AB Generics L.P.

100 CONNECTICUT AVENUE, NORWALK, CT 06850-3590 • (203) 853-0123 FAX (203) 838-1576

VIA OVERNIGHT MAIL

May 8, 1996

Per L. Galvin
BIOAVAILABILITY

SUBMITTED IN TRIPLICATE
GENERAL CORRESPONDENCE IN RESPONSE TO FDA REQUEST

Desk Copy:
Mr. William Russell (letter only)

Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Mr. Douglas Sporn

Re: Morphine Sulfate Controlled-Release 15, 30 & 60 mg Tablets
ANDA #74-862

Dear Mr. Sporn:

Reference is made to ANDA #74-862 for Morphine Sulfate Controlled-Release 30 mg Tablets submitted on February 23, 1996, and a supplement for Morphine Sulfate Controlled-Release 60 mg Tablets, submitted on March 11, 1996, and a supplement for Morphine Sulfate Controlled-Release 15 mg Tablets, submitted on May 3, 1996. Also, reference is made to a telephone conversation on February 8, 1996 between Dr. James Conover and Mr. Laurence Galvin whereby Mr. Galvin is requesting revised in vitro dissolution data.

In accordance with Mr. Galvin's request, enclosed please find replacement pages #360 R and #361 R, Section VI.3., Attachment #6, "*In Vitro Dissolution Data*" for Volume #5 of the 30 mg ANDA.

Please contact me at the telephone number provided below if you have any additional comments.

Yours truly,

AB Generics L.P.
By:

Mary Ann Traut KH

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MAY 09 1996
GEN

Mary Ann Traut
Associate
Drug Regulatory Affairs & Compliance
The Purdue Frederick Company
Telephone: (203) 854-7286

MAT:kh
Enclosure

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MORPHINE SULFATE EXTENDED RELEASE 30 MG F/C TABLETS

LOT# 4WE
REF. 1739-26 (1-6) & 1773-6 (7-12)
APPARATUS I - 50 RPM
900 ML WATER 37 DEG. C.
PF LABS METHOD# A99-9102-01

LOT NUMBER	4WE
ANALYSIS NO	94-1455
NOTEBOOK	1739-26 & 1773-6
DATE OF MFG	9/7/93
PLACE OF MFG	PF LABS, TOTOWA, NJ

MORPHINE SO4 MG/TABLET	
LABEL VALUE	30 MG

TABLET #	PERCENT MORPHINE SO4 DISSOLVED					
	HOUR 1	HOUR 2	HOUR 4	HOUR 6	HOUR 8	HOUR 12
1	[redacted]					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
MEAN	32.4	49.2	72.3	85.1	92.5	96.3
SD	1.9	2.0	1.5	2.7	3.2	3.4
MIN	[redacted]					
MAX						

(b)(4)(CC)

Theoretical Lot Size: [redacted] (b)(4)
equivalent to [redacted] (b)(4) Tablets

Actual Lot Size: [redacted] (b)(4)(CC) Tablets

Actual Yield: [redacted] Tablets

Assay (mg/tablet): 29.1

PERFORMED BY GARY RITCHIE
DATE 10/25/94 & 11/15/94

360 R

MS CONTIN DISSOLUTION 30 MG F/C TABLETS

LOT# 5FV
REF. 1739-26 (1-6) & 1773-6 (7-12)
APPARATUS I - 50 RPM
900 ML WATER 37 DEG. C.
PF LABS METHOD

LOT NUMBER	5FV
ANALYSIS NO	94-1455
NOTEBOOK	1739-26 & 1773-6
DATE OF MFG	6/2/94
PLACE OF MFG	PF LABS, TOTOWA, NJ

MORPHINE SO4 MG/TABLET	
LABEL VALUE	30 MG

TABLET	PERCENT MORPHINE SO4 DISSOLVED					
#	HOUR 1	HOUR 2	HOUR 4	HOUR 6	HOUR 8	HOUR 12
1	[redacted]					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
MEAN	32.2	49.2	72.0	84.5	92.0	95.7
SD	0.5	0.9	1.4	1.4	1.9	2.3
MIN	[redacted]					
MAX						

(b)(4)(CC)

PERFORMED BY GARY RITCHIE
DATE 10/25/94 & 11/15/94

Theoretical Lot Size: [redacted] (b)(4)
equivalent to [redacted] (b) Tablets

Actual Lot Size: [redacted] (b)(4)(CC) Tablets

Actual Yield: [redacted] (b)(4)(CC) Tablets

Assay (mg/tablet): 28.5

AB Generics L.P.

100 CONNECTICUT AVENUE, NORWALK, CT 06850-3590 • (203) 853-0123 FAX (203) 838-1576

VIA OVERNIGHT MAIL

May 8, 1996

Re L. Galvin
BIOAVAILABILITY

NEW CORRESP

SUBMITTED IN TRIPLICATE
GENERAL CORRESPONDENCE IN RESPONSE TO FDA REQUEST

Desk Copy:
Mr. William Russell (letter only)

RECEIVED

MAY 0 9 1996

GENERIC DRUGS

Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Mr. Douglas Sporn

Re: Morphine Sulfate Controlled-Release 15, 30 & 60 mg Tablets
ANDA #74-862

Dear Mr. Sporn:

Reference is made to ANDA #74-862 for Morphine Sulfate Controlled-Release 30 mg Tablets submitted on February 23, 1996, and a supplement for Morphine Sulfate Controlled-Release 60 mg Tablets, submitted on March 11, 1996, and a supplement for Morphine Sulfate Controlled-Release 15 mg Tablets, submitted on May 3, 1996. Also, reference is made to a telephone conversation on February 8, 1996 between Dr. James Conover and Mr. Laurence Galvin whereby Mr. Galvin is requesting revised in vitro dissolution data.

In accordance with Mr. Galvin's request, enclosed please find replacement pages #331 R and #332 R, Section VI.3., Attachment #6, "*In Vitro Dissolution Data*" for Volume #4 of the 60 mg ANDA supplement.

Please contact me at the telephone number provided below if you have any additional comments.

Yours truly,

AB Generics L.P.
By:

Mary Ann Traut

Mary Ann Traut
Associate
Drug Regulatory Affairs & Compliance
The Purdue Frederick Company
Telephone: (203) 854-7286

MAT:kh
Enclosure

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MS Extended Release 60 mg Tablets

Lot 4WF
PRC Method 210-DS2-LS1
P.F. Laboratories Analysis #2441
Date of Test: 10/13/95

Tablet #	Percent Morhine Sulfate Dissolved					
	Hour 1	Hour 2	Hour 4	Hour 6	Hour 8	Hour 12
1	(b)(4)(CC)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	29.8	46.0	67.3	82.3	92.6	98.4
Min	(b)(4)(CC)					
Max						

THEORETICAL LOT SIZE: (b)(4)(CC)

ACTUAL LOT SIZE:

ACTUAL YIELD:

ASSAY (mg/tablet): 59.28

MS Contin 60 mg Tablets

Lot 7AY
PRC Method 210-DS2-LS1
P.F. Laboratories Analysis #2441
Date of Test: 10/13/95

Tablet #	Percent Morhine Sulfate Dissolved					
	Hour 1	Hour 2	Hour 4	Hour 6	Hour 8	Hour 12
1	(b)(4)(CC)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	29.4	45.9	68.9	84.6	95.2	103.5
Min	(b)(4)(CC)					
Max						

THEORETICAL LOT SIZE: (b)(4)(CC)

ACTUAL LOT SIZE:

ACTUAL YIELD:

ASSAY (mg/tablet): 60.72

JUL 18 1996

Morphine Sulfate CR Tablet
30 mg and 60 mg
ANDA # 74-862
Reviewer: Moheb H. Makary
WP 74862SD.296

AB Generics L.P.
Norwalk, CT
Submission Date:
February 23, 1996
March 11, 1996

Review of Bioequivalence Studies and Dissolution Data

I. Objective:

The firm has submitted single-dose bioequivalence studies on its Morphine Sulfate Controlled Release (CR) Tablets, 30 mg and 60 mg under fasting conditions and dissolution data as compared to Purdue Frederick's MS Contin® Controlled Release Tablets 30 mg and 60 mg, respectively.

The firm had submitted following studies (ANDA #74-769, submission dated October 16, 1995 and February 16, 1996):

1. Study #MO93-0602
A single dose randomized four-way crossover bioequivalence study on 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 on Morphine Sulfate Controlled Release (CR) 200 mg tablets under fasting conditions. The study was found to be incomplete by the Division of Bioequivalence.

3. Study #MO94-1002
A single dose randomized two-way crossover bioequivalence study on Morphine Sulfate Controlled Release (CR) 100 mg tablets under fasting conditions. The study was found to be incomplete by the Division of Bioequivalence.

However, the following reviews of the 30 mg and 60 mg strengths are independent of the 200 mg strength, the approval of the current studies will be 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^{R}) is marketed by Purdue Frederick.

III. Study #MO94-1103 For Single-Dose, Two-Way Crossover Of Morphine Sulfate Controlled Release Tablets, 30 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^{R}), following an oral administration of a single 30 mg dose (1x30 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:	November 22, 1994 - December 21, 1994
Analysis dates:	Not reported
Subjects:	Twenty-five (25) normal, adult healthy male

and female subjects (15 male and 10 female, five subjects were Black, 19 were Caucasian and 1 Native American) were accepted for entry into the clinical portion of the study. Twenty-four (24) subjects successfully completed the study.

Inclusion criteria: Inclusion criteria required that the subjects be 21 to 45 years old, have a body weight of 60 to 94 kg for females and be free of significant abnormal health findings. The females were to have a negative serum pregnancy test at screening and be using reliable contraception (but not oral contraceptives or implants). The subjects were to be free of frequent attacks of nausea or emesis, with no history of prior alcohol or drug abuse.

Exclusion criteria: Consisted of adverse reactions or allergy to opioid drugs, history of significant medical or surgical conditions or disease, any contraindication to blood sampling or positive HIV or Hepatitis B blood tests. The subjects had to be able to abstain from food for 10 hours prior to dosing and 4 hours following drug administration. In the time period preceding the study, the subjects were to be free of significant illness (4 weeks), not use any prescription (2 weeks), OTC or supplemental medication (7 days), not smoke heavily (>10 cigarettes day), be alcohol free for 48 hours, and not have donated blood for the previous 30 days. The female subjects were excluded if using any systemic contraceptive agents and could not be post-menopausal or taking concomitant estrogen supplements.

Dosing regimens: A. Reference product: MS Contin® 1x30 mg tablet (Purdue Frederick Company), lot #5FV, Exp. 6/97, potency (not reported), content uniformity (not reported), administered following a 10 hours overnight fast.
B. Test product: Morphine Sulfate Controlled-Release 1x30 mg tablet (Purdue Frederick Company), lot #4WE, batch size (b)(4)(CC) Tablets, Exp. 9/95, potency (not reported), content uniformity (not reported), administered following a 10 hours overnight fast.

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 ingested with dosing (240 mL).

Treatment Group	Subject Number
A->B	3, 4, 5, 6, 11, 12, 13, 15, 18, 20, 23, 24
B->A	1, 2, 7, 8, 9, 10, 14, 16, 17, 19, 21, 22, 25, 26.

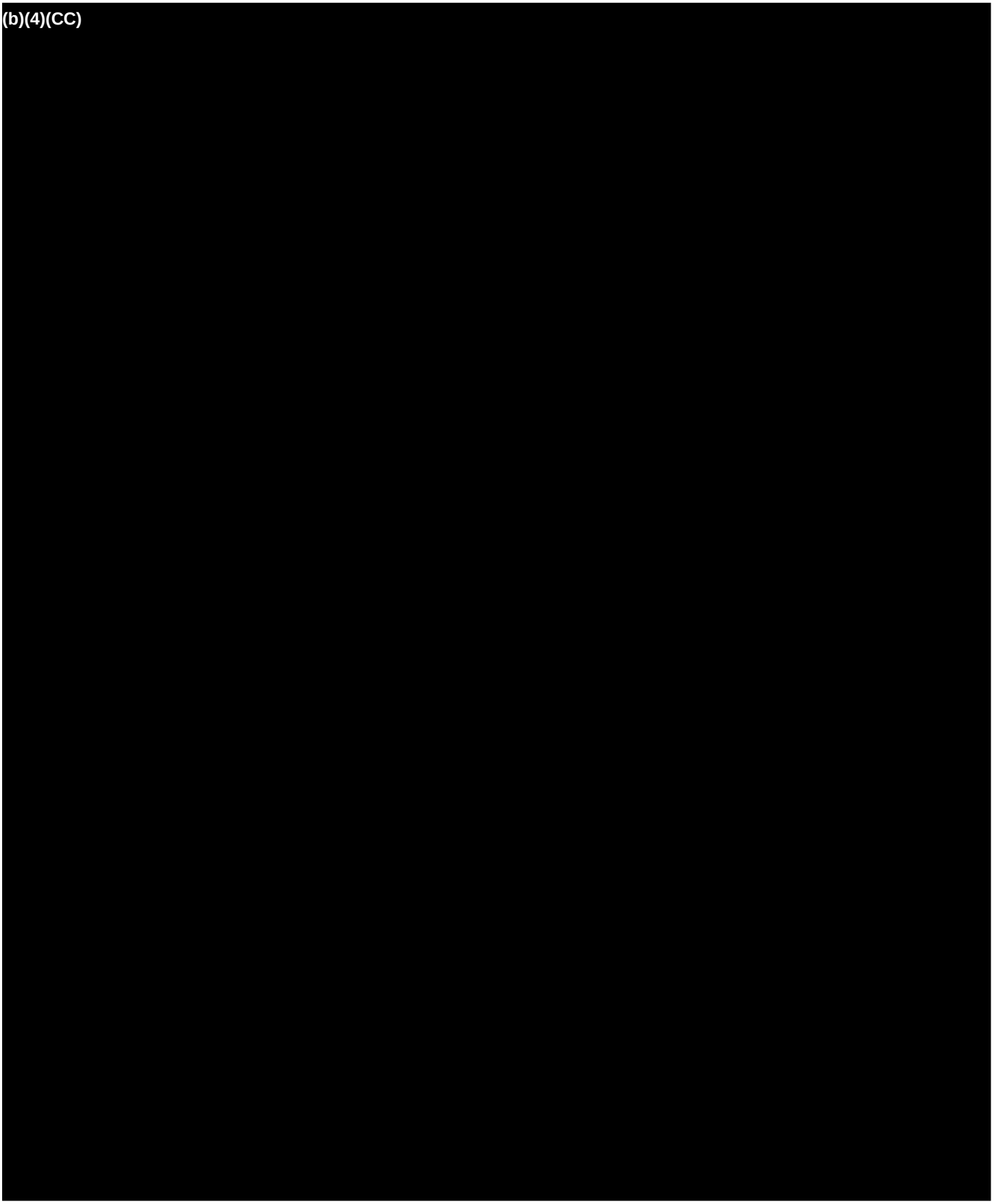
Treatments Codes:	A=MS Contin 30 mg fasting B=MS (Generics) 30 mg Fasting
Blood sample times:	Pre-dose (0 hr) and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 18, 24, 30 and 36 hours after dosing.
Subject welfare:	Vital signs (blood pressure and pulse rate) were measured just prior to each dose (within 30 minutes) and at 12, 24 and 36 hours post-dose.

Assay Methodology

Morphine

(b)(4)(CC)

(b)(4)(CC)



(b)(4)(CC)

[redacted]

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-five (25) normal, healthy male and female subjects were enrolled and twenty-four (24) completed the study. Subject #4 was discontinued 6 days after receiving 30 mg MS Contin® due to intercurrent illness (viral symptoms) of headache, fever, vomiting, body aches and diarrhea. The adverse events were not related to use of study medication.

Eighty-two (82) adverse experiences were reported during the study. Eleven were considered to be of moderate severity, 70 were considered mild, and 1 rated as severe. None was considered to be serious. Overall, 9 adverse experiences were considered unrelated to study drug, 38 were considered probably related and 16 were considered possibly related. Nineteen events were considered to be definitely related to the study drug. The adverse experiences were those standardly reported with the use of morphine or other opioid analgesics. These included nausea, headache, dizziness, asthenia, somnolence and vomiting.
The results indicate that the nature of adverse experiences were similar between the test and reference drugs under fasting conditions for both male and female subjects. The male subjects reported a smaller number of adverse experiences with the test product due to the absence of any reports during Phase II.

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 30 mg Morphine Sulfate Controlled Release Tablet under Fasting Conditions
(N=24)

Time hr	A Fasting Reference Lot #5FV ng/mL(CV)	B Fasting Generics-Test Lot #4WE ng/mL(CV)
0	0	0
0.5	6.5 (60.4)	6.3 (51.6)
1	10.4 (51.4)	11.9 (48.8)
1.5	12.4 (43.8)	12.7 (62.7)
2	13.2 (47.0)	10.9 (45.4)
2.5	11.3 (68.1)	10.8 (65.2)
3	9.4 (47.2)	10.3 (51.9)
3.5	8.7 (98.7)	8.7 (50.8)
4	8.6 (84.1)	8.5 (63.8)
5	8.9 (111.6)	8.1 (64.5)
6	5.8 (69.9)	6.3 (70.6)
8	4.0 (79.8)	4.6 (98.4)
10	2.4 (61.8)	3.3 (109.8)
12	1.5 (54.3)	2.2 (102.5)
18	1.4 (66.2)	1.8 (57.4)
24	1.7 (50.1)	2.0 (55.2)
30	1.4 (59.5)	1.3 (73.3)
36	0.9 (65.4)	0.9 (68.4)

			90% CI
AUC(0-36) (ng.hr/mL)	108.5(46)	117.1(50)	
AUCinf (ng.hr/mL)	112.6(45)	121.5(49)	
Cmax(ng/mL)	16.6(57)	16.6(51)	
Tmax (hr)	2.2	1.8	
LnAUC(0-36)			95.5-123.4
LnAUCinf			95.3-123.2
LnCmax			87.9-113.3

Morphine

1. For morphine, the least squares means for AUC(0-36) and AUCinf values were 7.9% higher for the test product than for the reference product under fasting conditions. The Cmax value for

the test product was the same as the Cmax value for the reference product. 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 1.5 and 2 hours for the test and reference products, respectively, following their administration under fasting conditions.

3. There were no statistically significant effects for AUC(0-36), AUCinf and Cmax between the two treatments.

Table II

Mean Plasma M-6-G Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 30 mg Morphine Sulfate Controlled Release Tablet under Fasting Conditions
(N=24)

Time hr	A Fasting Reference Lot #5FV ng/mL(CV)	B Fasting Generics-Test Lot #4WE ng/mL(CV)
0	0	0
0.5	13.2 (97.3)	11.2 (102.6)
1	39.7 (49.8)	40.1 (37.1)
1.5	61.4 (34.5)	65.5 (27.4)
2	70.0 (34.9)	72.8 (27.1)
2.5	73.2 (29.5)	71.9 (32.1)
3	63.6 (38.6)	73.4 (26.4)
3.5	62.0 (30.5)	65.1 (27.7)
4	56.4 (36.3)	65.9 (27.6)
5	60.0 (30.5)	58.8 (43.1)
6	50.4 (39.9)	49.7 (45.3)
8	35.9 (47.9)	31.9 (37.0)
10	18.8 (61.1)	20.8 (67.3)
12	10.4 (87.0)	14.7 (88.4)
18	8.2 (105.4)	10.1 (88.3)
24	9.0 (72.3)	9.8 (107.5)
30	5.3 (95.2)	4.3 (137.6)
36	2.0 (151.6)	2.1 (210.2)

		90% CI
AUC(0-36) (ng.hr/mL)	661.4(46)	698.1(39)
AUCinf (ng.hr/mL)	672.1(34)	720.8(46)
Cmax(ng/mL)	87.4(22)	88.9(21)

Tmax (hr)	2.6	2.6	
LnAUC(0-36)			90.9-121.6
LnAUCinf			90.9-122.5
LnCmax			93.8-111.8

Morphine-6-Glucuronide

1. For M-6-G, the least squares means for AUC(0-36), AUCinf and Cmax values were 5.5%, 7.2% and 1.8% 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-6-glucuronide plasma levels peaked at 3 and 2.5 hours for the test and reference products, respectively, following their administration under fasting conditions.

3. There were no statistically significant effects for AUC(0-36), AUCinf and Cmax between the two treatments.

V. Formulations: **Not To Be Released Under FOI**

The formulations of AB Generics L.P. and Purdue Frederick for Morphine Sulfate Controlled-Release Tables, 30 mg are shown below:

	AB Generics L.P. Morphine Sulfate Controlled-Release Tablets 30 mg	Purdue Frederick MS Contin® Morphine Sulfate Controlled-Release Tablets 30 mg
Component		
Morphine Sulfate (Pentahydrate), USP	30.0 mg	30.0 mg
(b)(4)(TS) Lactose, NF Hydroxyethyl Cellulose, NF Cetostearyl Alcohol, NF Talc, USP Magnesium Stearate, NF Purified Water, USP		(b)(4)(TS)
Colorant		
Purified Water, USP (b)(4)(TS) Lavender**	Lavender**	(b)(4)(TS)

* 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 water for 1, 2, 4, 6, 8 and 12 hours.
Number of Tablets:	12
Test Product:	AB Generics' Morphine Sulfate Controlled-Release tablets, 30 mg, Lot #4WE.
Reference Product:	Purdue's MS Contin® Morphine Sulfate Controlled-Release tablets, 30 mg, Lot #5FV

The dissolution testing results are presented in Table III.

VII. Study #MO94-1003 For Single-Dose, Two-Way Crossover Of Morphine Sulfate Controlled Release Tablets, 60 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 60 mg dose (1x60 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:	April 24, 1995 - May 14, 1995
Dosing dates:	April 29 and May 6, 1995 (subjects #1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24) May 6 and May 13, 1995 (subjects #2, 25 and 26).
Analysis dates:	June 5-July 5, 1995 and September 22-25, 1995.
Subjects:	Twenty-six (26) normal, adult healthy male and female subjects (14 male and 12 female, four subjects were Black and 22 were Caucasian) were accepted for entry into the clinical portion of the study. Two subjects did not report to the facility the evening prior to dosing and one subject withdrew consent to study participation. Three additional subjects were screened, enrolled as replacements, and completed the study. A total of twenty-six (26) subjects successfully completed the study (14 males and 12 females).
Inclusion and Exclusion criteria:	Same as Study #MO94-1103 above.
Dosing regimens:	A. Reference product: MS Contin® 1x60 mg tablet (Purdue Frederick Company), lot #7AY, Exp. 9/99, potency (not reported), content uniformity (not reported), administered following a 10 hours overnight fast. B. Test product: Morphine Sulfate Controlled-Release 1x60 mg tablet (Purdue Frederick Company), lot #4WF, batch size (b)(4)(CC) Tablets, Exp. 9/95, potency (not reported), content uniformity (not reported), administered following a 10 hours overnight fast.
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, 6, 8, 9, 12, 15, 16, 21, 22, 25
B->A	1, 3, 5, 7, 10, 11, 13, 14, 17, 20, 23, 24, 26

Treatments Codes: A=MS Contin 60 mg fasting
B=MS (Generics) 60 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 and 36 hours after dosing.

Subject welfare: Vital signs (blood pressure and pulse rate) were measured just prior to each dose (within 30 minutes) and at 12, 24 and 36 hours post-dose.

Assay Methodology

Determination of Morphine and Morphine-6-Glucuronide (M-6-G) plasma samples were performed by (b)(4)(CC) [redacted] #93-0909 as study #MO94-1103 above.

The firm has indicated that due to an aliquoting error in subject #1, phase I, 1-8 hour samples were reassayed during the period of September 22-25.

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.

VIII. In Vivo Results:

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

Two subjects deviated from the protocol. Subject #24, had taken OTC medication consisting of 500 mg X 1 of Tylenol and 500 mg X 1 Excedrin PM one day before study start. Subject #2, took a prescription medication of erythromycin 2-3 days before the study

start. The two subjects were allowed to continue and completed the study.

Two subjects had significant clinical laboratory values. Subject #3 had elevated triglycerides and cholesterol. The triglycerides were 362 mg/dL at screening (normal range is 40 to 160 mg/dL) that increased to 661 mg/dL at visit 2. The cholesterol was normal at screening, 228 mg/dL (normal range 0 to 240 mg/dL), but increased to 349 mg/dL at visit 2. Subject #21 had normal hematology at screening but low values for RBC and hemoglobin at visit 2, and low hematocrit at screening and at visit 2.

One hundred eighty-six (186) adverse experiences were reported during the study. Twenty-four (24) were considered to be of moderate severity and 162 were considered mild. None was considered to be serious. Overall, 8 adverse experiences were considered unrelated to study drug, 109 were considered probably related and 24 were considered possibly related. Forty-five (45) events were considered to be definitely related to the study drug. The adverse experiences were those standardly reported with the use of morphine or other opioid analgesics. These included nausea, headache, dizziness, pruritus, somnolence and vomiting. The results indicate that the nature of adverse experiences were similar between the test and reference drugs under fasting conditions for both male and female subjects. The results indicate that, overall, female subjects reported more adverse experience than male subjects.

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

Table IV

Mean Plasma Morphine Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 60 mg Morphine Sulfate Controlled Release Tablet under Fasting Conditions
(N=26)

Time hr	A Fasting Reference Lot #7AY ng/mL(CV)	B Fasting Generics-Test Lot #4WF ng/mL(CV)
0	0	0
0.5	4.8 (72.4)	5.6 (76.2)
1	14.2 (40.6)	13.6 (53.2)

1.5	16.8 (40.6)	18.2 (62.2)
2	13.8 (36.8)	16.4 (45.2)
2.5	14.1 (40.6)	16.7 (47.4)
3	14.3 (44.4)	15.2 (38.3)
3.5	12.2 (47.6)	13.1 (40.8)
4	10.8 (43.0)	12.4 (48.7)
6	9.7 (47.1)	10.3 (45.2)
8	6.1 (53.1)	6.1 (43.4)
10	3.6 (58.7)	3.7 (56.6)
12	2.0 (76.7)	2.4 (73.7)
18	1.5 (121.5)	1.5 (90.3)
24	2.2 (83.2)	1.8 (75.0)
30	1.7 (70.3)	2.0 (80.4)
36	1.5 (73.5)	1.6 (67.1)

			90% CI
AUC(0-36) (ng.hr/mL)	142.5(34)	151.1(34)	
AUCinf (ng.hr/mL)	152.8(38)	157.3(34)	
Cmax(ng/mL)	20.7(30)	23.0(44)	
Tmax (hr)	1.9	2.1	
LnAUC(0-36)			91.8-121.3
LnAUCinf			89.3-119.4
LnCmax			91.7-125.4

Morphine

1. For morphine, the least squares means for AUC(0-36), AUCinf and Cmax values were 6.0%, 2.9% and 11.3% 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. It should be noted that the subjects were dosed on three dates: April 29, May 6 and May 13. Therefore, the following model

Y = Seq Subj(Seq) Per Trt; (whereas period = 3)

was employed in the statistical analysis of the study, resulted in the following 90% confidence intervals:

LnAUC(0-36)	91.4-121.9%
LnCmax	90.5-124.0%

The 90% confidence intervals for the above pharmacokinetic parameters calculated using the above model are within the acceptable range of 80-125%.

3. It should be pointed out that the triglycerides value for

subject #3 was noted to be above the upper limit of normal range at baseline and the subject should not have been included in the study. After excluding subject #3 from the statistical analysis of the study, the 90% confidence intervals for AUC(0-36), AUCinf and Cmax are within the acceptable range of 80-125%.

4. The morphine plasma levels peaked at 1.5 for both the test and reference products following their administration under fasting conditions.

5. There were no statistically significant effects for AUC(0-36), AUCinf and Cmax between the two treatments.

Table V

Mean Plasma M-6-G Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 60 mg Morphine Sulfate Controlled Release Tablet under Fasting Conditions
(N=26)

Time hr	A Fasting Reference Lot #7AY ng/mL(CV)	B Fasting Generics-Test Lot #4WF ng/mL(CV)
0	0	0
0.5	8.7 (117.6)	10.0 (90.5)
1	57.9 (69.6)	40.7 (57.5)
1.5	99.1 (37.6)	90.9 (39.5)
2	112.2 (28.3)	115.7 (31.3)
2.5	117.1 (26.2)	123.3 (27.2)
3	120.4 (32.1)	123.6 (29.4)
3.5	107.8 (31.7)	120.0 (29.1)
4	100.5 (36.3)	104.3 (29.5)
6	87.7 (40.4)	89.3 (42.3)
8	49.5 (33.8)	50.5 (47.8)
10	30.6 (42.0)	27.6 (50.5)
12	18.5 (56.2)	16.8 (64.6)
18	10.5 (90.4)	10.6 (73.1)
24	12.2 (60.5)	11.4 (64.7)
30	9.4 (57.5)	10.1 (68.3)
36	6.9 (69.7)	6.5 (79.0)

			90% CI
AUC(0-36) (ng.hr/mL)	1060.3(23)	1055.1(28)	
AUCinf			

(ng.hr/mL)	1087.9(23)	1082.0(29)
Cmax(ng/mL)	144.9(22)	147.6(22)
Tmax (hr)	3.0	2.9

LnAUC(0-36)	88.3-110.4
LnAUCinf	88.0-110.0
LnCmax	90.8-114.1

Morphine-6-Glucuronide

1. For M-6-G, the least squares means for AUC(0-36) and AUCinf values were 0.5% lower for the test product than for the reference product under fasting conditions. The Cmax value was 2% higher for the test product than for the reference product. 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 for both the test and reference products following their administration under fasting conditions.

3. There were no statistically significant effects for AUC(0-36), AUCinf and Cmax between the two treatments.

IX. Formulations: **Not To Be Released Under FOI**

The formulations of AB Generics L.P. and Purdue Frederick for Morphine Sulfate Controlled-Release Tables, 60 mg are shown below:

	AB Generics L.P. Morphine Sulfate Controlled-Release Tablets 60 mg	Purdue Frederick MS Contin® Morphine Sulfate Controlled-Release Tablets 60 mg
Component		
Morphine Sulfate (Pentahydrate), USP	60.0 mg	60.0 mg
(b)(4)(TS) Lactose, NF Hydroxyethyl Cellulose, NF Cetostearyl Alcohol, NF Talc, USP Magnesium Stearate, NF Purified Water, USP	(b)(4)(TS)	
Colorant		
Purified Water, USP (b)(4)(TS) Orange** Lt Orange**	(b)(4)(TS)	

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

(b)(4)(TS)

X. In vitro Dissolution Testing:

Method:	USP 23 apparatus I (basket) at 50 rpm
Medium:	900 mL of water for 1, 2, 4, 6, 8 and 12 hours.
Number of Tablets:	12
Test Product:	AB Generics' Morphine Sulfate Controlled-Release tablets, 60 mg, Lot #4WF.
Reference Product:	Purdue's MS Contin® Morphine Sulfate Controlled-Release tablets, 60 mg, Lot #7AY

The dissolution testing results are presented in Table III.

XI. Comments:

1. In the single-dose bioequivalence studies #MO94-1103 and #MO94-1003, the firm calculated AUC_{0-36} and not AUC_{0-t} by the trapezoidal rule. The AUC(0-inf) was estimated as follows:

a. If C(36) = 0, the AUC(0-36) was taken as AUC(0-inf).
B. If C(36)> 0, then the quantity C(36)/kel was added to AUC(0-36) to estimate AUC(0-inf), where Kel is the terminal first order apparent elimination rate constant.

By using the above calculation method the values of AUC_{0-36} are the same as AUC(0-inf) values for some subjects.

2. The firm conducted the in vitro dissolution testing on its Morphine Sulfate Controlled-Release 30 mg and 60 mg tablets in water. In the previous studies, the firm conducted the dissolution testing on its Morphine Sulfate Controlled-Release

200 mg and 100 mg Tablets in Simulated Gastric Fluid (SGF).

3. All vomiting events occurred at least three hours after drug administration.

4. The formulations of the Morphine Sulfate Controlled-Release 30 mg and 60 mg strengths are qualitatively different from the 200 mg and 100 mg strengths.

XII. Deficiency Comments:

The following comments apply to the biostudies #MO94-1103 (Morphine Sulfate Controlled-Release 30 mg Tablets) and #MO94-1003 (Morphine Sulfate Controlled-Release 60 mg Tablets)

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 Morphine and Morphine-6-Glucuronide data.

5. The firm is advised to submit dissolution testing data on its Morphine Sulfate Controlled-Release 30 and 60 Tablets in Simulated Gastric Fluid and on its Morphine Sulfate Controlled-Release 200 mg and 100 mg Tablets in water.

The following comments apply to the study #MO94-1103 (Morphine Sulfate Controlled-Release 30 mg Tablets)

1. The representative (b)(4)(CC) submitted by the firm for subjects (#2, #12, #18, #19 and #21) are not legible. The firm is advised to submit (b)(4)(CC) with legible labels.

2. In the study report section, the firm stated that "Drug administration occurred at 0800 hours on study Day 1 and 8 (Phase 1 and Phase 2, respectively)". Table 4A (page 92) indicated that the subjects were dosed on different days. The dosing dates are as following:

Subjects No.	Phase I	Phase II

	Date	Date
22, 23, 24, 25	12/12/94	12/19/94
2	12/12/94	12/20/94
16,17, 19, 21	12/13/94	12/19/94
1, 3, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 18, 20, 26	12/13/94	12/20/94

The firm should explain these discrepancies.

XIII. Recommendations:

1. The single-dose bioequivalence study #MO94-1103, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 30 mg tablets, lot #4WE, comparing it to MS Contin[R] Controlled-Release 30 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 single-dose bioequivalence study #MO94-1003, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 60 mg tablets, lot #4WF, comparing it to MS Contin[R] Controlled-Release 60 mg tablets manufactured by Purdue Frederick Company, has been found incomplete by the Division of Bioequivalence for the reasons given in deficiency comments.

3. The dissolution testing conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 30 mg and 60 mg Tablets lot #4WE and 4WF, respectively, has been found incomplete by the Division of Bioequivalence for the reason given in deficiency comment #5.

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

/S/ [redacted]

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

RD INITIALLED RMHATRE /S/ [redacted]
FT INITIALLED RMHATRE [redacted] Date: 7/18/96

Concur: /S/ [redacted] Date: _____

Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/7-18-96 wp 74862SD.296
cc: ANDA #74-862, 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, 30 mg
Dose Strength:30 mg Tablets
ANDA No.:74-862
Firm: A.B. Generics L.P.
Submission Date: February 23, 1996
File Name: 74862SD.296

I. Conditions for Dissolution Testing:

USP 23 Basket: X Paddle: RPM: 50
No. Units Tested: 12
Medium:900 mL water for 1, 2, 4, 6, 8 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 #4WE Strength(mg) 30			Reference Product Lot # 5FV Strength(mg) 30		
	Mean %	Range	%CV	Mean %	Range	%CV
1	32.4	(b)(4)(CC)	5.9	32.2	(b)(4)(CC)	1.6
2	49.2		4.1	49.2		1.8
4	72.3		2.1	72.0		1.9
6	85.1		3.2	84.5		1.7
8	92.5		3.5	92.0		2.1
12	96.3		3.5	95.7		2.4

II. Results of In Vitro Dissolution Testing:

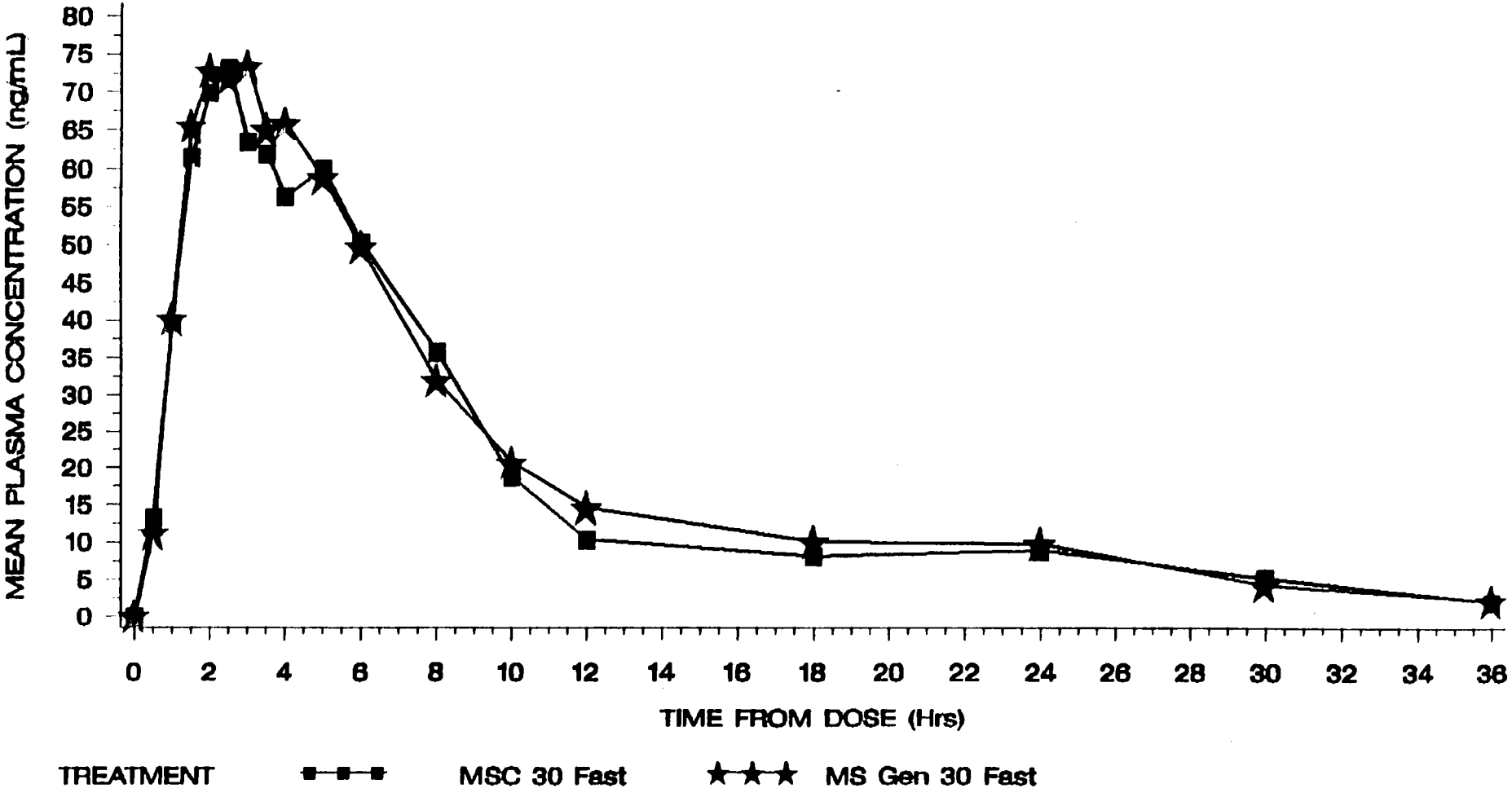
Sampling Times (hr)	Test Product Lot #4WF Strength(mg) 60			Reference Product Lot # 7AY Strength(mg) 60		
	Mean %	Range	%CV	Mean %	Range	%CV
1	29.8	(b)(4)(CC)	4.0	29.4	(b)(4)(CC)	3.0
2	46.0		2.4	45.9		2.2
4	67.3		2.1	68.9		1.7
6	82.3		1.8	84.6		1.5
8	92.6		1.6	95.2		1.6
12	98.4		1.7	103.5		2.0

PROTOCOL NO. MO94-1103

FIGURE II

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

Population: Valid for Pharmacokinetic & Safety Analysis

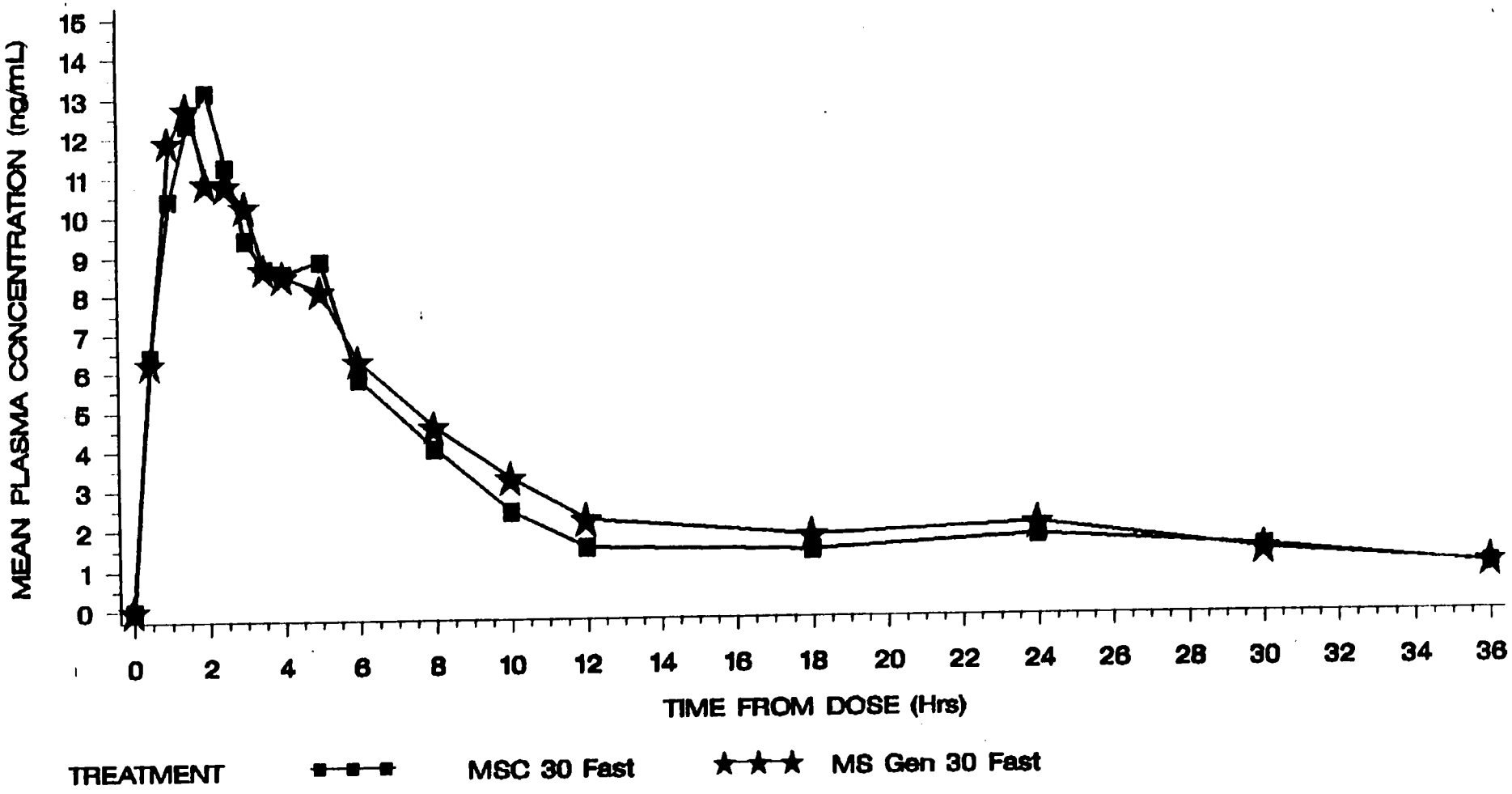


PROTOCOL NO. MO94-1103

FIGURE I

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

Population: Valid for Pharmacokinetic & Safety Analysis

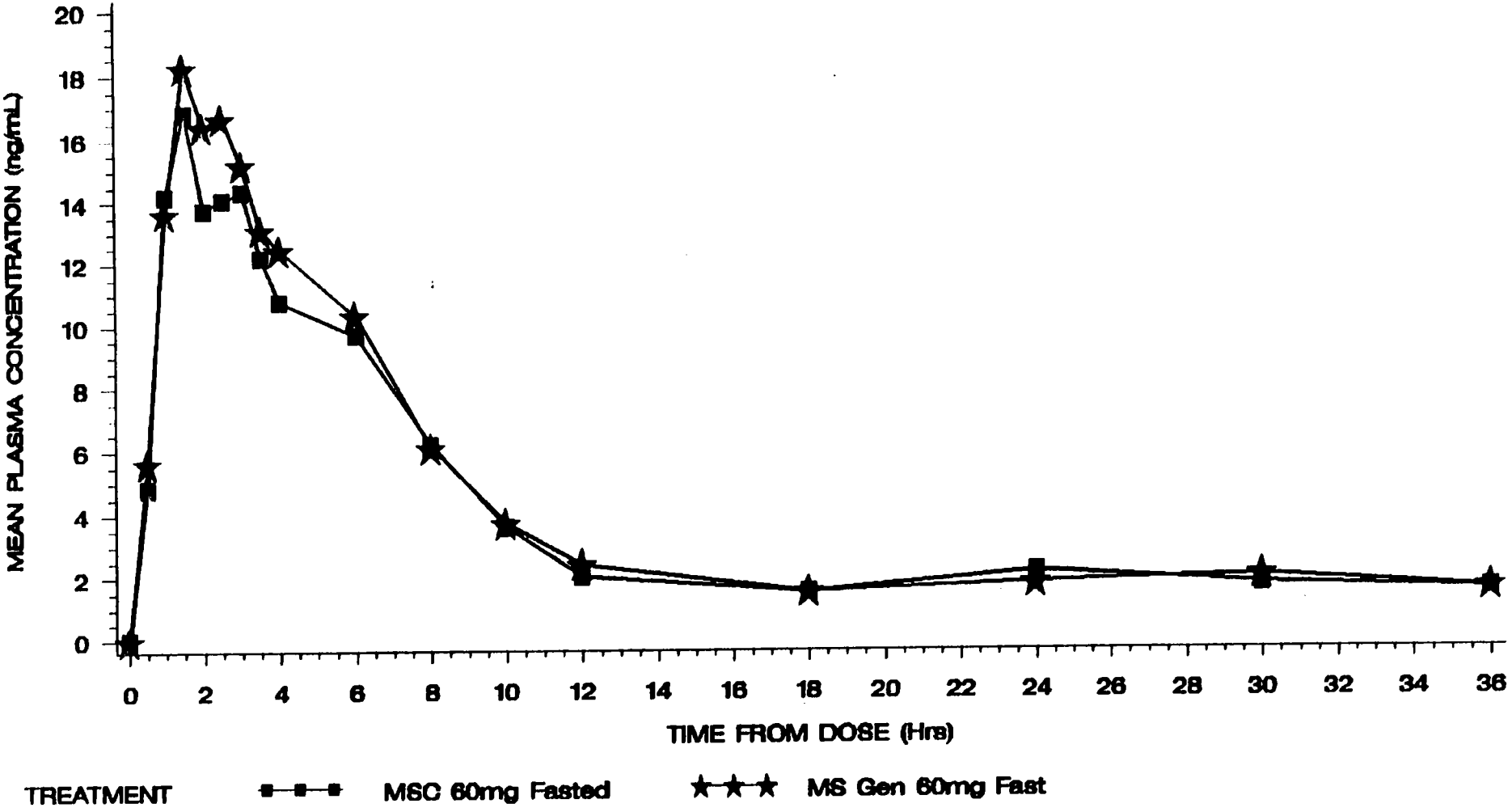


PROTOCOL NO. MO94-1003

FIGURE I

MEAN PLASMA MORPHINE CONCENTRATION (NG/ML) OVER TIME

Population: Valid for Pharmacokinetic & Safety Analysis



PROTOCOL NO. MO94-1003

FIGURE II

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

Population: Valid for Pharmacokinetic & Safety Analysis