

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74769

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-769

APPLICANT: AB Generics, L.P.

DRUG PRODUCT: Morphine Sulfate Controlled Release Tablets, 100 and 200 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of simulated gastric fluid at 37°C, using USP 23 apparatus I (basket) at 50 rpm. Based on the submitted data the following tentative specifications are recommended:

- 1 hour (b)(4)(CC)
- 2 hours
- 3 hours
- 4 hours
- 8 hours

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/s/ [Redacted Signature]

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 74-769
ANDA DUPLICATE
DIVISION FILE
HFD-655/ S. Nerurkar for Office Level BIOSign Off Queue
HFD-651/ Bio Secretary - Bio Drug File
HFD-650/ M. Makary
HFD-655/ R. Mhatre

X:\NEW\FIRMSAM\ABGENERI\LTRS&REV\74769SD.696
Printed in final on 11/26/97

Endorsements: (Final with Dates)

HFD-658/ M. Makary /S/ [REDACTED]
HFD-655/ R. Mhatre
HFD-617/ N. Chamberlin
HFD-650/ D. Conner /S/ [REDACTED] 12/24/97

BIOEQUIVALENCY - ACCEPTABLE submission date: 10 July 1996, 08
October, 97, and 03 December 1997

- | | | |
|----|---|--------------------------------------|
| 1. | STUDY AMENDMENT (STA)
July 10, 1997 | Strengths: all
Outcome: AC |
| 2. | OTHER (OTH) _____
08 Oct 97 | Diskettes
Outcome: NC |
| 3. | DISSOLUTION (DIS)
3 December 97 | <u>Strengths: All</u>
Outcome: AC |

Outcome Decisions: AC - Acceptable

WINBIO COMMENTS:

Morphine Sulfate CR Tablet
200 mg
ANDA # 74-769
Reviewer: Moheb H. Makary
WP 74769SD.696

AB Generics L.P.
Norwalk, CT
Submission Date:
July 10, 1996
October 8, 1997
October 14, 1997
December 3, 1997

Review of Study Amendment

I. Objective:

The firm has replied to the reviewer's comments made in the review of the October 16, 1995 submission (bioequivalence studies on Morphine Sulfate CR 200 mg Tablets and dissolution data).

Comment #I

1. The firm was asked to clarify that the test product is AB Generics' product and not Purdue Frederick's product. The firm had indicated that the morphine sulfate controlled-release 200 mg tablet, lot #4WD, Purdue Frederick Company, is the test product used in the bioequivalence studies

The firm replied that the test product is lot #4WD manufactured by (b)(4)(CC) for AB Generics L.P. The reference product is lot #3GP manufactured by Purdue Frederick Laboratories, Inc. for Purdue Frederick Company.

Reply to Comment #1

The firm's response to the comment is acceptable.

Comment #II

The firm was asked to submit the potency and content uniformity for the test and reference products.

The firm submitted the potency and content uniformity for the test and reference products.

	Test Product	Reference Product
	Lot #4DW	Lot #3GP
Potency	103.1%	100.1%
Content uniformity	102.1%	98.9%

Reply to Comment #II

The firm's response to the comment is acceptable.

Comment #III

The firm was advised to submit the analytical raw data for all subjects in the studies.

The firm submitted the analytical raw data for all subjects in the study.

Reply to Comment #III

The firm's response to the comment is acceptable.

Comment #IV

The firm was asked to submit its criteria for acceptance of batch runs based on standard curves and quality control samples used

(b)(4)(CC)

The firm submitted the criteria for acceptance of batch runs based on standard curves and quality control samples used in the above studies.

Reply to Comment #IV

The firm's response to the comment is acceptable.

Comment #V

The firm was asked to submit AUC_{0-t} (area under the plasma concentration-time curve from time zero to time t, calculated by the trapezoidal rule, where t is the last measurable time point) and AUC_{0-inf} (where $AUC_{0-inf} = AUC_t + C_t/Kel$, C_t is the last measurable drug concentration and Kel is the terminal elimination rate constant calculated according to an appropriate method) for morphine and morphine-6-glucuronide for study# MO93-0602.

The firm submitted the AUC_{0-t} and AUC_{0-inf} for morphine and morphine-6-glucuronide for each subject in the study.

C/A (Nonfasting)	
AUC(0-t)	1.07
AUCinf	1.06
Cmax	1.11

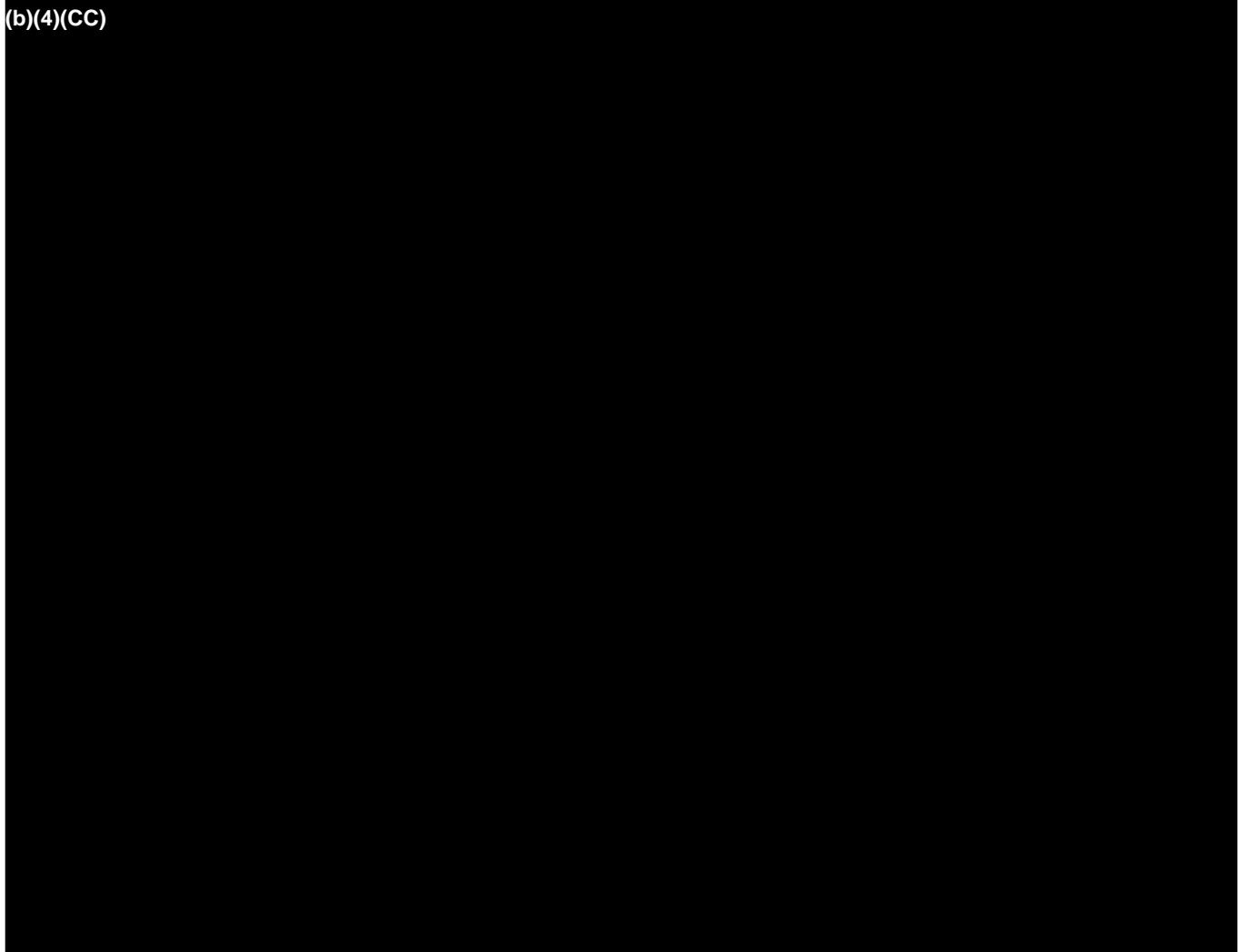
All confidence intervals remained within the acceptable 80-125% range under fasting conditions. Also, the ratios of the test arithmetic means to the reference arithmetic means remained within the acceptable range of 0.8-1.2 for the above parameters under nonfasting conditions.

Reply to Comment #V

The firm's response to the comment is acceptable.

Comment #VI

(b)(4)(CC)



(b)(4)(CC)

A large black rectangular redaction box covers the top portion of the page, starting below the first redaction code and extending down to the beginning of the first paragraph.

There were no significant difference among the results as the coefficient of variation were all less than 12%. The firm indicated that this work was generated over the period of August 14-24, 1995.

Reply to Comment #VI

The firm's response to the comment is acceptable.

Comment #VII

(b)(4)(CC)

A large black rectangular redaction box covers the bottom portion of the page, starting below the second redaction code and extending down to the bottom of the page.

(b)(4)(CC)

Reply to Comment #VII

The firm's response to the comment is acceptable.

XI. Recommendations:

1. The single-dose bioequivalence study #MO93-0602 under fasting and nonfasting conditions, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 200 mg tablet, lot #4WD, comparing it to MS Contin^R Controlled-Release 200 mg tablet manufactured by Purdue Frederick Company, has been found acceptable by the Division of Bioequivalence. The study demonstrates that AB Generics' Morphine Sulfate Controlled-Release 200 mg Tablet is bioequivalent to the reference product MS Contin^R Controlled-Release, 200 mg Tablet, manufactured by Purdue Frederick Company.

2. The multiple-dose steady-state bioequivalence study #MO94-0309, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 200 mg tablets, lot #4WD, comparing it to MS Contin^R Controlled-Release 200 mg tablets manufactured by Purdue Frederick Company, has been found acceptable by the Division of Bioequivalence. The study demonstrates that AB Generics' Morphine Sulfate Controlled-Release 200 mg Tablet is bioequivalent to the reference product MS Contin^R Controlled-Release, 200 mg Tablet, manufactured by Purdue Frederick Company.

3. The dissolution testing conducted by AB Generics L.P., on its Morphine Sulfate Controlled-Release 200 mg tablets, lot #4WD, is acceptable. The dissolution testing should be conducted in 900 mL of simulated gastric fluid at 37°C using USP 23 apparatus I (basket) at 50 rpm. Based on the submitted data the following tentative specifications are recommended:

1	hour	(b)(4)(CC)
2	hours	(b)(4)(CC)
3	hours	(b)(4)(CC)
4	hours	(b)(4)(CC)
8	hours	(b)(4)(CC)

The firm should be informed of the above recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE/S/ [REDACTED]
FT INITIALLED RMHATRE [REDACTED]

Date: 11/28/97

/S/

Concur: _____

Date: 12/23/97

Rabindra Patnaik, Ph.D.

fr Acting Director

Division of Bioequivalence

Mmakary/10-20-97, 11-26-97 wp 74769SD.696

cc: ANDA #74-769, original, HFD-650 (Director), HFD-658 (Makary),
Drug File, Division File.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-769 SPONSOR: AB Generics L.P.
DRUG: Morphine Sulfate CR Tablet
DOSAGE FORM: tablets CR
STRENGTH(s): 200 mg and 100 mg
TYPE OF STUDY: Single/Multiple Fasting/Fed
STUDY SITE:

STUDY SUMMARY: The bioequivalence studies conducted on Morphine Sulfate CR Tablet 200 mg are acceptable. The bioequivalence study conducted on Morphine Sulfate CR Tablet 100 mg is acceptable.

DISSOLUTION: The dissolution testing is acceptable

PRIMARY REVIEWER: [redacted] BRANCH: III

INITIAL: [redacted] DATE: 11/26/97

BRANCH CHIEF: BRANCH:

INITIAL: [redacted] DATE: 11/28/97

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: [redacted] DATE: 12/24/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE:

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-769

APPLICANT: AB Generics, L.P.

DRUG PRODUCT: Morphine Sulfate Controlled Release Tablets, 100
and 200 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of simulated gastric fluid at 37°C, using USP 23 apparatus I (basket) at 50 rpm. Based on the submitted data the following tentative specifications are recommended:

- | | | |
|---|-------|------------|
| 1 | hour | (b)(4)(CC) |
| 2 | hours | |
| 3 | hours | |
| 4 | hours | |
| 8 | hours | |

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/s/ [Redacted Signature]

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FEB 19 1997

FEB 19 1997

Morphine Sulfate CR Tablet
100 mg
ANDA # 74-769
Reviewer: Moheb H. Makary
WP 74769SD.096

AB Generics L.P.
Norwalk, CT
Submission Date:
October 7, 1996

Review of a Study Amendment

I. Objective:

The firm has replied to the reviewer's comments made in the review of the February 16, March 11 and May 8, 1996 submissions (a bioequivalence study on Morphine Sulfate CR 100 mg Tablet and dissolution data).

II. Comment #1

The firm was asked to submit the potency and content uniformity for the test and reference products.

The firm submitted the firm submitted the potency and content uniformity for the test and reference products.

	Test Product	Reference Product
	Lot #4XC	Lot #6FW
Potency	98.7%	99.6%
Content uniformity	99.6%	97.7%

Reply to Comment #1

The firm's response to the comment is acceptable.

Comment #2

The firm was advised to submit the analytical raw data for all subjects in the study and the (b)(4)(CC) with legible labels for subjects #1, #6, #11, #15 and #22.

The firm submitted the analytical raw data for all subjects and legible (b)(4)(CC) for subjects #1, 6, 11, 15 and 22.

Reply to Comment #2

The firm's response to the comment is acceptable.

Comment #3

The firm was asked to submit AUC_{0-t} (area under the plasma concentration-time curve from time zero to time t, calculated by the trapezoidal rule, where t is the last measurable time point) and AUC_{0-inf} (where $AUC_{0-inf} = AUC_t + C_t/Kel$, C_t is the last measurable

drug concentration and K_{el} is the terminal elimination rate constant calculated according to an appropriate method) for morphine and morphine-6-glucuronide.

The firm submitted the AUC_{0-t} and AUC_{0-inf} for morphine and morphine-6-glucuronide for each subject in the study.

Morphine

	<u>Test</u>	<u>Reference</u>	<u>90% CI</u>
AUC(0-t) (ng.hr/mL)	390.5 (32)	374.1 (34)	96.6-116.5
AUCinf (ng.hr/mL)	405.4 (30)	390.7 (33)	96.6-115.6

Morphine-6-Glucuronide

	<u>Test</u>	<u>Reference</u>	<u>90% CI</u>
AUC(0-t) (ng.hr/mL)	1823.3 (26)	1745.4 (33)	98.1-119.6
AUCinf (ng.hr/mL)	1886.5 (25)	1810.1 (34)	97.8-119.8

Reply to Comment #3

The firm's response to the comment is acceptable.

Comment #4

The firm was advised to submit 3.5" Diskettes in ASCII code for the bioequivalence study #MO94-1002.

The firm submitted a 3.5" Diskette contains all pharmacokinetic data for morphine and morphine-6-glucuronide.

Reply to Comment #4

The firm's response to the comment is acceptable.

Comment #5

In the study report section, the firm stated that twenty-six (26) subjects were enrolled and completed the study. In the analytical report section (page 145), the firm stated that "of the 26 subjects that were enrolled in the study, subject #3 dropped out after Phase I". The firm was asked to explain this discrepancy.

The firm has indicated that the sentence referring to "subject 3 dropping out" was inadvertently left in the text of the study report from a previous study report since a template approach to study report writing was used.

Reply to Comment #5

The firm's response to the comment is acceptable.

Comment #6

The firm was asked to submit comparative dissolution testing using 900 mL of water at 37°C, USP 23 apparatus I (basket) at 50 rpm.

The firm has indicated that the original dissolution method utilized for MS Contin^R 100 mg tablets used water as the dissolution medium. Following review of that NDA supplement, FDA advised Purdue to change the medium from water to simulated gastric fluid. The comparative dissolution data submitted with this ANDA was simulated gastric fluid.

For informational purpose, the firm submitted dissolution testing data on MS Contin^R Controlled-Release 100 mg tablets which was generated in 1984 using 900 mL of water at 37°C, USP 23 apparatus I (basket) at 50 rpm.

Reply to Comment #6

The firm's response to the comment is acceptable.

Comments:

1. The firm's in vivo single-dose bioequivalence study #M094-1002 on its Morphine Sulfate CR Tablet, 100 mg under fasting conditions is acceptable. The 90% confidence intervals for morphine and morphine-6-glucuronide are all within the acceptable range of 80-125% for AUC(0-t), AUCinf and Cmax under fasting conditions.
2. The in vitro dissolution testing previously submitted by the firm on its Morphine Sulfate CR Tablet, 100 mg is acceptable.
3. The firm had previously submitted following studies (ANDA #74-769, submission dated October 16, 1995) :
 - a. Study #M093-0602
A single dose randomized four-way crossover bioequivalence study of Morphine Sulfate Controlled Release (CR) 200 mg tablets under fasting and nonfasting conditions.
 - b. Study #M094-0309
A two-way crossover, multiple-dose bioequivalence study of Morphine Sulfate Controlled Release (CR) 200 mg tablets under fasting conditions.

The above bioequivalence studies on the 200 mg strength have been found incomplete by the Division of Bioequivalence. However, the review of the 100 mg strength is independent of the 200 mg strength, the approval of the current study (Morphine Sulfate CR Tablet, 100 mg under fasting conditions) will be pending on the 200 mg strength approval.

Recommendation:

The single-dose bioequivalence study #M094-1002, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 100 mg tablets, lot #4XC, comparing it to MS Contin^R Controlled-Release 100 mg tablets manufactured by Purdue Frederick Company, has been found acceptable by the Division of Bioequivalence. However, the approval of the above strength will be pending on the 200 mg strength approval.

The firm should be informed of the comments and recommendation.

/s/ [Redacted]

for M.M.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE /s/ [Redacted] Date: 2/13/97
FT INITIALLED RMHATRE /s/ [Redacted]

Concur: /s/ [Redacted] Date: 2/19/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/1-29-97 wp 74769SD.096
cc: ANDA #74-769, original, HFD-658 (Makary), Drug File, Division File.

JUN 20 1996

Morphine Sulfate CR Tablet
100 mg
ANDA # 74-769
Reviewer: Moheb H. Makary
WP 74769SD.296

AB Generics L.P.
Norwalk, CT
Submission Date:
February 16, 1996
March 11, 1996
May 8, 1996

Review of Bioequivalence Study and Dissolution Data

I. Objective:

The firm has submitted a single-dose bioequivalence study under fasting conditions to assess the bioequivalence of the AB Generics s Morphine Sulfate Controlled Release (CR) Tablets, 100 mg, to Purdue Frederick s MS Contin^R Controlled Release 100 mg Tablets. Dissolution profiles comparing AB Generics s Morphine Sulfate (CR) tablets and MS Contin[®] tablets were submitted.

The firm had submitted following studies (ANDA #74-769, submission dated October 16, 1995) :

1. Study #MO93-0602

A single dose randomized four-way crossover bioequivalence study of Morphine Sulfate Controlled Release (CR) 200 mg tablets under fasting and nonfasting conditions. The study was found to be incomplete by the Division of Bioequivalence.

2. Study #MO94-0309

A two-way crossover, multiple-dose bioequivalence study of Morphine Sulfate Controlled Release (CR) 200 mg tablets under fasting conditions. The study was found to be incomplete by the Division of Bioequivalence.

However, the following review of the 100 mg strength is independent of the 200 mg strength, the approval of the current study will pending on the 200 mg strength approval.

II. Introduction:

Morphine is indicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesics over periods of more than a few days.

Following oral administration of a given dose of morphine, the amount ultimately absorbed is essentially the same whether the source is controlled release or a conventional formulation. Because of pre-systemic elimination (i.e., metabolism in the gut wall and liver) only about 40% of the administered dose reaches the central compartment, and peak plasma concentrations occurring between 30 minutes to 1.5 hours. The elimination half-life of the drug is estimated to be 3-4 hours. Morphine undergoes conjugation with glucuronic acid, to form the major inactive metabolite,

morphine-3-glucuronide (M-3-G), the active metabolite, morphine-6-glucuronide (M-6-G) and the inactive metabolite, morphine-3,6-diglucuronide (M3,6G). The drug is excreted in urine mainly as metabolites and free morphine accounts for less than 10% of an administered dose. About 90% of the total urinary excretion occurs within 24 hours. About 7-10% of a dose of morphine is excreted in feces mostly via bile, and there is also some enterohepatic recycling.

Morphine Sulfate is available commercially as an oral solution, oral tablets, oral soluble tablets, oral extended-release tablets, oral film-coated, extended-release tablets, parenteral injection and rectal suppositories. Morphine Sulfate Controlled Release 200 mg Tablet (MS Contin[®]) is marketed by Purdue Frederick.

III. Study #MO94-1002 For Single-Dose, Two-Way Crossover Of Morphine Sulfate Controlled Release Tablets, 100 mg, Under Fasting Conditions:

The objective of the study was to compare the bioavailability of Morphine Sulfate Controlled Release (CR) tablets manufactured by AB Generics, with that of Purdue Frederick product (MS Contin[®]), following an oral administration of a single 100 mg dose (1x100 mg tablet) of each product under fasting conditions. Morphine and its metabolite, morphine-6-glucuronide, concentrations in plasma were assayed.

Clinical site:

(b)(4)(CC)

Analytical site:

Investigators:

Sponsor:

The Purdue Frederick Company, Norwalk, CT.
(AB Generics is a new generic company associated with The Purdue Frederick Company)

Study design:

Single-dose, two-way crossover bioequivalence study, under fasting conditions.

Study dates:

March 9, 1995 - March 27, 1995

Dose dates

March 18 and March 25, 1995

Analysis dates:

May 9 - June 9, 1995

Subjects:

Twenty-six (26) normal, adult healthy male and female subjects (11 male and 15 female) were accepted for entry into the clinical portion of the study. One (1) subject was

Hispanic, one (1) subject Asian and twenty-four (24) were Caucasian. Twenty-six (26) subjects successfully completed the study.

Inclusion criteria: Male and female subjects were between 21 to 45 years of age. All subjects were within $\pm 10\%$ of their ideal body weight for height and body frame as described in the Metropolitan Life Insurance Company Statistical Bulletin, 1983. Subjects were judged to be in good health following a complete physical examination, ECG and medical history within fourteen days of the start of the study. In addition, urine samples at the time of the medical examination were free of drug abuse (including marijuana). Good health was confirmed by normal findings in the following tests: biochemical profile, hematology and urinalysis. Female subjects had a negative serum pregnancy test at screening and at time of dosing. Subjects had a negative Narcan^R challenge test.

Exclusion criteria: Consisted of adverse reactions or allergy to opioid drugs, history of alcohol or drug abuse, history of cardiovascular, neurological, neuropsychiatric, gastrointestinal, hepatic, renal, hematological and/or respiratory diseases, use of prescription medication, including vitamin and/or mineral supplements within two weeks prior to study initiation or OTC medication during the seven days preceding study initiation and throughout this study and female subjects taking systemic contraceptive agents.

Dosing regimens:

A. Reference product: MS Contin[®] 1x100 mg tablet (Purdue Frederick Company), lot #6FW, Exp. 5/96, potency (not reported), content uniformity (not reported), administered following a 10 hours overnight fast.

B. Test product: Morphine Sulfate Controlled-Release 1x100 mg tablet (Purdue Frederick Company), lot #4XC, batch size (b)(4)(CC) Tablets, Exp. 9/95, potency (not reported), content uniformity (not reported), administered following a 10 hours overnight fast.

Narcan^R Challenge Test: Prior to dosing in

period I, and after ascertainment of a (negative urine drug screen, a Narcan^R (Naloxone) challenge test was administered. This test was conducted after subjects have checked into the facility 26 hours prior to test medication dosing and before receiving their first dose TrexanTM (the test should not be performed in a subject showing clinical symptoms of opioid withdrawal or in a subject whose urine contains opioids).

Trexan^R Administration: After it was determined that, for each subject, both the urine drug screen and the Narcan^R challenge test results were negative, 2x50 mg tablets of naltrexone HCl (TrexanTM) were administered at least 24 hours prior to the scheduled time of dosing in period I. This dose of naltrexone was administered again at the time of dosing and again at 24 hours after dosing. Naltrexone is an antagonist competing for the same receptor sites as morphine and is expected to diminish the potential adverse effects of morphine, especially respiratory depression. The use of a twice a day oral dose of 50 mg of naltrexone slightly alter the absolute bioavailability of oral morphine, but do not interfere with the determination of the comparative bioavailability.

Washout period:

One week

Food and fluid intake:

All subjects fasted for ten hours prior to dosing. Lunch was served four hours after dosing. Dinner was served eleven hours after dosing. Water was not allowed four hours after dosing, except for the dosing water (240 mL).

Treatment Group

Subject Number

A- B

2, 4, 5, 8, 9, 10, 13, 14, 17, 19, 21, 23

B- A

1, 3, 6, 7, 11, 12, 15, 16, 18, 20, 22, 24, 25, 26

Treatments Codes:

A=MS Contin 100 mg fasting
B=MS (Generics) 100 mg Fasting

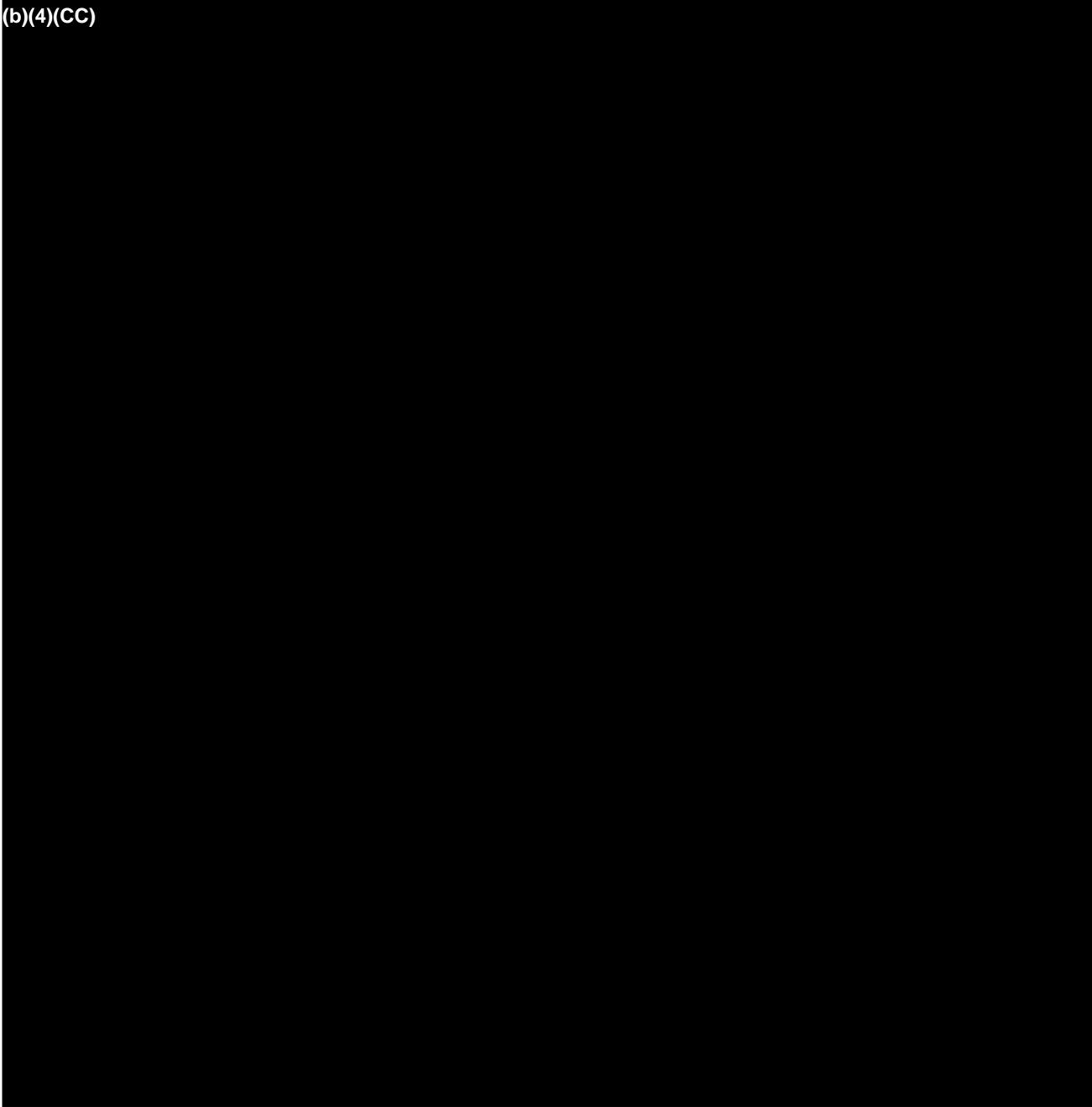
Blood sample times: Pre-dose (0 hr) and 0.5, 1, 1.5, 2, 2.5, 3,

3.5, 4, 6, 8, 10, 12, 18, 24, 30, 36 and 48 hours after dosing.

Subject welfare: Vital signs (blood pressure and pulse rate) were measured just prior to each dose (within 30 minutes) and at 2, 4, 8, 12, 24 and 48 hours post-dose.

Assay Methodology

(b)(4)(CC)



Statistical Analysis:

Statistical analysis was performed on morphine and morphine-6-glucuronide data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The two one-sided tests were used to estimate the 90% confidence interval.

IV. In Vivo Results:

Twenty-six (26) normal, healthy male and female subjects were enrolled and completed the study.

Fourteen (14) adverse experiences were reported during the study. Two were considered to be of moderate severity and the remainder were considered mild. None was considered to be serious. Overall, 25 adverse experiences were considered unrelated to study drug, 11 were considered possibly related. The adverse experiences were those standardly reported with the use of morphine or other opioid analgesics. These included nausea, headache, dizziness,

asthenia, amnesia, vomiting and hypesthesia. The results indicate that the incidence of adverse experiences were similar between the test and reference drugs under fasting conditions. There were no striking differences between the gender groups in the incidence and nature of the reports.

The plasma concentrations and pharmacokinetic parameters for Morphine and Morphine-6-Glucuronide (G-6-G) are summarized in Tables I and II.

Table I

Mean Plasma Morphine Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 100 mg Morphine Sulfate Controlled Release Tablet under Fasting Conditions
(N=26)

<u>Time</u> hr	A		B	
	<u>Fasting</u> Reference Lot #6FW ng/mL (CV)		<u>Fasting</u> Generics-Test Lot #4XC ng/mL (CV)	
0	0		0	
0.5	11.5	(46.6)	12.2	(60.2)
1	21.0	(48.5)	21.6	(59.6)
1.5	25.1	(52.0)	27.1	(54.2)
2	25.5	(47.8)	31.2	(56.0)
2.5	30.1	(40.3)	32.8	(40.5)
3	30.9	(40.1)	31.0	(48.1)
3.5	29.7	(36.2)	30.5	(52.3)
4	25.4	(40.7)	27.8	(50.2)
6	20.4	(36.0)	23.0	(38.4)
8	15.7	(48.9)	14.8	(34.5)
10	11.4	(56.1)	10.6	(32.1)
12	10.7	(50.5)	11.6	(43.9)
18	6.9	(48.5)	6.9	(39.3)
24	5.7	(54.6)	5.8	(41.0)
30	4.4	(59.6)	4.2	(39.1)
36	1.7	(76.6)	1.8	(61.8)
48	1.0	(105.1)	1.1	(97.3)

90% CI

AUC(0-48)		
(ng.hr/mL)	378.6 (32)	384 (31)
AUCinf		
(ng.hr/mL)	387.2 (33)	401.6 (31)
Cmax (ng/mL)	37.1 (34)	39.3 (42)
Tmax (hr)	2.6	2.6

LnAUC	96.5-115.4
LnAUCinf	96.0-115.9
LnCmax	90.3-118.8

Morphine

1. For morphine, the least squares means for AUC(0-48), AUCinf and Cmax values were 5.2%, 4.9% and 6.5% higher, respectively, for the test product than for the reference product under fasting conditions. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data.

2. The morphine plasma levels peaked at 2.5 and 3 hours for the test and reference products, respectively, following their administration under fasting conditions.

3. There were no statistically significant effects for AUC(0-48), AUCinf and Cmax between the two treatments.

Table II

Mean Plasma M-6-G Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 100 mg Morphine Sulfate Controlled Release Tablet under Fasting Conditions
(N=26)

<u>Time</u> hr	A		B	
	<u>Fasting</u> Reference Lot #6FW ng/mL (CV)		<u>Fasting</u> Generics-Test Lot #4XC ng/mL (CV)	
0	0		0	
0.5	10.9	(56.4)	11.0	(64.0)
1	64.4	(48.3)	59.5	(48.1)
1.5	99.1	(39.1)	93.5	(41.5)
2	113.2	(35.4)	122.9	(32.0)
2.5	138.0	(30.1)	144.0	(23.8)
3	150.5	(24.1)	158.6	(26.2)
3.5	153.9	(32.1)	157.7	(27.9)
4	134.9	(36.8)	146.2	(23.5)
6	106.9	(46.6)	118.3	(34.0)
8	80.1	(43.5)	75.2	(43.6)
10	60.5	(50.7)	55.4	(40.7)
12	49.6	(53.8)	53.6	(48.5)
18	31.0	(48.5)	35.4	(43.2)
24	24.4	(52.5)	26.4	(46.5)
30	18.4	(74.4)	17.1	(47.8)
36	8.1	(75.1)	8.6	(51.2)

48 4.5 (106.9) 4.4 (102.2)

90% CI

AUC(0-48)		
(ng.hr/mL)	1766.0(32)	1845.5(25)
AUCinf		
(ng.hr/mL)	1802.8(34)	1879.2(26)
Cmax(ng/mL)	173.5(24)	180.7(21)
Tmax (hr)	3.60	3.25
LnAUC		98.2-119.3
LnAUCinf		97.9-119.7
LnCmax		97.6-114.0

Morphine-6-Glucuronide (M-6-G)

1. For M-6-G, the least squares means for AUC(0-48), AUCinf and Cmax values were 5.8%, 5.6% and 5.0% higher, respectively, for the test product than for the reference product under fasting conditions. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data.

2. The M-6-G plasma levels peaked at 3 and 3.5 hours for the test and reference products, respectively, under fasting conditions.

V. Formulations: Not To Be Released Under FOI

The formulations of AB Generics L.P. and Purdue Frederick for Morphine Sulfate Controlled-Release Tablets, 100 mg are shown below:

<u>AB Generics L.P.</u>	<u>Purdue Frederick</u>
Morphine Sulfate Controlled-Release Tablets 100 mg	MS Contin ^R Morphine Sulfate Controlled-Release Tablets 100 mg

Component

Morphine Sulfate (Pentahydrate), USP	100.0 mg	100.0 mg
Hydroxyethyl Cellulose, NF	(b)(4)(TS)	
Cetostearyl Alcohol, NF		
Talc, USP		
Magnesium Stearate, NF		
Purified Water, USP		

Colorant

Purified Water, USP

(b)(4)(TS)

(b)(4)(TS)

Gray**
Gray**

* Appears in the finished dosage form as residual moisture.
** Side-by-side qualitative comparison of colorant compositions are shown below:

(b)(4)(TS)

VI. In vitro Dissolution Testing:

Method: USP 23 apparatus I (basket) at 50 rpm
Medium: 900 mL of Simulated Gastric Fluid for 1, 2, 3, 4, 6, 8, 9 and 12 hours.
Number of Tablets: 12
Test Product: AB Generics' Morphine Sulfate Controlled-Release tablets, 100 mg, Lot #4XC.
Reference Product: Purdue's MS Contin® Morphine Sulfate Controlled-Release tablets, 100 mg, Lot #6FW

The dissolution testing results are presented in table III.

VII. Comments:

1. In the single-dose bioequivalence study #MO94-1002, the firm calculated AUC_{0-48} and not AUC_{0-t} by the trapezoidal rule. The $AUC(0-\infty)$ was estimated as follows:

- a. If $C(48) = 0$, the $AUC(0-48)$ was taken as $AUC(0-\infty)$.
- B. If $C(48) > 0$, then the quantity $C(48)/k_{el}$ was added to $AUC(0-48)$ to estimate $AUC(0-\infty)$, where k_{el} is the terminal first order apparent elimination rate constant.

By using the above calculation method the values of AUC_{0-48} are the same as $AUC(0-\infty)$ values for some subjects.

2. The in vitro dissolution testing for the test product Morphine Sulfate Controlled-Release 100 tablets is acceptable.

VIII. Deficiency Comment:

1. The potency and content uniformity for the test and reference products should be submitted.

2. The firm is advised to submit the analytical raw data for all subjects in the studies.

3. The following pharmacokinetic parameters should be submitted for morphine and morphine-6-glucuronide, AUC_{0-t} (area under the plasma concentration-time curve from time zero to time t, calculated by the trapezoidal rule, where t is the last measurable time point) and AUC_{0-inf} (where $AUC_{0-inf} = AUC_t + C_t/Kel$, C_t is the last measurable drug concentration and Kel is the terminal elimination rate constant calculated according to an appropriate method).

4. The firm is advised to submit 3.5 Diskettes in ASCII code for the bioequivalence study #M094-1002.

5. The representative (b)(4)(CC) submitted by the firm for subjects (#1, #6, #11, #15 and #22) are not legible. The firm is advised to submit (b)(4)(CC) with legible labels.

6. In the study report section, the firm stated that twenty-six (26) subjects were enrolled and completed the study. In the analytical report section (page 145), the firm stated that of the 26 subjects that were enrolled in the study, subject #3 dropped out after Phase I. The firm should explain this discrepancy.

IX. Recommendations:

1. The single-dose bioequivalence study #M094-1002, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 100 mg tablets, lot #4XC, comparing it to MS Contin^R Controlled-Release 100 mg tablets manufactured by Purdue Frederick Company, has been found incomplete by the Division of Bioequivalence for the reasons given in deficiency comments.

2. The dissolution testing conducted by AB Generics L.P., on its Morphine Sulfate Controlled-Release 100 mg tablets, lot #4XC, is acceptable. The dissolution testing should be conducted in 900 mL of simulated gastric fluid at 37°C using USP 23 apparatus I (basket) at 50 rpm. Based on the submitted data the following tentative specifications are recommended:

1	hour	(b)(4)(CC)
2	hours	
3	hours	

4 hours (b)(4)(CC)
8 hours

3. From the bioequivalence point of view the firm has not met the requirements of in vivo testing for the reasons given in deficiency comments and the bioequivalence study is incomplete.

The firm should be informed of the deficiency comments and recommendations.

/s/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED, RMHATRE Date: 6/17/96

/s/ Date: 6/20/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/6-14-96 wp 74769SD.296
cc: ANDA #74-769, original, HFD-600 (Hare), HFD-630, HFD-344
(CViswanathan), HFD-658 (Mhatre, Makary), Drug File, Division
File.

Table III In Vitro Dissolution Testing

Drug (Generic Name): Morphine sulfate Controlled-Release Tablets, 100 mg
 Dose Strength: 100 mg Tablets
 ANDA No.: 74-769
 Firm: A.B. Generics L.P.
 Submission Date: February 16, 1996
 File Name: 74769SD.296

I. Conditions for Dissolution Testing:

USP 23 Basket: X Paddle: RPM: 50
 No. Units Tested: 12
 Medium: 900 mL SGF for 1, 2, 3, 4, 6, 8, 9 and 12 hours
 Specifications:
 Reference Drug: Purdue Frederick's MS Contin
 Assay Methodology:

II. Results of In Vitro Dissolution Testing:

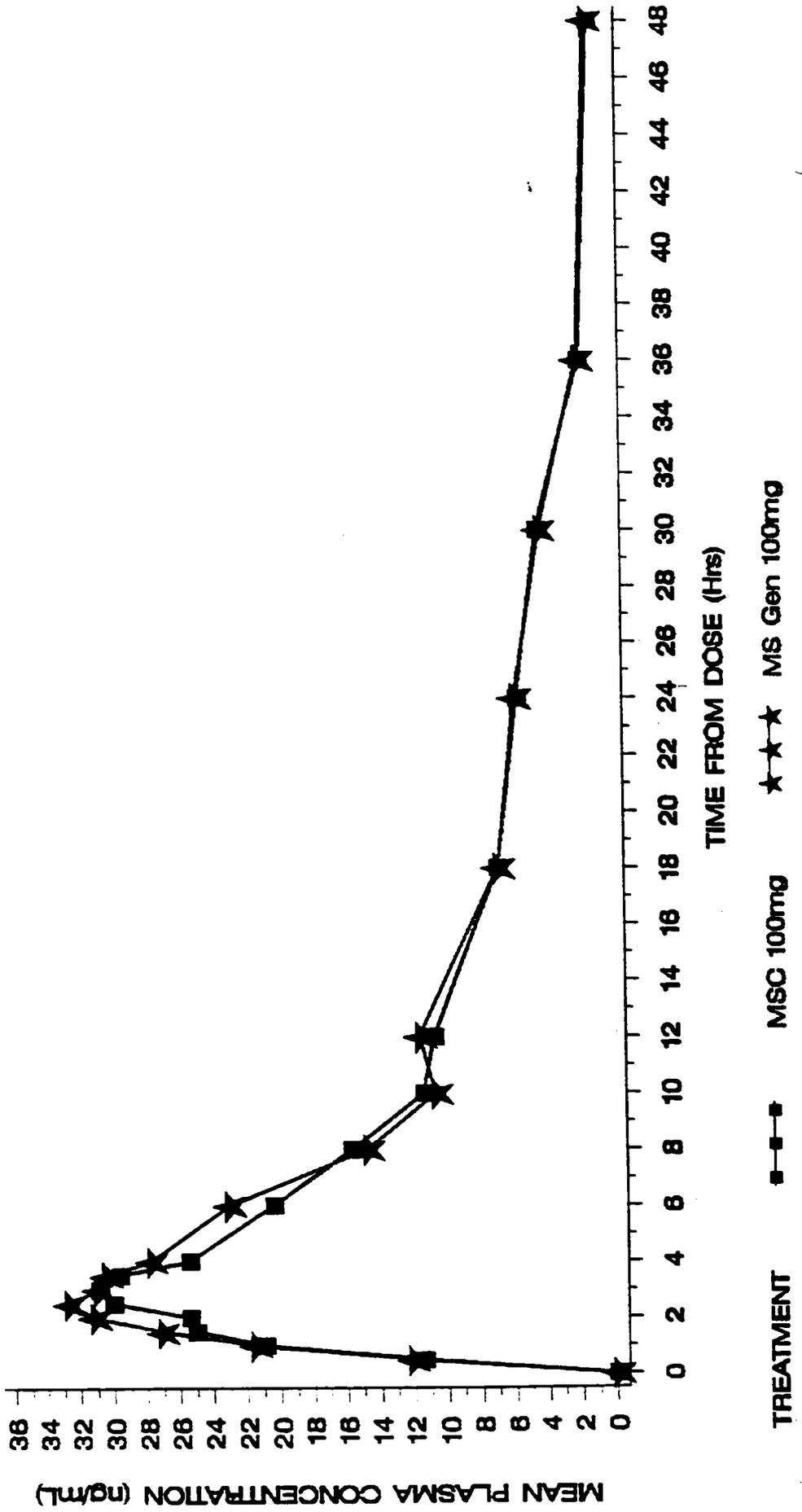
Sampling Times (hr)	Test Product Lot #4XC Strength(mg) 100			Reference Product Lot # 6FW Strength(mg) 100		
	Mean %	Range	%CV	Mean %	Range	%CV
1	30.6	(b)(4)(CC)	4.4	30.9	(b)(4)(CC)	3.2
2	47.6	(b)(4)(CC)	4.2	48.0	(b)(4)(CC)	2.9
3	60.5	(b)(4)(CC)	3.3	60.9	(b)(4)(CC)	2.5
4	70.8	(b)(4)(CC)	3.0	71.0	(b)(4)(CC)	2.3
6	85.4	(b)(4)(CC)	2.8	85.4	(b)(4)(CC)	2.0
8	94.7	(b)(4)(CC)	2.6	94.5	(b)(4)(CC)	2.0
9	97.8	(b)(4)(CC)	2.7	97.4	(b)(4)(CC)	2.1
12	101.5	(b)(4)(CC)	2.7	100.5	(b)(4)(CC)	2.1

PROTOCOL NO. MOB4-1002

FIGURE I

MEAN PLASMA MORPHINE CONCENTRATION (NG/ML) OVER TIME

Population: Valid for Pharmacokinetic & Safety Analysis



PROTOCOL NO. M084-1002

FIGURE II

MEAN PLASMA MORPHINE-6-GLUCURONIDE CONCENTRATION (NG/ML) OVER TIME

Population: Valid for Pharmacokinetic & Safety Analysis

