CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74862

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS

ANDA: [redacted] and 74-769 APPLICANT: AB Generics

DRUG PRODUCT: Morphine Sulfate CR Tablets, 200 mg, 100 mg, 60 mg, 30 mg and 15 mg

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

Please acknowledge that the following dissolution testing specifications have been incorporated into your stability and quality control programs:

For Morphine Sulfate CR Tablets, 200 mg, 100 mg

The dissolution testing should be conducted in 900 mL of simulated gastric fluid, at 37 °C using USP Apparatus 1 (basket) at 50 rpm. The test product should meet the following specifications:

	100 mg Tablets	200 mg Tablets
1 hr	(b)(4)(CC)	
3 hr		
9 hr		

For Morphine Sulfate CR Tablets, 60 mg, 30 and 15 mg

The dissolution testing should be conducted in 900 mL of water, at 37 °C using USP Apparatus 1 (basket) at 50 rpm. The test product should meet the following specifications:

1 hr	(b)(4)(CC)
2 hr	
6 hr GT	

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]

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

Morphine Sulfate CR Tablets
200 , 100, 60, 30 and 15 mg
ANDA #74-769 and 74-862
Reviewer: Moheb H. Makary
WP 74862SDW.298

AB Generics L.P.
Norwalk, CT
Submission Date:
February 17,1998

Addendum to the November 28 and December 24 1997 Reviews

Dissolution testing data were reviewed and tentative specifications were recommended in the earlier reviews. This addendum describes revised dissolution specifications which the firm would like to use. The firm has indicated that these specifications are currently approved for the innovator product, MS Contin® Tablets manufactured by Purdue Frederick (AB Generics is a new generic company associated with the Purdue Frederick Company). Reviewer ascertained this information by scanning Excalibur.

The followings are the firm's proposed dissolution specifications and the FDA's tentative dissolution specifications:

ANDA #74-862 Morphine Sulfate CR Tablets, 15 mg, 30 mg and 60 mg

	AB Generics L.P.	FDA's tentative specifications
1 hr	(b)(4)(CC)	1 hr (b)(4)(CC)
2 hr		2 hr
6 hr GT		4 hr
		8 hr

ANDA #74-769 Morphine Sulfate CR Tablets, 200 mg and 100 mg

	AB Generics L.P. 100 mg 200 mg	FDA's tentative specifications 100 mg and 200 mg Tablets
1 hr	(b)(4)(CC)	1 hr (b)(4)(CC)
3 hr		2 h
9 hr		3 h
		4 h
		8 h

The firm's proposed dissolution specifications are acknowledged.

Recommendation:

The firm's proposed dissolution specifications for its Morphine Sulfate CR Tablets, 15 mg, 30 mg, 60 mg, 100 mg and 200 mg are acceptable.

8-1

NOV 28 1997

Morphine Sulfate CR Tablet
15 mg, 30 mg and 60 mg
ANDA #74-862
Reviewer: Moheb H. Makary
WP 74862SDW.797

AB Generics L.P.
Norwalk, CT
Submission Date:
July 1, 1997

Review of Studies Amendment

I. Objective:

The firm has replied to the reviewer's comments made in the review of the December 10 and 27, 1996 amendments, for Morphine Sulfate CR 15 mg, 30 mg and 60 Tablets.

II. Comment #1

1. The firm was asked to submit its criteria for acceptance of batch runs based on standard curves and quality control samples used for the study #MO93-0903 (Morphine Sulfate CR Tablets, 15 mg), the study #MO94-1103 (Morphine Sulfate CR Tablets, 30 mg) and the study #MO94-1003 (Morphine Sulfate CR Tablets, 60 mg).

The firm indicated that at the time of the above studies were conducted the acceptance or rejection of the standard curve was based on the correlation coefficient of each curve. The minimal number of points required for acceptance of a standard curve was 5 with a correlation coefficient of 0.998 or greater.

A standard curve was used at the start of each sequence and two control samples consisting of a combination of either low, medium or high samples were placed after every 10 unknowns. These controls must be within ±15% (±20% for the low quality control sample) of their nominal concentration. If both values of the controls were out of the allowable range, then 5 samples on either side of the control combination were rejected and then reassayed. When one control value of the combination was out of range, but the other was acceptable, then the unknowns associated with that combination were accepted.

Reply to Comment #1

The firm's response to the comment is acceptable.

Comment #2

The firm was asked to explain the criteria to select and reassay samples based on sample processing error, (b)(4)(CC) and pharmacokinetic outlier in the above studies.

The firm indicated that sampling processing errors include: documented samples lost due to broken tube, spillage of by analyst, or sample not processed as specified in the method. (b)(4)(CC)

pharmacokinetic outlier reassay is based on an anomalous appearing value compared to the adjacent time points without an assignable cause justifying its value.

Reply to Comment #2

The firm's response to the comment is acceptable.

Comments:

1. The single-dose bioequivalence study #MO93-0903 under fasting and nonfasting conditions, the single-dose bioequivalence study #MO94-1103 under fasting conditions and the single-dose bioequivalence study #MO94-1003 under fasting conditions conducted on Morphine Sulfate CR Tablets, 15 mg, 30 mg and 60 mg, respectively, are 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 for the above studies.

2. The in vitro dissolution testing previously submitted by the firm on its Morphine Sulfate CR Tablets, 15 mg, 30 mg and 60 mg is acceptable.

3. The approved dissolution medium for the 30 mg MS Contin^{R} Tablets (Purdue Frederick) was water. When the supplements for MS Contin^{R} 15, 60, 100 and 200 mg Tablets were filed, each one used water as the dissolution medium. The 15 and 60 mg MS Contin^{R} Tablets were approved by the Pilot Drug Division with water as dissolution medium. The 100 and 200 mg MS Contin^{R} Tablets were approved by the Division of Biopharmaceutics with simulated gastric fluid without enzymes as dissolution medium. The reviewer

in the Division of Biopharmaceutics objected to the use of water as the dissolution medium for the higher strength tablets. The AB Generics L.P., is a new generic company associated with Purdue Frederick Company. Based on the above information, the firm requested that the dissolution testing methods for its test products to be the same as the reference products, i.e., 100 and 200 mg morphine sulfate CR tablets (AB Generics) be approved with simulated gastric fluid without enzymes as dissolution medium and the 15, 30 and 60 mg strengths be approved with water as dissolution medium.

Recommendations:

1. The single-dose bioequivalence study #MO93-0903, under fasting and nonfasting conditions, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 15 mg Tablet, lot #4WM, comparing it to MS Contin^{R} Controlled-Release 15 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 15 mg Tablet is bioequivalent to the reference product MS Contin^{R} Controlled-Release, 15 mg Tablet, manufactured by Purdue Frederick Company.

2. The single-dose bioequivalence study #MO94-1103, under fasting conditions, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 30 mg Tablet, lot #4WE, comparing it to MS Contin^{R} Controlled-Release 30 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 30 mg Tablet is bioequivalent to the reference product MS Contin^{R} Controlled-Release, 30 mg Tablet, manufactured by Purdue Frederick Company.

3. The single-dose bioequivalence study #MO94-1003, under fasting conditions, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 60 mg Tablet, lot #4WF, comparing it to MS Contin^{R} Controlled-Release 60 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 60 mg Tablet is bioequivalent to the reference product MS Contin^{R} Controlled-Release, 60 mg Tablet, manufactured by Purdue Frederick Company.

4. The dissolution testing conducting by AB Generics L.p., on its

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-862 APPLICANT: AB Generics, L.P.

DRUG PRODUCT: Morphine Sulfate Extended Release Tablets, 15, 30, and 60 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 water at 37°C, using USP 23 apparatus I (basket) at 50 rpm. The test product should meet the following tentative specifications:

1 hr	(b)(4)(CC)
2 hrs	
4 hrs	
8 HRS	

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/

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

Morphine Sulfate Controlled-Release 15 mg, 30 mg and 60 mg Tablets, lots #4WM, 4WE and 4WF, respectively, is acceptable. The formulations for the 15 mg, 30 and 60 mg strengths are proportionally similar to the 200 mg strength of the test product which underwent acceptable bioequivalence testing.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus I (basket) at 50 rpm. The test product should meet the following tentative specification:

1 hr	(b)(4)(CC)
2 hrs	
4 hrs	
8 HRS	

The firm should be informed of the above recommendations.

/S/

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

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ Date: 11/28/97

/S/

Concur: Date: 11/28/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Mmakary/10-20-97, 11-26-97 wp 74862SDW.797
cc: ANDA #74-862, original, HFD-650 (Director), HFD-658 (Makary), Drug File, Division File.

APR 30 1997

Morphine Sulfate CR Tablet
15 mg
ANDA # 74-862
Reviewer: Moheb H. Makary
WP 74862SD.D96

AB Generics L.P.
Norwalk, CT
Submission Date:
December 10, 1996

Review of a Study Amendment

I. Objective:

The firm has replied to the reviewer's comments made in the review of the May 3, 1996 submissions (a bioequivalence study on Morphine Sulfate CR 15 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 Lot #4WM	Reference Product Lot #4GS
Potency	101.3%	97.5%
Content uniformity	102.3%	95.6%

Reply to Comment #1

The firm's response to the comment is acceptable.

Comment #2

The firm was asked to submit the analytical raw data for all subjects in the study and (b)(4)(CC) [redacted] with legible labels.

The firm submitted the analytical raw data for all subjects in the study and (b)(4)(CC) [redacted] with legible labels.

The firm is advised to submit its criteria for acceptance of batch runs based on standard curves and quality control samples used for the morphine (study #MO93-0309).

The firm should explain the criteria to select and reassay samples based on sample processing error, (b)(4)(CC) [redacted] and pharmacokinetic outlier.

Reply to Comment #2

The firm's response to the comment is incomplete.

Comment #3

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

The firm has indicated that the original dissolution method utilized for MS Contin® 15 mg tablets used water as the dissolution medium. The comparative dissolution data submitted with this ANDA was generated using water.

Reply to Comment #3

The firm's response to the comment is acceptable.

III. Deficiency Comments:

1. The firm should explain the criteria to select and reassay samples based on sample processing error, (b)(4)(CC) and pharmacokinetic outlier.

2. The firm is advised to submit its criteria for acceptance of batch runs based on standard curves and quality control samples used for the morphine (study #MO93-0309).

IV. Recommendation:

The single-dose bioequivalence study #MO93-0903 under fasting and nonfasting conditions, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 15 mg tablets, lot #4WM, comparing it to MS Contin® Controlled-Release 15 mg tablets manufactured by Purdue Frederick Company, has been found incomplete by the Division of Bioequivalence for the reasons given in deficiency comments.

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

/S/

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

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ Date: 4/18/97

Concur: /S/ Date: 4/20/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

MMakary/4-18-97 wp 74862SD.D96
cc: ANDA #74-862, original, Makary, HFD-658, Division File, Drug File

APR 30 1997

Morphine Sulfate CR Tablet
30 mg and 60 mg
ANDA # 74-862
Reviewer: Moheb H. Makary
WP 74862SDW.D96

AB Generics L.P.
Norwalk, CT
Submission Date:
December 27, 1996

Review of Study Amendments

I. Objective:

The firm has replied to the reviewer's comments made in the review of the March 11, 1996 submissions (bioequivalence studies on Morphine Sulfate CR 30 mg and 60 mg Tablets and dissolution data).

II. Morphine Sulfate CR Tablets 30 mg

Comment #1

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 Lot #4WE	Reference Product Lot #4FV
Potency	97.0%	97.6%
Content uniformity	98.8%	95.5%

Reply to Comment #1

The firm's response to the comment is acceptable.

Comment #2

The firm was asked to submit the analytical raw data for all subjects in the study and (b)(4)(CC) with legible labels for subjects #2, 12, 18, 19, and 21.

The firm submitted the analytical raw data for all subjects in the study and (b)(4)(CC) with legible labels.

The firm is advised to submit its criteria for acceptance of batch runs based on standard curves and quality control samples used for the morphine Sulfate CR 30 mg Tablets (study #MO94-1103).

The firm should explain the criteria to select and reassay samples based on sample processing error, (b)(4)(CC) and

pharmacokinetic outlier.

Reply to Comment #2

The firm's response to the comment is incomplete.

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 Kel 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

	Test	Reference	90% CI
AUC(0-t) (ng.hr/mL)	116.61(50)	108.2(46)	95.6-122.8
AUCinf (ng.hr/mL)	121.8(49)	112.7(45)	95.3-123.6

Morphine-6-Glucuronide

	Test	Reference	90% CI
AUC(0-t) (ng.hr/mL)	678.3(40)	642.7(35)	90.3-123.1
AUCinf (ng.hr/mL)	729.8(45)	690.9(34)	89.6-119.8

Reply to Comment #3

The firm's response to the comment is acceptable.

Comment #4

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

The firm stated the following "The original dissolution method utilized for MS Contin^R Tablets 100 mg 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. In addition, FDA provided specifications Purdue

was expected to meet. The comparative dissolution data submitted with the ANDA for Morphine Sulfate Controlled-Release Tablets 30 mg was generated utilizing simulated gastric fluid which is approved method for MS Contin® Tablets".

The firm submitted dissolution testing for the 30 mg and 60 mg strengths using water as the dissolution medium and for the 200 mg and 100 mg strengths Simulated Gastric Fluid as the dissolution medium.

Reply to Comment #4

The firm's response to the comment is acceptable for the 30 mg and 60 mg strengths.

Comment #5

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 Date	Phase II 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 was asked to explain these discrepancies.

The firm indicated that Table 4A concerns vital signs and the date used was not the dosing date but was the visit date at the top of the Case Report Form which was sometimes different from the actual dosing date. The actual dosing dates for period I (December 13, 1994) and period II (December 20, 1994), were inadvertently not listed in the Final Study Report.

Reply to Comment #5

The firm's response to the comment is acceptable.

III. Morphine Sulfate CR Tablets 60 mg

Comment #1

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

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

	Test Product Lot #4WF	Reference Product Lot #7AY
Potency	98.8%	101.2%
Content uniformity	98.0%	

Reply to Comment #1

The firm's response to the comment is acceptable.

Comment #2

The firm was asked to submit the analytical raw data for all subjects in the study and (b)(4)(CC) with legible labels.

The firm submitted the analytical raw data for all subjects in the study and (b)(4)(CC) with legible labels.

The firm is advised to submit its criteria for acceptance of batch runs based on standard curves and quality control samples used for the morphine Sulfate CR 60 mg Tablets (study #MO94-1003).

The firm should explain the criteria to select and reassay samples based on sample processing error, (b)(4)(CC) and pharmacokinetic outlier.

Reply to Comment #2

The firm's response to the comment is incomplete.

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 Kel 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

	Test	Reference	90% CI
AUC(0-t) (ng.hr/mL)	150.7(34)	142.5(34)	91.6-120.7
AUCinf			

AUCinf (ng.hr/mL)	156.9(34)	152.8(38)	89.1-118.8

1. 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-t)	91.3-121.3%
LnAUCinf	89.6-120.3
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%.

2. 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-t), AUCinf and Cmax are within the acceptable range of 80-125%.

Morphine-6-Glucuronide

	Test	Reference	90% CI
AUC(0-t) (ng.hr/mL)	1055.1(28)	1060.3(23)	88.3-110.4
AUCinf	1082.9(29)	1090.6(23)	87.8-109.9

The statistical analysis of the study after employed three period in the model, resulted in the following 90% confidence intervals:

LnAUC(0-t)	87.7-110.3%
LnAUCinf	87.3-110.0
LnCmax	89.9-112.5%

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

Furthermore, after excluding subject #3 from the statistical analysis of the study, the 90% confidence intervals for AUC(0-t), AUCinf and Cmax are within the acceptable range of 80-125%.

Reply to Comment #3

The firm's response to the comment is acceptable.

IV. Deficiency Comments:

1. The firm is advised to submit its criteria for acceptance of batch runs based on standard curves and quality control samples used for the study #MO94-1103 (Morphine Sulfate CR Tablets, 30 mg) and the study #MO94-1003 (Morphine Sulfate CR Tablets, 60 mg).

2. The firm should explain the criteria to select and reassay samples based on sample processing error, (b)(4)(CC) and pharmacokinetic outlier in the above studies.

V. 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.

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 /S/
FT INITIALLED RMHATRE Date: 4/24/97

/S/

Concur: _____ Date: 4/30/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

AUG 16 1996

Morphine Sulfate CR Tablet
15 mg
ANDA # 74-862
Reviewer: Moheb H. Makary
WP 74862SD.596

AB Generics L.P.
Norwalk, CT
Submission Date:
May 3, 1996
May 8, 1996

Review of Bioequivalence Study and Dissolution Data

I. Objective:

The firm has submitted a single dose randomized four-way crossover bioequivalence study on its Morphine Sulfate Controlled Release (CR) 15 mg tablets under fasting and nonfasting conditions and dissolution data as compared to Purdue Frederick's MS Contin^{R} Controlled Release Tablets 15 mg.

The firm had submitted following studies (ANDA #74-769, submission dated October 16, 1995, February 16, 1996 and March 11, 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.

4. Study #MO94-1003
A single dose randomized two-way crossover bioequivalence study on Morphine Sulfate Controlled Release (CR) 60 mg tablets under fasting conditions. The study was found to be incomplete by the Division of Bioequivalence.

5. Study #MO94-1103
A single dose randomized two-way crossover bioequivalence study on Morphine Sulfate Controlled Release (CR) 30 mg tablets under fasting conditions. The study was found to be incomplete by the

However, the following review of the 15 mg strength is independent of the 200 mg strength, the approval of the current study 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, 100 mg, 60 mg, 30 mg and 15 mg Tablets (MS Contin^{R}) are marketed by Purdue Frederick.

III. Study #MO93-0903 For a Single-Dose, Four-Way Crossover Of Morphine Sulfate Controlled Release Tablets, 15 mg, Under Fasting and nonfasting 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 15 mg dose (1x15 mg tablet) of each product under fasting and nonfasting conditions. Morphine concentrations only 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, four-way crossover bioequivalence study, under fasting and nonfasting conditions.
Dose dates:	November 20, 1993 and December 4, 11, 18, 1993
Analysis dates:	December 27, 1993-January 13, 1994 April 19, 1994-May 6, 1994. The initial analysis from December to January completed all Phases 1 and 2. Due to a priority study interruption, Phase 3 had only 19 of 27 subjects completed. The remainder of this Phase and Phase 4 were assayed in April.
Subjects:	Twenty-eight (28) normal, adult healthy male and female subjects (13 males and 15 females, on subject was Black and 27 were Caucasian) were accepted for entry into the clinical portion of the study. Twenty-seven (27) 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® 1x15 mg tablet (Purdue Frederick Company), lot #4GS, Exp. 5/95, administered within five minutes after completion of a high fat breakfast.
B. Reference product: MS Contin® 1x15 mg tablet (Purdue Frederick Company), lot #4GS, Exp. 5/95, potency (not reported), content uniformity (not reported), administered following a 10 hours overnight fast.
C. Test product: Morphine Sulfate Controlled-Release 1x15 mg tablet (Purdue Frederick Company), lot #4WM, administered within five minutes after completion of a high fat breakfast.
D. Test product: Morphine Sulfate Controlled-Release 1x15 mg tablet (Purdue Frederick Company), lot #4WM, batch size (b)(4)(CC) Tablets, Exp. 10/95, potency (not reported), content uniformity (not reported), administered following a 10 hours overnight fast.

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). Subjects on regimen A and C ingested the tablet with 240 mL of water within 5 minutes after a standardized high-fat breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice).

Treatment Group	Subject Number
A->D->B->C	4, 6, 12, 14, 20, 24, 27
B->A->C->D	2, 8, 11, 13, 18, 22, 28
C->B->D->A	3, 5, 10, 15, 19, 23, 26
D->C->A->B	1, 7, 9, 16, 17, 21, 25

Treatments Codes: A=MS Contin 15 mg nonfasting
B=MS Contin 15 mg fasting
C=MS (Generics) 15 mg nonfasting
D=MS (Generics) 15 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

(b)(4)(CC)

[redacted]

Analytical Report: The firm stated that the initial analysis for morphine concentration yielded a large percentage of samples with plasma

concentrations below the limit of quantation (b)(4)(CC) with dosage of 15 mg morphine. As a result the firm modified the assay to provide for a limit of morphine quantation of (b)(4)(CC) (b)(4)(CC) and fully reanalyzed all samples with values (b)(4)(CC) This did not leave sufficient plasma for subsequent analyses for the metabolite, morphine-6-glucuronide.

IV. In Vivo Results:

Twenty-eight (28) normal, healthy male and female subjects were enrolled and 27 subjects completed all four periods of dosing. Thirteen (13) males and 15 females were selected. One subject #28 failed to return to the study site for first dosing and did not complete the study.

Sixty-seven (67) adverse experiences were reported during the study. Ten of the reports were considered to be of moderate severity and the remainder were considered mild. None was considered to be serious. Overall, twenty-one adverse experiences were considered unrelated to study drug, while the rest were possibly, probably or definitely related. The adverse experiences were those standardly reported with the use of morphine or other opioid analgesics. These included nausea, headache, dizziness, abdominal pain and vasodilation.
The results indicate that the incidence of adverse experiences were similar between the test and reference drugs under fasting and nonfasting conditions for both male and female subjects. Except for an increased incidence of headaches and nausea in the females, there were no striking differences between the gender groups in the incidence and nature of the reports.

Protocol deviations among the subjects who completed the study were due to the ingestion of concomitant medications. Subjects 2, 4, 5, 10, 15, 16, 20, 23, 24 and 26 took ibuprofen. In no instance were the concomitant medications taken the day of study drug dosing.

The plasma concentrations and pharmacokinetic parameters for Morphine are summarized in Tables I.

Table I

Mean Plasma Morphine Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 15 mg Morphine Sulfate Controlled Release Tablet under Fasting and nonfasting Conditions
(N=27)

Time hr	B Fasting Reference Lot #4GS ng/mL(CV)	D Fasting Generics-Test Lot #4WM ng/mL(CV)	A Nonfasting Reference Lot #4GS ng/mL(CV)	C Nonfasting Generics-Test Lot #4WM ng/mL(CV)
0	0	0	0	0
0.5	1.89 (48.1)	2.20 (48.2)	1.61 (83.5)	1.60 (88.5)
1	3.10 (36.5)	3.52 (45.6)	3.00 (64.4)	3.15 (69.2)
1.5	4.01 (37.5)	3.99 (41.6)	3.87 (54.3)	3.72 (51.0)
2	3.79 (42.2)	3.88 (39.5)	3.99 (45.6)	4.17 (49.1)
2.5	3.88 (35.8)	3.79 (36.0)	4.60 (38.8)	4.91 (47.1)
3	3.36 (37.4)	3.45 (36.2)	4.05 (40.8)	4.06 (35.9)
3.5	3.17 (36.6)	3.09 (36.1)	3.99 (31.4)	3.90 (42.4)
4	3.10 (43.2)	3.12 (45.2)	3.38 (28.8)	3.50 (34.0)
5	2.95 (32.2)	3.47 (35.7)	3.66 (34.4)	3.97 (42.0)
6	2.36 (37.5)	2.53 (35.8)	2.91 (33.4)	3.23 (31.6)
8	1.50 (32.1)	1.67 (34.4)	1.89 (45.8)	2.32 (48.0)
10	0.98 (55.6)	1.21 (54.5)	1.30 (72.7)	1.40 (54.2)
12	0.79 (75.4)	0.79 (45.7)	0.75 (76.3)	0.98 (67.9)
18	0.58 (53.5)	0.68 (47.4)	0.61 (46.2)	0.64 (84.7)
24	0.69 (49.3)	0.74 (41.2)	0.66 (54.3)	0.78 (88.3)
30	0.55 (62.0)	0.60 (47.1)	0.46 (66.1)	0.56 (54.4)
36	0.38 (62.7)	0.44 (62.2)	0.38 (92.5)	0.40 (97.1)

				90% CI
AUC(0-36) (ng.hr/mL)	40.57(29)	43.89(30)	43.96(31)	48.65(38)
AUCinf (ng.hr/mL)	42.80(30)	47.16(30)	47.10(41)	51.75(44)
Cmax(ng/mL)	4.73(33)	4.77(33)	5.63(32)	5.62(41)
Tmax (hr)	2.37	2.30	2.61	3.65

LnAUC (Fasting)	97.8-117.1
LnAUCinf (Fasting)	98.1-121.5
LnCmax (Fasting)	90.6-110.2
LnAUC (Nonfasting)	100.3-120.1
LnAUCinf (Nonfasting)	98.5-122.1
LnCmax (Nonfasting)	89.0-108.3

1. For morphine, the least squares means for AUC(0-36), AUCinf and Cmax values were 7.6%, 9.5% and 0.25% 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 1.5 hours for both the test and reference products following their administration under fasting conditions.

3. For AB Generics' test product, the least squares means for AUC(0-36), AUCinf and Cmax values were 11.1%, 10.3% and 0.3% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-36), AUCinf and Cmax. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data.

4. The morphine plasma levels peaked at 2.5 hours for both the test and the reference products, respectively, under nonfasting conditions.

5. For the test and reference products, the mean Cmax values after dosing with food were about 117.8% and 118.0%, respectively, of the values reported in the fasting state.

6. There were no statistically significant carry-over effects for AUC(0-36), AUCinf and Cmax between the four 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, 15 mg are shown below:

Component	AB Generics L.P. Morphine Sulfate Controlled-Release Tablets 15 mg	Purdue Frederick MS Contin® Morphine Sulfate Controlled-Release Tablets 15 mg
Morphine Sulfate (Pentahydrate), USP	15.0 mg	15.0 mg
(b)(4)(CC) 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)(CC) -A Blue** (b)(4)(TS)
Blue **

* 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, 15 mg, Lot #4WM.
Reference Product:	Purdue's MS Contin® Morphine Sulfate Controlled-Release tablets, 15 mg, Lot #4GS

The dissolution testing results are presented in Table II.

VII. Comments:

1. The firm modified the assay to provide for a limit of morphine quantitation of (b)(4)(CC) and fully reanalyze all of the samples with plasma concentrations below the limit of quantitation (b)(4)(CC) which represented a large percentage of samples. As a result, sufficient plasma for subsequent analyses for the metabolite, morphine-6-glucuronide was not available. The firm did not analyze the active metabolite, morphine-6-glucuronide in the above study.

2. It should be noted that the firm conducted the single-dose bioequivalence study on its Morphine Sulfate CR 15 mg Tablets under fasting and nonfasting conditions (four-way crossover) which is more than the OGD requires.

3. In the previous studies, the firm conducted bioequivalence studies on its Morphine Sulfate CR 200 mg, 100 mg, 60 mg and 30

mg Tablets. In each study the 90% confidence intervals for LnAUC, LnAUCi and LnCmax were within the acceptable range of 80-125% for morphine and morphine-6-glucuronide. In addition, the formulation of Morphine Sulfate CR 15 mg Tablets is proportionally similar to the 30 mg and 60 mg strengths.

4. However, the firm did not provide pharmacokinetics data for morphine-6-glucuronide which is required by the Division of Bioequivalence. The 90% confidence intervals for LnAUC, LnAUCinf and LnCmax were within the acceptable range of 80-125% for morphine under fasting and nonfasting conditions. The morphine data in the above study demonstrates that the test product is bioequivalent to the reference product . Therefore, evaluation of the study on Morphine Sulfate CR 15 mg Tablets is based only on the morphine pharmacokinetic parameters.

5. The firm conducted the in vitro dissolution testing on its Morphine Sulfate Controlled-Release 15 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) and on the 30 mg and 60 mg tablets in water.

VIII. Deficiency Comments:

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 representative (b)(4)(CC) submitted by the firm are not legible. The firm is advised to submit (b)(4)(CC) with legible labels.

4. The firm is advised to submit dissolution testing data on its Morphine Sulfate Controlled-Release 15 Tablets in Simulated Gastric Fluid. The dissolution method in which the firm plans to use along with proposed dissolution specifications (NLT and NMT at each time point) should be submitted.

IX. Recommendations:

1. The single-dose bioequivalence study #MO93-0903 under fasting and nonfasting conditions, conducted by AB Generics L.p., on its Morphine Sulfate Controlled-Release 15 mg tablets, lot #4WM, comparing it to MS Contin® Controlled-Release 15 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 15 mg Tablets lot #4WM, has been found incomplete by the Division of Bioequivalence for the

reason given in deficiency comment #4.

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] Date: 8/12/96
FT INITIALLED RMHATRE

/S/ [redacted]

Concur: _____ Date: 8/16/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/8-12-96 wp 74862SD.596
cc: ANDA #74-862, original, Makary, HFD-658, Division File, Drug File.

Table II In Vitro Dissolution Testing

Drug (Generic Name): Morphine sulfate Controlled-Release Tablets, 30 mg
Dose Strength: 15 mg Tablets
ANDA No.:74-862
Firm: A.B. Generics L.P.
Submission Date: May 3, 1996
File Name: 74862SD.596

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:

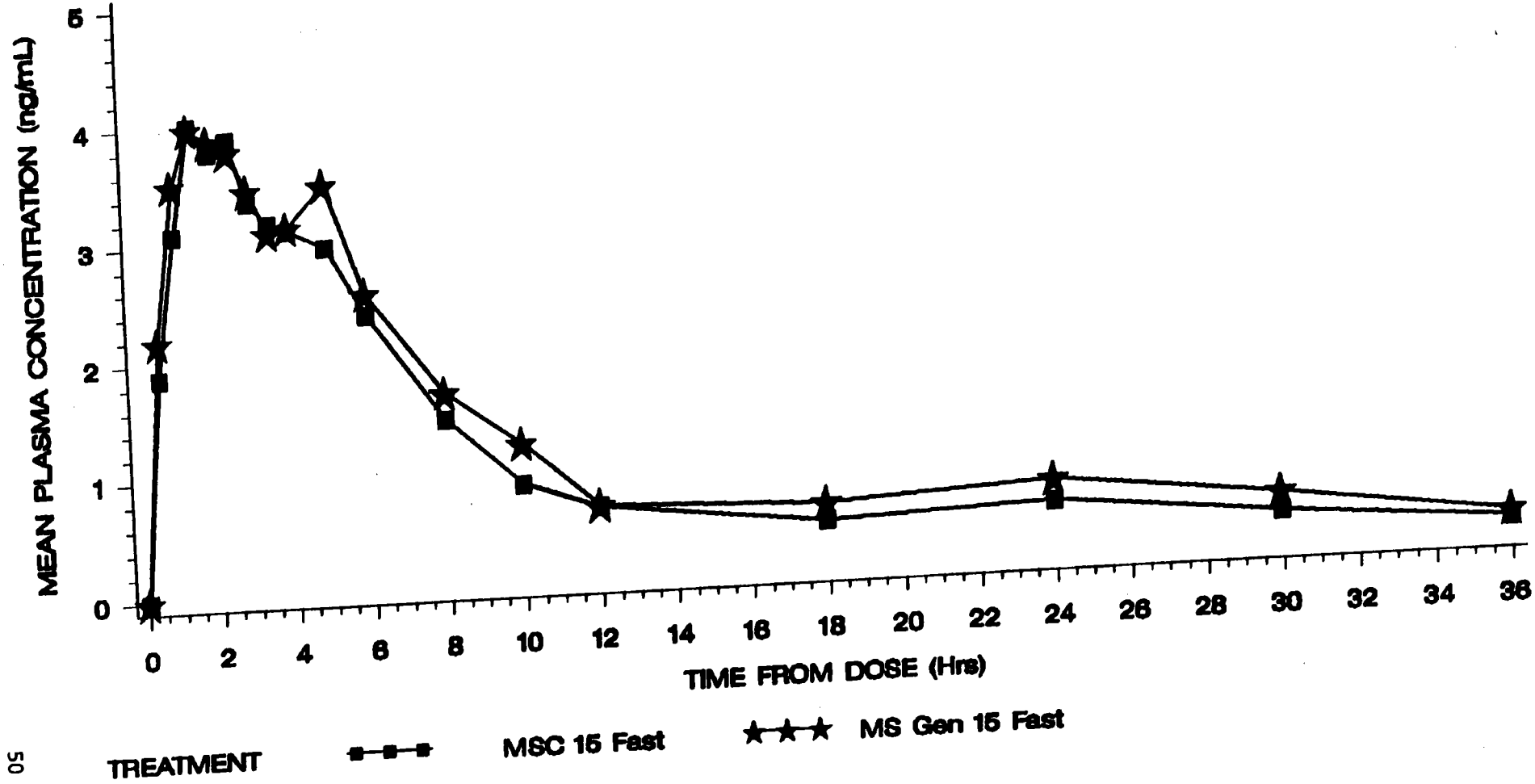
Sampling Times (hr)	Test Product Lot #4WM Strength(mg) 15			Reference Product Lot # 4GS Strength(mg) 15		
	Mean %	Range	%CV	Mean %	Range	%CV
1	38.2	(b)(4)(CC)	1.3	37.2	(b)(4)(CC)	1.4
2	55.6		1.9	54.5		1.9
4	77.3		1.7	75.5		2.5
6	91.0		1.6	88.0		3.2
8	99.9		1.7	94.3		2.9
12	106.2		1.6	98.7		2.8

PROTOCOL NO. MO93-0903

FIGURE I

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

Population: Valid for Pharmacokinetic & Safety Analysis

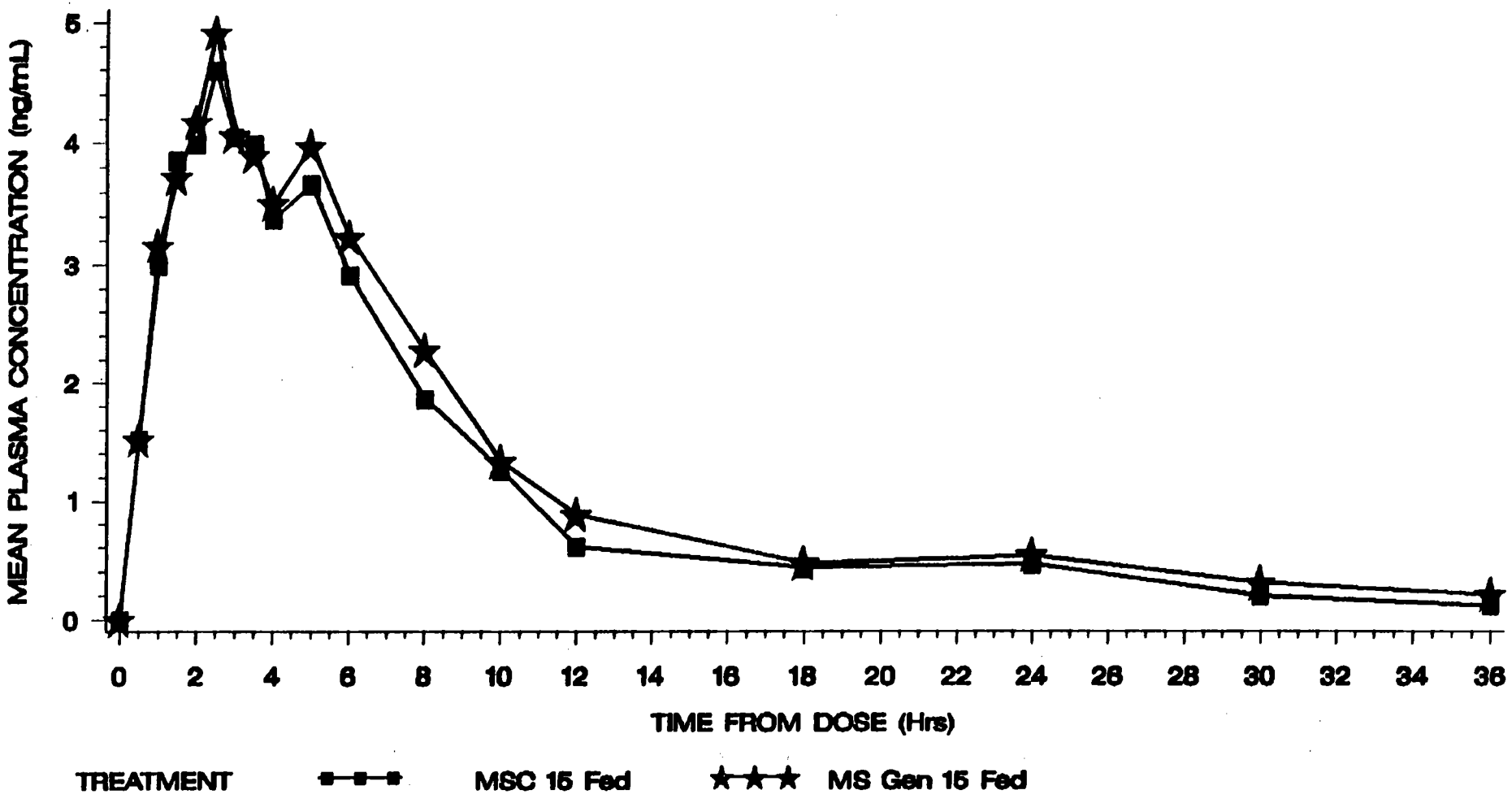


PROTOCOL NO. MO93-0903

FIGURE II

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

Population: Valid for Pharmacokinetic & Safety Analysis

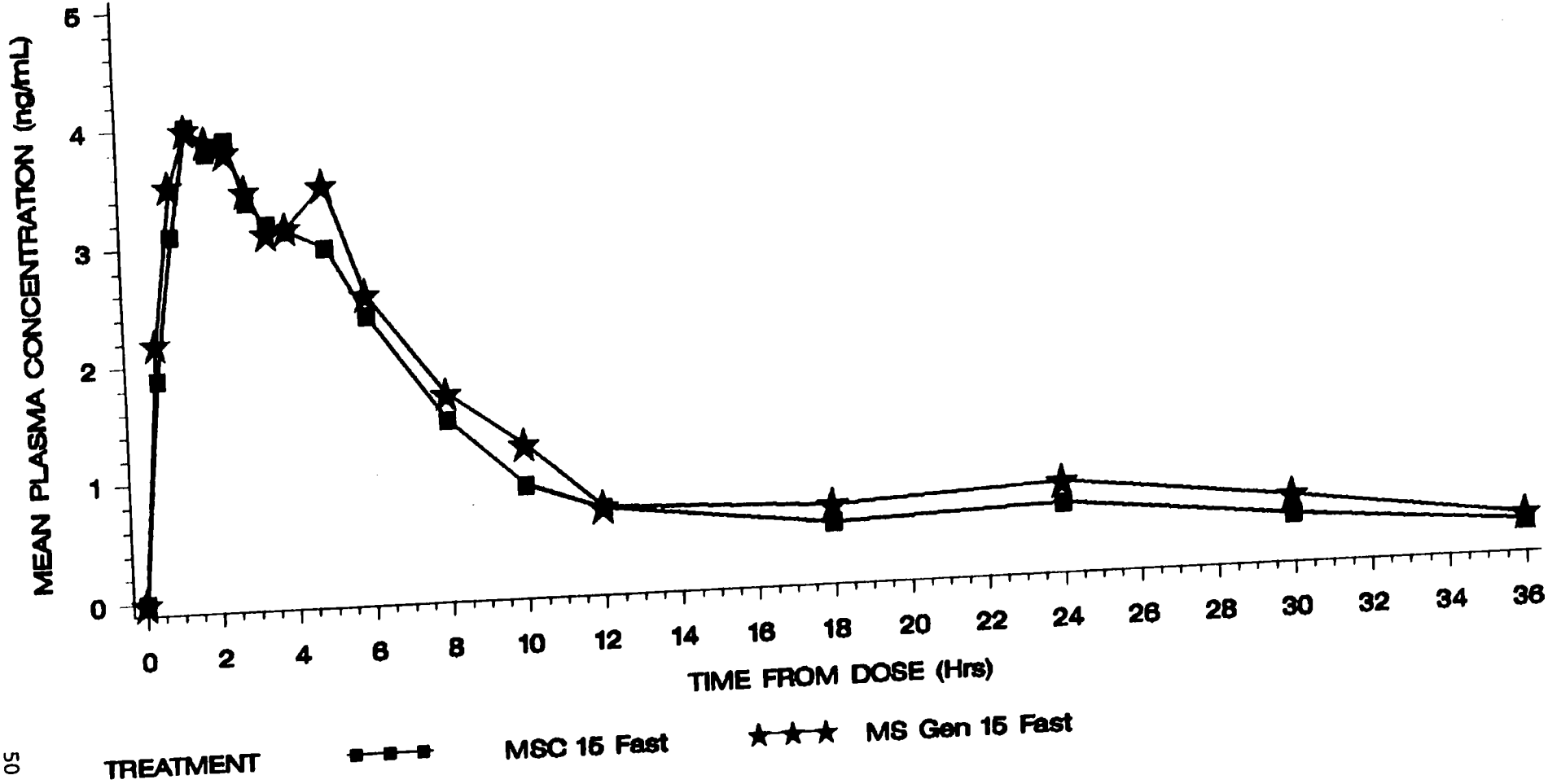


PROTOCOL NO. MO93-0903

FIGURE I

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

Population: Valid for Pharmacokinetic & Safety Analysis



PROTOCOL NO. MO93-0903

FIGURE II

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

Population: Valid for Pharmacokinetic & Safety Analysis