on comparison of the AUC_{72-84} values, the 10 mg sustained release tablets had a relative bioavailability of 108% compared to 10 mg of the oral solution. Both C_{max} and AUC_{72-84} values were within the limits of the FDA bioequivalency criteria. The sustained release properties of the formulation were adequately characterized.

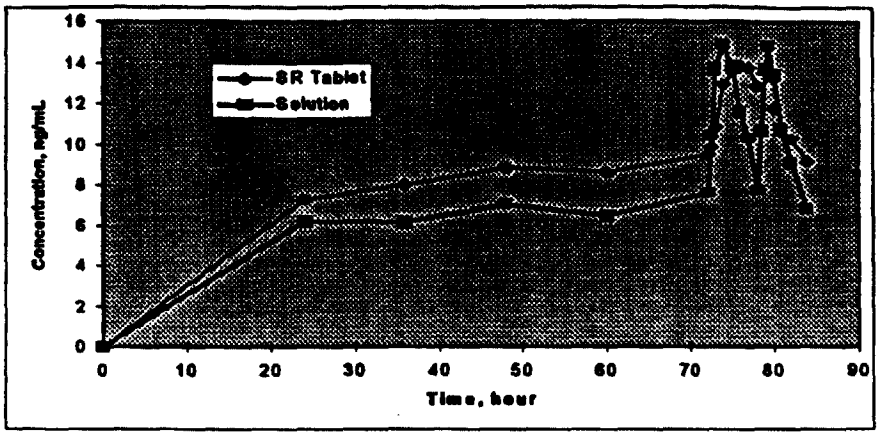


Figure 1. Mean plasma concentration Vs time profiles of oxycodone when administered 10 mg equivalent multiple doses of oxycodone solution (5 mg every 6 hours) and oxycodone 10 mg SR tablet (every 12 hours).

Table 1. Oxycodone pharmacokinetic parameters (mean (% CV)) when administered 10 mg equivalent multiple doses of oxycodone solution (5 mg every 6 hours) and oxycodone 10 mg SR tablet (every 12 hours).

Pharmacokinetic Parameter	SR tablet	Solution	90% Confidence Intervals SR Tablet/Solution
C_{max}, ng/mL	14.6 (25)	15.7 (20)	87.9-98.1
c_{min}, ng/mL	9.36 (28)	7.42 (25)	118.2-134.0
t_{max}, hour	4.0 (40)	1.3 (22)	262.1-346.3
AUC_{72-84}, ng hour/mL	122.68 (26)	113.25 (21)	102.5-114.3
Fluctuation Index 1	0.59 (36)	1.15 (23)	43.5-60.0
Fluctuation Index 2	0.52 (28)	0.88 (15)	53.1-65.5
c_{avg}, ng/mL	10.22 (26)	9.44 (21)	102.5-114.3

FOOD EFFECT

Study Type: Food effect.

Study Title: A single-dose, four-way cross-over, food effect study of the 10 mg formulation of oxycodone sustained release tablets and oxycodone immediate-release oral solution in healthy volunteers.

NDA: 20-932 Submission Date: December 29, 1997 Volume: 1.29 Protocol: 315-10

Clinical Investigators: Analytical Investigator:

Single Dose: Yes Cross-over: Four-way Other Design: Open, randomized

Fasted: yes (10 hour overnight) Fed: yes (FDA high fat breakfast)

Subject Breakdown

Normal Yes Young Yes

Subject Type: Male Group Normal N= 14 M= 14

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
Oxycodone SR Tablet	10 mg	SR Tablet	10 mg	939161	
Roxicodone® Solution	10 mg	Oral solution	5 mg/ 5 mL	941548	

Analytical Methodology

Objectives

To determine the effects of food on the pharmacokinetic characteristics of a 10 mg oxycodone SR tablet and a 10 mg/10 mL immediate release solution.

Study Design

This was a four treatment, four-way cross-over, single dose study conducted in 14 subjects with a one week washout period between each treatment. The four treatments were;

1. One 10 mg SR tablet administered under fasting conditions after a 10-hour overnight fast.
2. One 10 mg SR tablet administered immediately after the consumption of an FDA high-fat meal.
3. 10 mg of a 5 mg/ 5mL oral solution administered under fasting conditions after a 10-hour overnight fast.
4. 10 mg of a 5 mg/ 5mL oral solution administered immediately after an FDA high-fat meal.

Results And Discussion

Food significantly increased the rate of absorption of oxycodone from the sustained release tablet. There was a 57% increase in the C_{max} under fed conditions. However, the extent of absorption was not significantly different between the fed and fasting conditions. There was only a 10% increase in the $AUC_{0-\infty}$ under fed conditions. The sustained release tablet was bioequivalent (two one sided t-test procedures) under the two conditions with respect to $AUC_{0-\infty}$ but not for C_{max} (Table 1). For the oral solution, food had no significant effect on the rate of absorption of oxycodone in terms of the C_{max}. However, there was a significant increase in the extent of absorption under fed conditions with about 26% increase in the $AUC_{0-\infty}$. The oral solution was bioequivalent under the fed and fasted conditions with respect to the C_{max} but not for $AUC_{0-\infty}$.

Between the sustained release tablet and the oral solution, bioequivalency was achieved with respect to the extent of absorption ($AUC_{0-\infty}$) but not for C_{max} under both fed and fasting conditions.

Conclusions

C_{max} is significantly increased for the 10 mg sustained release tablet under fed conditions. The package insert needs to contain this information when the product is up for approval.

Table 1. Summary of bioequivalency determinations between the fed and fasted conditions of the SR tablet and oral solution.

Pharmacokinetic Parameter		Fasting	Fed	90% Confidence Interval*
SR Tablet	C_{max}, ng/mL	5.74 ± 0.94	8.92 ± 2.4	132-173
	$AUC_{0-\infty}$, ng hour/mL	119 ± 20.7	130 ± 37.3	95.4-121
Oral Solution	C_{max}, ng/mL	19 ± 3.7	17.7 ± 3.0	87.2-101
	$AUC_{0-\infty}$, ng hour/mL	105 ± 16.2	133 ± 25.2	118-133

* Log transformed parameters

TIME TO FOOD EFFECT

Study Type: Food effect.
Study Title: A Single Dose, four-way Cross-over, Time to Food Effect Study of 10 mg Oxycodone Sustained-Release Tablets in Healthy Volunteers
NDA: 20-932 Submission Date: December 29, 1997 Volume: 1.30 Protocol: 315-11
Clinical Investigators: Analytical Investigator:

Single Dose: Yes, Cross-over: Four-way Other Design: Open, randomized
Fasted: yes (10 hour overnight) Fed: One hour before, one hour after, two hours after dosing
Subject Breakdown
Normal Yes Young Yes Group Normal Number= 24 Male= 14 Female= 10

Male				Female			
Weight	Mean 72	Range	kg	Weight	Mean 60	Range	kg
Age	Mean 31	Range	yrs	Age	Mean 32	Range	yrs

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot	Lot Size
Fasting	10 mg	SR Tablet	10 mg	939161	
Fed one hour before dosing	10 mg	SR Tablet	10 mg	939161	
Fed one hour after dosing	10 mg	SR Tablet	10 mg	939161	
Fed two hours after dosing	10 mg	SR Tablet	10 mg	939161	

Analytical Methodology

Objective

To determine the effect of food administered at varying times relative to dosing, on the pharmacokinetic characteristics of a 10-mg oxycodone SR tablet formulation.

Study Design

This was an open-label, single-dose, randomized four-way cross-over study conducted in twenty four normal, healthy male and female volunteers. The four treatments were;

1. One 10 mg SR tablet administered under fasting conditions after a 10-hour overnight fast.
2. One 10 mg SR tablet administered one hour before the consumption of an FDA high-fat meal.
3. One 10 mg SR tablet administered one hour after the consumption of an FDA high-fat meal.
4. One 10 mg SR tablet administered two hours after the consumption of an FDA high-fat meal.

Results And Discussion

Dosing the 10 mg oxycodone sustained release tablet under fasting conditions, one before meal; one hour after meal, and two hours after meal showed that dosing after meal significantly increased the rate of absorption relative to dosing under fasting conditions. Dosing the SR tablet one hour before meals did not significantly increase the C_{max}. Oxycodone SR tablet dosed one hour before the meal was bioequivalent with respect to the C_{max} (Table 1). The food effect was more pronounced when the sustained release tablets were administered two hours after meal. There was a 24% and 36% increase in C_{max} when the tablets were administered one and two hours after the meal respectively (relative to fasting conditions). On the other hand, the extent of absorption in terms of $AUC_{0-\infty}$ was not significantly different between the four conditions.

Comparing these results with the results obtained with another study where food effect for this tablet was examined (protocol 315-10), about 57% increase in C_{max} was seen in the latter study when the tablets were administered within 5 minutes after eating the meal.

Conclusions

There is a significant food effect in terms of higher C_{max} when the 10 mg sustained release tablets are administered after meals.

Table 1. Summary of bioequivalency determinations between the fasted and various fed conditions of the SR tablet (mean ± SD).

Pharmacokinetic Parameter		Fasting	Fed	90% Confidence Interval#
1 Hour Before Meal	C_{max}, ng/mL	7.35 ± 1.9	7.96 ± 2.9	
	C_{max}, ng/mL/kg*	0.11 ± 0.04	0.12 ± 0.05	97.2-119
	$AUC_{0-\infty}$, ng hour/mL	137 ± 26.5	145 ± 36.4	-
	$AUC_{0-\infty}$, ng hour/mL/kg*	2.06 ± 0.63	2.17 ± 0.69	96.1-115
1 Hour After Meal	C_{max}, ng/mL	7.35 ± 1.9	8.74 ± 2.15	-
	C_{max}, ng/mL/kg*	0.11 ± 0.04	0.13 ± 0.05	108-130
	$AUC_{0-\infty}$, ng hour/mL	137 ± 26.5	141 ± 42.1	-
	$AUC_{0-\infty}$, ng hour/mL/kg*	2.06 ± 0.63	2.13 ± 0.86	94.2-113
2 Hours After Meal	C_{max}, ng/mL	7.35 ± 1.9	9.72 ± 2.37	-
	C_{max}, ng/mL/kg*	0.11 ± 0.04	0.15 ± 0.05	121-143
	$AUC_{0-\infty}$, ng hour/mL	137 ± 26.5	142 ± 33.8	-
	$AUC_{0-\infty}$, ng hour/mL/kg*	2.06 ± 0.63	2.14 ± 0.69	94.4-113

* Body weight normalized parameter.

Confidence intervals on untransformed C_{max} and $AUC_{0-\infty}$.

DOSE-PROPORTIONALITY

Study Type: Dose-proportionality

NDA: 20-932 Submission Date: December 29, 1997 Volume: 1.31-1.32 Protocol:315-12

Objectives

To determine the pharmacokinetic characteristics and clinical safety of single doses of oxycodone over the range of 10 to 100 mg when administered as oxycodone SR tablets and to assess the relationship of pharmacokinetic characteristics to dose.

Design

This was a four treatment, four-way cross-over, single dose study conducted in sixteen (16), healthy male and female subjects with a one week washout period between each treatment. The four treatments were;

1. One 10 mg oxycodone SR tablet (10 mg total dose).
2. One 30 mg oxycodone SR tablet (30 mg total dose).
3. Two 30 mg oxycodone SR tablets (60 mg total dose).
4. One 10 mg plus three 30 mg oxycodone SR tablets (100 mg total dose).

Formulation

Group	Dosage Form	Strength	Lot No.	Lot Size
10 mg	10 mg SR Tablet	10 mg	939161	
30 mg	30 mg SR Tablet	30 mg	949085	
60 mg	2x30 mg SR Tablets	30 mg	949085	
100 mg	1x10 plus 3x30 mg SR Tablets	10 & 30 mg	939161, 949085	

Analytical Methodology

Statistical analysis

To test for dose-proportionality, dose- and body-weight normalized $\ln C_{max}$ and lnAUC were analyzed using ANOVA (carry-over effect included). Pairwise treatment comparisons were also made on the dose- and body-weight normalized $\ln C_{max}$ and lnAUC. To test for dose-linearity, regression analysis was performed using a power model on body-weight normalized $\ln C_{max}$ and lnAUC Vs lndose.

Results And Discussion

This study was conducted in healthy volunteers using doses up to 100 mg of oxycodone without a naltrexone blockade. Evaluation of the safety parameters from the viewpoint of not providing a naltrexone blockade and administering high doses of oxycodone to healthy subjects is deferred to the reviewing medical officer.

Table 1 lists the pharmacokinetic parameters at the four administered doses 10, 30, 60, and 100 mg oxycodone. In general, as the dose was increased both C_{max} and AUC increased.

However, this increase was not proportional to the dose. Largest deviation from dose-proportionality occurred when the dose was increased from 60 to 100 mg. It is uncertain, if this deviation from dose-proportionality is due to the drug or the formulation.

Statistical analysis with the ANOVA, Pairwise comparison, and power model approaches indicated that C_{max} was not dose-proportional. The power model used indicated that doubling the dose results in a 1.86 fold increase in C_{max} (95% confidence of 1.78 to 1.95).

$AUC_{0-\infty}$ showed dose-proportionality by ANOVA and Pairwise comparison approaches. However, it failed to show dose-proportionality with the power model approach. The power model indicated that doubling the dose resulted in a 1.82 fold increase in $AUC_{0-\infty}$ (confidence interval of 1.68 to 1.97).

The clinical implications of these results from an efficacy standpoint is uncertain as no efficacy measurements could be made in this study. However from a safety standpoint, it is comforting that lack of dose-proportionality is resulting in less than proportional exposure to the drug rather than the other way where lack of dose-proportionality could result in more than proportional increase in exposure to the drug. Since, gross deviations from dose-proportionality were not seen (about 1.8 fold increase in C_{max} and $AUC_{0-\infty}$ with doubling the dose) and since the patients are titrated to effect at the higher doses of oxycodone employed in this study, clinically the less than proportional increases seen in C_{max} and $AUC_{0-\infty}$ may not be critical.

Conclusions

Both C_{max} and $AUC_{0-\infty}$ were less than dose-proportional at doses up to 100 mg using combinations of the 10 and 30 mg oxycodone SR tablets.

Table 1. Summary of mean oxycodone pharmacokinetic parameters (mean (%CV)).

Pharmacokinetic Parameter	10 mg	30 mg	60 mg	100 mg
C_{max}, ng/mL	7.26 (26)	20.4 (29)	38.3 (16)	55.8 (27)
C_{max} normalized to 10 mg dose	1	2.81	5.28	7.69
t_{max}, hour	4.93 (21)	4.8 (43)	4.87 (43)	4.47 (47)
AUC_{0-t}, ng hour/mL	106 (30)	327 (23)	616 (30)	900 (39)
AUC_{0-t} normalized to 10 mg dose	1	3.08	5.81	8.49
$AUC_{0-\infty}$, ng hour/mL	120 (26)	353 (21)	635 (30)	951 (39)
$AUC_{0-\infty}$, normalized to 10 mg dose	1	2.94	5.29	7.93
$t_{1/2}$, hour	7.94 (20)	10.0 (49)	6.89 (49)	8.80 (56)

DRUG PRODUCT DISSOLUTION TESTING

Date of Test	Lot No. /Strength	Collection Times (hr)	Units Tested	Average	Standard Deviation	RSD	Range (%)
12/5/94	939161/10 mg		12	18	2.4	13.5	
			12	26	3.1	11.8	
			12	51	2.7	5.2	
			12	75	2.6	3.5	
2/22/96	969006/10 mg		12	16	0.9	5.8	
			12	23	1.6	6.8	
			12	49	1.5	3.1	
			12	73	2.0	2.7	
8/2/96	969027/10 mg		12	13	0.5	4.0	
			12	19	1.0	5.2	
			12	43	1.2	2.8	
			12	67	1.8	2.6	
7/25/97	979018/10 mg		12	14	1.2	8.3	
			12	20	2.9	14.5	
			12	43	3.6	8.3	
			12	65	5.2	8.0	
11/21/94	949085/30 mg		12	20	0.9	4.5	
			12	28	1.3	4.6	
			12	50	1.3	2.6	
			12	70	1.8	2.6	
2/22/96	959074/30 mg		12	21	1.2	6.1	
			12	29	1.6	5.4	
			12	52	1.9	3.6	
			12	72	2.0	2.8	
7/26/96	969028/30 mg		12	21	0.9	4.1	
			12	30	1.4	4.7	
			12	53	2.1	4.0	
			12	73	2.2	2.9	
7/24/97	979019/30 mg		12	20	1.2	6.2	
			12	27	2.0	7.5	
			12	49	2.7	5.5	
			12	68	3.4	5.0	

POPULATION PHARMACOKINETIC-PHARMACODYNAMIC ANALYSIS

Study Type: Population Pharmacokinetic-Pharmacodynamic analysis.

NDA: 20-932 Submission Date: December 29, 1997 Volume: 1.31-132 Protocols: CBI-961/962 & CBI-1252

Formulation

Clinical Study	Dosage Form	Lot No.	Lot Size
CBI-961/962	10 mg SR Tablet	969006 939161	
	30 mg SR Tablet	949085 959074 969028	
	5 mg IR Tablet	951182 951905 960285 960783	
CBI-1252	10 mg SR Tablet	969006 939161	
	30 mg SR Tablet	959074 969028	
	5 mg IR Tablet	961565 951905 960285 960783	

Analytical Methodology

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-932
Name: Roxicodone™ SR Tablets 10 and 30 mg
Sponsor: Roxane Laboratories, Inc., P.O.Box 16532, Columbus, OH
Submission Type: Original NDA
Submission Dates: 12/29/97, 10/08/98, 10/23/98
Reviewer: Suresh Doddapaneni, Ph.D.

Addendum to the Primary Review

One of the deficiencies identified in the original review was dissolution methodology used and dissolution specifications proposed for the product (see original review dated September 16, 1998. A telecon was held on September 30, 1998 between the Agency and Roxane Laboratories to resolve this issue. Specifically, information concerning justification of dissolution specifications, rationale for the dissolution method, and data for the dissolution profile longer than hours, or at least % of the drug had been released was requested.

The report submitted this data on 10/08/98 which states that the drug release from the hydrophilic matrix of Roxicodone SR tablets are independent of pH, rotation speed, and ionic content of the dissolution media. Therefore, the sponsor selected dissolution conditions are adequate.

Appendix I provides the revised specifications. Essentially, dissolution was carried out up to hours and the new dissolution release specifications involve deletion of the hour time point and addition of a hour time point with a release specification of NLT %.

Appendix II includes results from twenty four hour dissolution testing performed on four lots of 10 mg and 30 mg Roxicodone SR tablets on stability. From the data presented on biobatches at release and on stability, sponsor's proposed specifications of NLT % released at hours for both 10 and 30 mg strengths seems reasonable. However, the specifications at hours should be changed and another time point at hours should be added. The following should be the final specifications;

%
%
%
%
%

Recommendation

Data submitted in submissions dated 10/08/98 & 10/23/98 adequately addressed the deficiency regarding the dissolution method and specifications (comment 3 on page 20 of the original review dated September 16, 1998). **However, the following comments (comments 1-3 are from the original review) should still be sent to the sponsor.**

1) In the population pharmacokinetic analysis, it was stated by the study author that in these studies there is no relationship between plasma oxycodone concentration and VAS measurement. However, it is more accurate to say that no relationship was found in the present analysis (not that it does not exist).

2) It was stated in the population pharmacokinetic analysis that the population pharmacokinetic analysis and pharmacokinetic-pharmacodynamic models and simulation results helped to explain and lend support to the efficacy analysis results. Since the results obtained in this analysis were not correlated to the clinical efficacy results and since PK/PD modeling portion of the analysis was not successful, the above statement is not completely true. However, it is more accurate to say that since similar steady-state plasma concentrations are obtained with either dosage form similar clinical efficacy may result.

3) In studies where 90% confidence intervals were used to evaluate t_{max} and $t_{1/2}$, a more appropriate approach would have been to use a non-parametric method.

4) Dissolution method selected by the sponsor is acceptable. However, the sponsor's proposed dissolution specifications need to be modified. The Agency recommended final dissolution specifications and dissolution method are provided below;

/S/ 10/23/98

Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist
Division of Pharmaceutical Evaluation II

FT initialed by Ramana Uppoor, Ph.D. /S/ 10/23/98

CC:
NDA 20-932, HFD-170 (Division files, McNeal, McCormick, Rappaport, Maturu, D'Sa), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Uppoor), HFD-340 (Viswanathan), Barbara Murphy (CDR).

Appendix I

Dissolution methodology and specifications for the 10 mg and 30 mg tablets.

	Original Method	New Method
Apparatus, USP		
Rotation Speed, rpm		
Volume, mL		
Media		
Sampling Times, hours		
Specifications		

Appendix II

10 mg tablet

(1) Drug Release results for NDA lots stored in bottles at room temperature (based on the average of six tablets)

Time (Hours)	Percent Released			
	Batch No. 939161	Batch No. 969006	Batch No. 969027	Batch No. 979018
Storage Time (Months)				

(2) Drug Release results for NDA lots stored in unit dose blisters at room temperature (based on the average of six tablets)

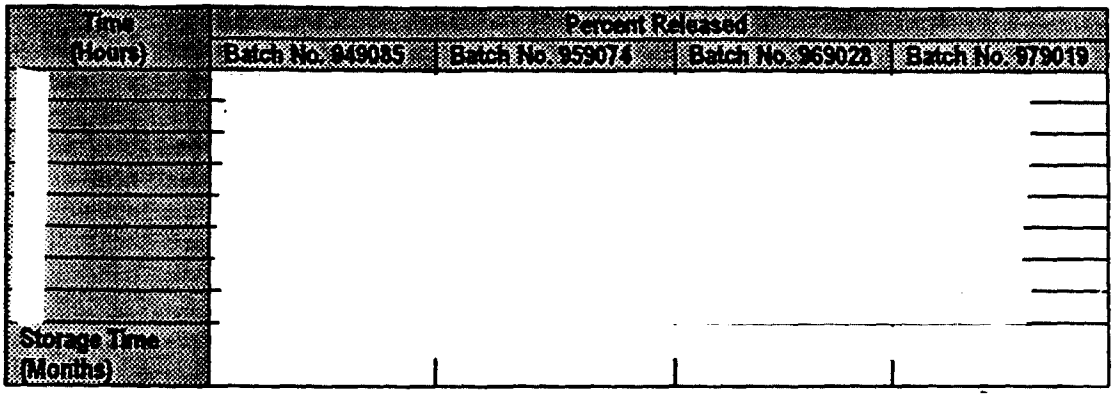
Time (Hours)	Percent Released		
	Batch No. 939161	Batch No. 969027*	Batch No. 979018
Storage Time (Months)			

*Based on 12 tablets.

APPEARS THIS WAY
ON ORIGINAL

30 mg tablet

(1) Drug Release results for NDA lots stored in bottles at room temperature (based on the average of six tablets)



(2) Drug Release results for NDA lots stored in unit dose blisters at room temperature (based on the average of six tablets).