

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number**    **74782** \_\_\_\_\_

**Trade Name**    **Ibuprofen Capsules 200mg** \_\_\_\_\_

**Generic Name**    **Ibuprofen Capsules 200mg** \_\_\_\_\_

**Sponsor**    **Pharmaceutical Formulations, Inc.** \_\_\_\_\_

# CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74782

## CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology				
Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 74782**

**APPROVAL LETTER**

JUL 6 1998

Pharmaceutical Formulations, Inc.  
Attention: Brian W. Barbee  
460 Plainfield Avenue  
Edison, NJ 08818

Dear Sir:

This is in reference to your abbreviated new drug application dated November 10, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ibuprofen Capsules 200 mg.

Reference is also made to your amendments dated September 8, December 15, and December 24, 1997; and January 23, April 15, May 18, May 29, June 8, and June 11, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted Over-the-Counter (OTC) labeling. Accordingly, the application is approved. The drug product, Ibuprofen Capsules 200 mg, can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Page 2

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

---

Douglas L. Sporn  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

7-6-88

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      74782**

**FINAL PRINTED LABELING**

**CONSUMER LABELING LEAFLET FOR IBUPROFEN CAPSULES**

**PLEASE SAVE THIS FOR FUTURE USE**

Only selected information is contained on the bottle label. Therefore, you should keep this sheet for future reference.

**IBUPROFEN CAPSULES 200 mg  
PAIN RELIEVER/FEVER REDUCER**

**WARNING: ASPIRIN SENSITIVE PATIENTS. DO NOT TAKE THIS PRODUCT IF YOU HAVE HAD A SEVERE ALLERGIC REACTION TO ASPIRIN, E.G. ASTHMA, SWELLING, SHOCK OR RIVES, BECAUSE EVEN THOUGH THIS PRODUCT CONTAINS NO ASPIRIN OR SALICYLATES, CROSS-REACTIONS MAY OCCUR IN PATIENTS ALLERGIC TO ASPIRIN.**

**ALCOHOL WARNING:** If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take IBUPROFEN and other pain relievers.

**INDICATIONS:** For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for reduction of fever.

**DIRECTIONS:** Adults: Take 1 capsule every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 1 capsule, 2 capsules may be used but do not exceed 6 capsules in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset, stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. Children: Do not give this product to children under 12 except under the advice and supervision of a doctor.

**WARNINGS:** Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if the painful area is red or swollen, consult a doctor. These could be signs of serious illness. If you are under a doctor's care for any serious conditions, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any non-prescription pain reliever, do not take ibuprofen capsules without first discussing it with your doctor. If you experience any symptoms which are unusual or seem unrelated to the condition for which you took ibuprofen, consult a doctor before taking any more of it. Although ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other ibuprofen-containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

**IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR, BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY.**

Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

**ACTIVE INGREDIENT:** Each capsule contains ibuprofen USP 200 mg.  
**Inactive Ingredients:** Croscarmellose Sodium, D&C Red #28, D&C Yellow #10, FD&C Blue #1, FD&C Red #40, Gelatin, Methylparaben, Microcrystalline Cellulose, Polysorbate 80, Povidone, Pregelatinized Starch, Propylparaben, Silicon Dioxide, Sodium Lauryl Sulfate, Sodium Starch Glycolate, Stearic Acid, Titanium Dioxide.

**STORE AT ROOM TEMPERATURE. AVOID EXCESSIVE HEAT 40°C (104°F).**

Revised

JUNE 1998

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IN 1051C  
MANUFACTURED BY:  
PHARMACEUTICAL FORMULATIONS, INC.  
EDISON, N.J. 08818

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APPROVED

JUL 0 1998

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**IBUPROFEN CAPSULES 200mg**

**PRODUCT CODE 22254Q**

**LOT G49136 EXP. 8/96**

Manufactured by: Pharmaceutical Formulations, Inc.  
Edison, NJ 08818

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**APPROVED**

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**IBUPROFEN CAPSULES 200mg**

**PRODUCT CODE 22254Q**

**LOT G49136 EXP. 8/96**

Manufactured by: Pharmaceutical Formulations, Inc.  
Edison, NJ 08818

PERF - - - - - PERF

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PLAISO

Health+Cross BRAND

NDC 10916-954-24

# IBUPROFEN

CAPSULES 200 mg  
PAIN RELIEVER /  
FEVER REDUCER

**24 CAPSULES\***  
\*Safety Seal Banded



**NON-  
PRESCRIPTION  
STRENGTH  
FORMULA-  
200 MG**



Health+Cross BRAND

NDC 10916-954-24

# IBUPROFEN

CAPSULES 200 mg  
PAIN RELIEVER /  
FEVER REDUCER

**24 CAPSULES\***  
\*Safety Seal Banded



**NON-  
PRESCRIPTION  
STRENGTH  
FORMULA-  
200 MG**

Health+Cross BRAND

# IBUPROFEN

CAPSULES 200 mg  
PAIN RELIEVER / FEVER REDUCER

**SAFETY SEAL BANDED CAPSULES.  
DO NOT USE IF THE IMPRINTED FOIL SEAL  
UNDER THE CAP IS BROKEN OR MISSING.**

**24 CAPSULES\***  
\*Safety Seal Banded

LOT:  
EXP:



serious side effects from taking any non-prescription pain reliever do not take ibuprofen capsules  
without first discussing it with your doctor. If you experience any symptoms which are unusual or  
seem unrelated to the condition for which you took ibuprofen, consult a doctor before taking any more  
of it. Although ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should  
not be taken with them except under a doctor's direction. Do not combine this product with any other  
ibuprofen containing product. As with any drug, if you are pregnant or nursing a baby, seek the advice  
of a health professional before using the product.  
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PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY.  
Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional  
assistance or contact a poison control center immediately.  
ACTIVE INGREDIENT: Each capsule contains ibuprofen USP 200 mg.  
Inactive Ingredients: Croscarmellose Sodium, D&C Red #28, D&C Yellow #10, FD&C Blue #1, FD&C Red  
#40, Gelatin, Methylparaben, Microcrystalline Cellulose, Polyoxylate 80, Polydioxanone, Polyethylene Glycol,  
Propylparaben, Silicon Dioxide, Sodium Lauryl Sulfate, Sodium Starch Glycolate, Stearic Acid, Titanium  
Dioxide.  
Made in U.S.A.  
Mfr. #10916-9254  
MANUFACTURED BY:  
PHARMACEUTICAL FORMULATIONS, INC., EDISON, N.J. 08818

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B094  
BX0788C

**WARNING: ASPIRIN SENSITIVE PATIENTS. DO NOT TAKE THIS PRODUCT IF YOU HAVE HAD A  
SEVERE ALLERGIC REACTION TO ASPIRIN, E.G. ASTHMA, SWELLING, SHOCK OR HIVES, BECAUSE  
EVEN THOUGH THIS PRODUCT CONTAINS NO ASPIRIN OR SALICYLATES, CROSS-REACTIONS MAY  
OCCUR IN PATIENTS ALLERGIC TO ASPIRIN.**  
**ALCOHOL WARNING:** If you generally consume 3 or more alcohol-containing drinks per day, you should  
consult your physician for advice on when and how you should take IBUPROFEN and other pain  
relievers.  
**INDICATIONS:** For the temporary relief of minor aches and pains associated with the common cold,  
headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of  
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**WARNINGS:** Do not take for pain for more than 10 days or for fever for more than 3 days unless directed  
by a doctor. If pain or fever persists for 10 days or if the painful area is red or  
swollen, consult a doctor. These could be signs of serious illness. If you are under a doctor's care for any  
serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if  
you have any condition which requires you to take prescription drugs or if you have had any problems or

JUL 9 1996  
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Health+Cross<sup>BRAND</sup>™

# IBUPROFEN

CAPSULES 200 mg

Health+Cross<sup>BRAND</sup>™

NDC 10916-954-04

# IBUPROFEN

CAPSULES 200 mg  
PAIN RELIEVER /  
FEVER REDUCER



**NON-  
PRESCRIPTION  
STRENGTH  
FORMULA-  
200 MG**

**24 CAPSULES\***

\*Safety Seal Banded

Health+Cross<sup>BRAND</sup>™

# IBUPROFEN

CAPSULES 200 mg

SAFETY SEAL BANDED CAPSULES.  
EACH DOSE IS INDIVIDUALLY SEALED IN PLASTIC OVER A FOIL  
BACKING. DO NOT USE IF THESE ARE TORN OR BROKEN.

22540  
5024  
083755C

Health+Cross<sup>BRAND</sup>™  
**IBUPROFEN**  
CAPSULES 200 mg

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**ACTIVE INGREDIENT:** Each capsule contains ibuprofen USP 200 mg.

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**AVOID EXCESSIVE HEAT 40°C (104°F).**

**STORE AT ROOM TEMPERATURE.**

**MANUFACTURED BY:**  
PHARMACEUTICAL FORMULATIONS, INC., EDISON, NJ 08818  
Made in U.S.A. Mfr. #10916-P254



**APPROVED**

JUL 6 1998



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EXP

JUL 6 1998

**SAFETY SEAL Banded Capsules.** DO NOT USE IF THE IMPRINTED FOIL SEAL UNDER THE CAP IS BROKEN OR MISSING. WARNING: ASPIRIN SENSITIVE PATIENTS: DO NOT TAKE THIS PRODUCT IF YOU HAVE HAD A SEVERE ALLERGIC REACTION TO ASPIRIN, E.G., ASTHMA, SWELLING, SHOCK OR RIVES, BECAUSE EVEN THOUGH THIS PRODUCT CONTAINS NO ASPIRIN OR SALICYLATES, CROSS-REACTIONS MAY OCCUR IN PATIENTS ALLERGIC TO ASPIRIN.

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**ACTIVE INGREDIENTS:** Each capsule contains ibuprofen USP 200 mg. **INACTIVE INGREDIENTS:** Cellulose, Sodium D & C Red #28, D & C Yellow #10, FD & C Red #40, Gelatin, Methylparaben, Microcrystalline Cellulose, Polysorbate 80, Polyethylene Glycol 400, Pregelatinized Starch, Propylparaben, Silicon Dioxide, Sodium Lauryl Sulfate, Sorbitol, Starch, Stearic Acid, Titanium Dioxide.

**STORE AT ROOM TEMPERATURE. AVOID EXCESSIVE HEAT 40°C (104°F).**

**MANUFACTURED BY:** PHARMACEUTICAL FORMULATIONS, INC., EDISON, N.J. 08818  
Made in U.S.A. Mfr. #10916-P254 LA3055C 222540-1000



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NDC 10916-954-02

Health+Cross BRAND

# IBUPROFEN

CAPSULES 200 mg  
PAIN RELIEVER /  
FEVER REDUCER

NON-  
PRESCRIPTION  
STRENGTH  
FORMULA-  
200 MG

PAIN RELIEF  
FORMULA

1000  
CAPSULES\*  
\*Safety Seal Banded

000037

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      74782**

**CHEMISTRY REVIEW(S)**

1. CHEMISTRY REVIEW NO. 3
  2. ANDA # 74-782
  3. NAME AND ADDRESS OF APPLICANT  
Private Formulations, Inc.  
Attention: Brian Barbee  
460 Plainfield Avenue  
Edison, NJ 08818
  4. LEGAL BASIS FOR SUBMISSION  
Approved Product Midol® of Sterling Drug
  5. SUPPLEMENT(s)  
N/A
  6. PROPRIETARY NAME:  
Ibuprofen Gelatin Caplets
  7. NONPROPRIETARY NAME  
Ibuprofen Capsules
  8. SUPPLEMENT(s) PROVIDE(s) FOR:  
N/A
  9. AMENDMENTS AND OTHER DATES:  
Application Submission Date November 10, 1995.  
Amendment Date September 16, 1996.  
'Acceptable for Filing' Date September 17, 1996.  
Facsimile Amendment Date March 24, 1997.  
EER Withhold Memo Date June 19, 1997.  
Major Amendment Date September 8, 1997.  
Amendment Date December 24, 1997.  
Amendment Date January 23, 1998 (Bioequivalency Related).  
Facsimile Amendment Date May 18, 1998 (See Attached Memo).
  10. PHARMACOLOGICAL CATEGORY  
Analgesic and Antipyretic
  11. Rx or OTC  
OTC
  12. RELATED IND/NDA/DMF(s): \_\_\_\_\_
  13. DOSAGE FORM  
Hard Gelatin Capsules, Oral
  14. POTENCY  
200 mg
  15. CHEMICAL NAME AND STRUCTURE  
As Per USP
  16. RECORDS AND REPORTS N/A
  17. COMMENTS  
See individual review sections; Also see note under Section 31.
  18. CONCLUSIONS AND RECOMMENDATIONS  
**Approvable**
  19. REVIEWER:  
U.S. Atwal
- DATE COMPLETED  
March 27, 1998
- DATE REVISED  
May 18, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER      74782

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-782  
DRUG: Ibuprofen  
DOSAGE FORM: Capsules  
STRENGTH(s): 200 mg  
TYPE OF STUDY: Single/Multiple  
STUDY SITE: (b)(4)(CC)

SPONSOR: Private Formulations, Inc.

Fasting/Non-Fasting

STUDY SUMMARY: The bioequivalence studies conducted on Ibuprofen 200 mg Capsules under fasting and nonfasting conditions are acceptable.

DISSOLUTION: Dissolution testing is acceptable.

PRIMARY REVIEWER: [redacted] BRANCH: III

INITIAL: [redacted] DATE: 2/26/98

BRANCH CHIEF: [redacted] BRANCH:

INITIAL: [redacted] DATE: 2/26/1998

DIRECTOR  
DIVISION OF BIOEQUIVALENCE

INITIAL: [redacted] DATE: 2/27/98

DIRECTOR  
OFFICE OF GENERIC DRUGS

INITIAL: \_\_\_\_\_ DATE: \_\_\_\_\_

BIOEQUIVALENCY COMMENTS

ANDA: 74-782

APPLICANT: Pharmaceutical Formulations, Inc.

DRUG PRODUCT: Ibuprofen Capsules 200 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:

The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2, at 37 °C using USP Apparatus 2 (paddle ) at 50 rpm. The test product should meet the following specifications:

Not less than (b)(4)(Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

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

Ibuprofen Capsules  
200 mg  
ANDA #74-782  
Reviewer: Moheb H. Makary  
WP 74782SD.198

Private Formulations, Inc.  
Edison, NJ.  
Submission date:  
January 23, 1998

Review of An Amendment to Bioequivalence Study, and  
Dissolution Data

I. Objective:

The firm has replied to the reviewer's comment made in the review of the September 8, 1997 and December 15 and 24, 1997 submissions (a bioequivalence study on Ibuprofen Capsules 200 mg and dissolution data).

II. Comment

The firm was asked to conduct dissolution testing on its Ibuprofen Capsules 200 mg under the following conditions:

Apparatus: USP 23 apparatus II (paddle) at 50 RPM  
Medium: 900 mL of phosphate buffer pH 7.2 at 37°C  
Sampling Time: 15, 30, 45 and 60 minutes.  
specifications: NLT (b)(4)(C) in 45 minutes.

The firm submitted the dissolution data, utilizing the above method. The dissolution testing results are shown in Table I.

Reply to Comment

The firm's response to the comment is acceptable.

III. Recommendations:

1. The bioequivalence studies under fasting and nonfasting conditions, conducted by Private Formulations Inc., on its Ibuprofen Capsule 200 mg, lot #G49136, comparing it to McNeil's Motrin<sup>R</sup> Gelcap 200 mg, have been found acceptable by the Division of Bioequivalence.

2. The dissolution testing conducted by Private Formulations Inc., on its Ibuprofen Capsule 200 mg, lot #G49136 is acceptable. 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 phosphate buffer pH 7.2 at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specification:

Not less than (b)(4)(C) of the labeled amount of the drug in dosage form is dissolved in 45 minutes.

The firm should be informed of the above recommendations.

/S/ [REDACTED]

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

Date: 2/26/98

RD INITIALLED SNERURKAR  
FT INITIALLED SNERURKAR

/S/ [REDACTED]

Date: 2/26/1998

Concur: /S/ [REDACTED]

Date: 2/27/98

Dale P. Conner, Pharm.D.  
Director  
Division of Bioequivalence

Mmakary/2-25-98, 2-26-98, 74782SD.198

cc: ANDA #74-782, original, HFD-658( Makary), Drug File, Division  
File.

**Table I In Vitro Dissolution Testing**

Drug (Generic Name): Ibuprofen  
 Dose Strength: 200 mg Capsules  
 ANDA No.:74-782  
 Firm: Private Formulations, Inc.  
 Submission Date: January 23, 1998  
 File Name: 74782SD.198

**I. Conditions for Dissolution Testing:**

USP 23 Basket: Paddle:X RPM: 50  
 No. Units Tested: 12  
 Medium: 900 mL of phosphate buffer pH 7.2  
 Specifications: NLT 75 % in 45 minutes  
 Reference Drug: Motrin 200 mg Tablets  
 Assay Methodology:UV

**II. Results of In Vitro Dissolution Testing:**

Sampling Times (Minutes)	Test Product Lot #G49136 Capsule Strength(mg) 200			Reference Product Lot # 01AXX Tablet Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
15	84.8	(b)(4)(CC)	7.9	99.5	(b)(4)(CC)	2.35
30	95.3	(b)(4)(CC)	4.4	100.1	(b)(4)(CC)	2.7
45	97.0	(b)(4)(CC)	3.0	100.5	(b)(4)(CC)	2.5
60	99.0	(b)(4)(CC)	1.5	100.2	(b)(4)(CC)	2.5

BIOEQUIVALENCY COMMENTS

ANDA: 74-782

APPLICANT: Pharmaceutical Formulations, Inc.

DRUG PRODUCT: Ibuprofen Capsules 200 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:

The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2, at 37 °C using USP Apparatus 2 (paddle ) at 50 rpm. The test product should meet the following specifications:

Not less than (b)(4)(Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

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

CC: ANDA #74-782  
ANANDA DUPLICATE  
DIVISION FILE  
HFD-651/ Bio Secretary - Bio Drug File  
HFD-658 / Reviewer Makary

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Printed in final on / /98

Endorsements: (Final with Dates)

HFD-658 / Reviewer /S/ [REDACTED] 2/26/98  
HFD-65 / Team Leader [REDACTED]  
HFD-617/ L. Sanchez [REDACTED]  
HFD-650 / D. Conner [REDACTED]

BIOEQUIVALENCY - ACCEPTABLE

- 1. **FASTING STUDY (STF)** Strengths: 200 mg  
Clinical: (b)(4)(CG) Outcome: **AC**  
Analytical: \_\_\_\_\_
- 2. **FOOD STUDY (STP)** Strengths: 200 mg  
Clinical: (b)(4)(CG) Outcome: **AC**  
Analytical: \_\_\_\_\_
- 3. **STUDY AMENDMENT (STA)** Strengths: 200 mg  
Outcome: **AC**
- 3. **DISSOLUTION DATA (DIS)** All Strength 200 mg  
Outcome: **AC**

Outcome: **AC**  
Outcome Decisions:  
AC - Acceptable )

Ibuprofen Capsules  
200 mg  
ANDA #74-782  
Reviewer: Moheb H. Makary  
WP 74782SD.997

Private Formulations, Inc.  
Edison, NJ.  
Submission date:  
September 8, 1997  
December 15 & 24, 1997

Review of a Bioequivalence Study

I. Objective:

The firm has submitted a bioequivalence study under fasting conditions on its Ibuprofen 200 mg Capsules to comparing the test product to McNeil's Motrin<sup>R</sup> IB Gelcap (Gelatin-Coated Capsule-Shaped Tablets) 200 mg.

II. Background:

The firm has submitted a second in vivo bioequivalence study on its Ibuprofen Capsules 200 mg under fasting conditions as a response to the Agency's letter dated April 14, 1997. In the letter the firm was advised that the in vivo bioequivalence study submitted with the original ANDA (submission dated November 10, 1995) was unacceptable. The confidence interval of Cmax was outside the acceptable range of 80-125%. The same lot of Ibuprofen Capsules that was given in the original studies (the fasting and nonfasting studies) was also administered in the new study. Since the original bioequivalence studies were performed, the reference listed drug changed from Nuprin<sup>R</sup> Tablets to Motrin<sup>R</sup> IB Gelcap 200 mg (see the attached Emails). Subsequently, the Division of Bioequivalence informed the firm that the nonfasting bioequivalence study conducted by the firm on its Ibuprofen Capsules 200 mg versus Nuprin<sup>R</sup> Tablets was acceptable and the fasting study should be repeated using the new reference listed drug (Motrin<sup>R</sup> IB Gelcap).

III. Study-068-54 for Determination of Single Dose Bioequivalence Of Private Formulations's Ibuprofen 200 mg Capsules to Motrin<sup>R</sup> IB Gelcap Under Fasting Conditions

Study site:

(b)(4)(CC)

(b)(4)(CC)

Investigator:

Study date: July 1-8, 1997

Study design: A single-dose, randomized, two-treatment, two-period crossover design.

Subjects: Twenty-six (26) healthy male subjects enrolled and completed the study.

Selection criteria: Subjects selected for the study met the following acceptance criteria:

1. Ages 18 - 45 years,  $\pm$  15% of the ideal weight for his height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983 (see pp 18).
2. Healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests (blood chemistry, hematology, urinalysis).

Exclusion criteria:

1. History of concurrent illness, acute or chronic diseases or history of serious cardiovascular, pulmonary, endocrine, immunologic, dermatologic, renal, G.I., hepatic, hematologic, neurologic, or psychiatric disease.
2. History of hypersensitivity to ibuprofen or other nonsteroidal anti-inflammatory drugs.

Restrictions:

1. No ingestion of any alcohol, caffeine or xanthine-containing food or beverages within the 48 hours prior to initial dose of study medication.
2. No Rx or OTC drugs beginning 72 days prior to the study.

Dose and treatment: All subjects completed an overnight fast (at least ten hours) before any of the following drug treatments:

Test Products: a) 1x200 mg Ibuprofen Capsule (Private Formulations), lot #G49136, batch size (b)(4)(CC) Capsules, potency 97.6%, content uniformity 98.6% (%CV=1.04).

Reference Product: b) 1x200 mg Motrin<sup>R</sup> IB Gelcap (McNeil), lot #01AXX, Exp. 9/99, potency 100.4%.

Randomization: See pp 19 (Vol 1.1)

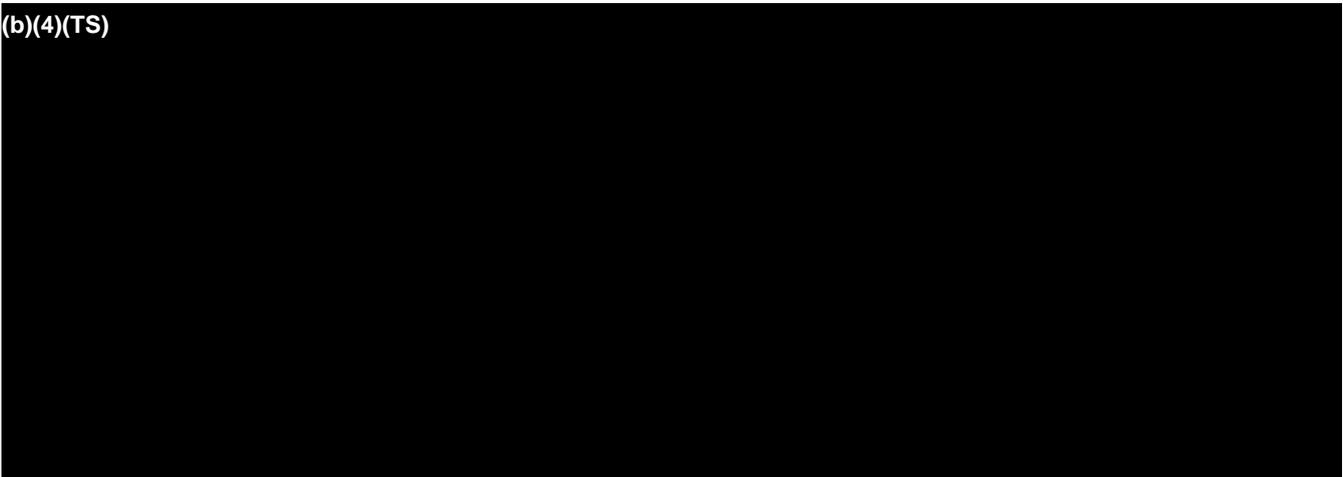
Washout period: One week

Food and fluid intake: A 200 mg ibuprofen capsule or tablet of the test or the reference product, respectively, was administered with 240 mL of water following a 10 hour fast. Subjects continued fasting for 4 hours post-dose. Water intake was not permitted from 1 hour before and until 1 hour after the dose.

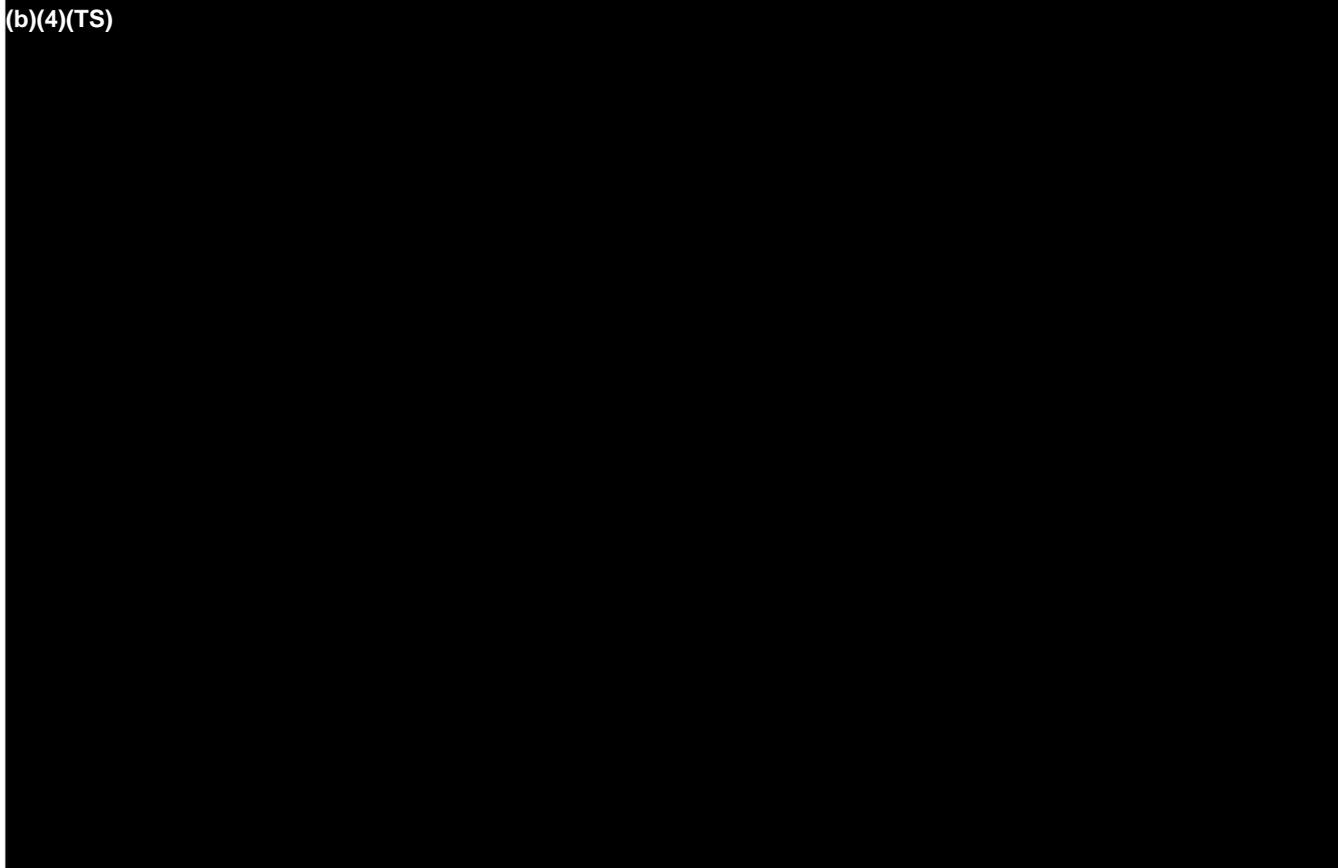
Blood samples: Blood samples were collected at: 0 (prior to dosing), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 9 and 12 hours after dosing. Plasma samples were separated by centrifugation and then frozen at -20°C, and kept frozen, packed in dry ice, and sent to (b)(4)(CC)

#### Assay Methodology

(b)(4)(TS)



(b)(4)(TS)



#### Statistical Methods

AUC(0-t), AUCinf, Cmax, Tmax, Ke and T1/2 were calculated from the individual concentration versus time data for ibuprofen. An analysis of variance (ANOVA) was applied to log-transformed bioequivalence parameters to determine any statistically significant differences between the drug formulations. The 90% confidence intervals were calculated for each bioequivalence parameter.

#### IV. In Vivo Results:

The study was conducted at (b)(4)(CC) during the period of July 2 to 8, 1997. Twenty-six (26) male subjects enrolled and completed the study. No serious or unexpected adverse experience occurred during the conduct of the study (pp 81).

Protocol Deviation: Minor protocol deviation were reported (pp 14). In reviewer's opinion these deviations may not influence bioequivalence evaluation.

The plasma concentrations for ibuprofen are summarized in Table I.

Table I

Mean Ibuprofen Plasma Concentrations and Pharmacokinetic  
Parameters Following an Oral Dose of 1x200 mg Ibuprofen  
Capsule/Tablet Under Fasting Conditions  
(N=26)

Time hr	A	B
	Private Formulations Test Product Lot #G49136 ug/mL (CV%)	McNeil Reference Product Lot #01AXX ug/mL (CV%)
0	0.00	0.00
0.25	1.54 (161.2)	2.70 (158 )
0.50	7.60 ( 77.6)	9.20 (86.1)
0.75	10.95 ( 70.7)	12.61 (72.0)
1.00	12.99 ( 62.6)	15.41 (53.3)
1.25	15.24 ( 47.2)	16.47 (46.5)
1.50	15.52 ( 41.4)	16.85 (37.3)
2.00	15.85 ( 28.6)	16.71 (23.0)
2.50	14.68 ( 22.4)	14.03 (27.7)
3.00	12.73 ( 20.5)	11.80 (27.6)
4.00	9.16 ( 30.8)	8.30 (29.5)
6.00	3.87 ( 44.6)	3.95 (52.8)
9	1.40 ( 65.6)	1.45 (65.1)
12	0.52 (105.7)	0.52 (96.3)

Pharmacokinetic Parameters

	A	B	A/B	90% CI log-transf
	<u>Test</u>	<u>Reference</u>		
AUC(0-t) (ug.hr/mL)	70.90 (22)	71.91 (23)	0.98	94.9-102.9
AUCinf (ug.hr/mL)	72.78 (24)	73.75 (25)	0.99	95.0-102.8
Cmax (ug/mL)	20.13 (17)	21.17 (21)	0.95	89.2-103.5
Tmax (hr)	1.75	1.56	1.12	
Kel (1/hr)	0.38	0.38	1.00	
t1/2 (hr)	1.88	1.90	0.99	

1. 90% CI values are based on reviewer's calculations using AUC, AUCinf and Cmax data reported by the sponsor. The reviewer has varified the AUC and AUCinf values to be accurate.

2. For Private Formulations test product, the means AUC(0-t), AUCinf and Cmax values were 2%, 1 and 5 lower than those of the reference product values. The differences were not statistically significant. The 90% confidence intervals of the log-transformed parameters are within the acceptable range of 80-125% for AUC(0-t), AUCinf and Cmax.

3. The ibuprofen mean plasma levels peaked at 1.5 and 2 hours for the reference and test products, respectively, following their administration under fasting conditions.

#### V. Formulation:

Private's formulation for its Ibuprofen 200 mg capsule is shown in Table II.

#### VI. In Vitro Dissolution Testing:

Method: USP 23, apparatus I (basket) at 100 rpm  
Medium: 900 mL of phosphate buffer, pH 7.2  
Number of Tablets: 12  
Test products: Ibuprofen (PFI), 200 mg Capsules, lot #G49136

Reference products: Motrin<sup>R</sup> (McNeil), 200 mg Gelcap, lot #01AXX

The dissolution testing results are given in Table III.

#### VII. Comment:

1. The firm's in vivo bioequivalence study under fasting conditions, conducted on its 200 mg ibuprofen capsule is acceptable. The confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125%.

2. The firm had previously conducted an acceptable in vivo bioequivalence study under nonfasting conditions (submission to ANDA #74-782 dated November 10, 1995). The ratios of the test mean to the reference mean were within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cmax.

3. The apparatus used for dissolution testing is not appropriate

for ibuprofen capsules. Therefore, the in vitro testing for the test product is incomplete. The firm is advised to conduct dissolution testing under the following conditions:

Apparatus: USP 23 apparatus II (paddle) at 50 RPM  
Medium: 900 mL of phosphate buffer pH 7.2 at 37°C  
Sampling Time: 15, 30, 45 and 60 minutes.  
specifications: NLT (b)(4)(C) in 45 minutes.

VIII. Deficiency:

The firm is advised to conduct dissolution testing under the following conditions:

Apparatus: USP 23 apparatus II (paddle) at 50 RPM  
Medium: 900 mL of phosphate buffer pH 7.2 at 37°C  
Sampling Time: 15, 30, 45 and 60 minutes.  
specifications: NLT (b)(4)(C) in 45 minutes.

IX. Recommendations:

1. The bioequivalence study under fasting conditions (study #068-54), conducted by Private Formulations Inc., on its Ibuprofen Capsule 200 mg, lot #G49136, comparing it to McNeil's Motrin<sup>R</sup> Tablet 200 mg, has been found acceptable by the Division of Bioequivalence.

2. The dissolution testing conducted by Private Formulations Inc., on its Ibuprofen Capsule 200 mg, lot #G49136 has been found incomplete by the Division of Bioequivalence for the reason given in comment #3.

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

From the bioequivalence stand point, this application is incomplete.

/s/

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

Date: 1/8/98

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P  
W

RD INITIALLED RMHATRE  
FT INITIALLED RMHATRE

/S/ [REDACTED]

Date: 1-9-98

Concur: /S/ [REDACTED]

Date: 1/12/98

Dale Conner, Pharm.D.  
Director  
Division of Bioequivalence

Mmakary/12-29-97, 1-8-97 wp 74782SDW.997  
cc: ANDA #74-782, original, HFD-658 (Makary), Drug File, Division  
File.

**Table III In Vitro Dissolution Testing**

Drug (Generic Name): Ibuprofen  
 Dose Strength: 200 mg Capsules  
 ANDA No.: 74-782  
 Firm: Private Formulations, Inc.  
 Submission Date: September 8, 1997  
 File Name: 74782SD.997

**I. Conditions for Dissolution Testing:**

USP 23 Basket: X Paddle: RPM: 100  
 No. Units Tested: 12  
 Medium: 900 mL of phosphate buffer pH 7.2  
 Specifications: NLT (b)(4)(C) in 45 minutes  
 Reference Drug: Motrin 200 mg Tablets  
 Assay Methodology: (b)(1).

**II. Results of In Vitro Dissolution Testing:**

Sampling Times (Minutes)	Test Product Lot #G49136 Capsule Strength(mg) 200			Reference Product Lot # 01AXX Tablet Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
10	69.8	(b)(4)(CC)	7.6	100.7	(b)(4)(CC)	1.15
20	98.6	(b)(4)(CC)	1.6	99.9	(b)(4)(CC)	2.5
30	100.7	(b)(4)(CC)	1.4	102.2	(b)(4)(CC)	2.2

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 74-782

APPLICANT: Private Formulations, Inc.

DRUG: Ibuprofen Capsules, 200 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

You are advised to conduct dissolution testing under the following conditions:

Apparatus: USP 23 apparatus II (paddle) at 50 RPM  
Medium: 900 mL of phosphate buffer pH 7.2 at 37°C  
Sampling Time: 15, 30, 45 and 60 minutes.  
Specifications: NLT (b)(4)(CC) n 45 minutes.

Sincerely yours,

(b)(4)(CC)

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

CC: ANDA 74-782  
ANDA DUPLICATE  
DIVISION FILE  
FIELD COPY  
HFD-651/ Bio Secretary - Bio Drug File  
HFD-650/ Makary

Endorsements: (Final with Dates)

HFD-658/ Makary  
HFD-655/ Bio team I/S/ [redacted] 1-8-98  
HFD-650/ D. Conner [redacted]

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Drafted letter on 1/8/97  
Printed in final on 1/ /

BIOEQUIVALENCY - DEFICIENCIES submission date: September 8,  
1997; December 15 & 24, 1997

1-8-97

1. FASTING STUDY (STF) Strengths: 200 mg cap  
Clinical: (b)(4)(CC) [redacted]  
(b)(4)(CC) [redacted]  
Analytical: (b)(4)(CC) [redacted] Outcome: AC

~~2. DISSOLUTION DATA (DIS) All Strengths~~

OUTCOME DECISIONS: IC - Incomplete

WINBIO COMMENTS:

015-97<sup>2</sup> Other - d-zetles  
24, 1997 ~~Other~~  
3. Other - FAX info.

# Table II

## Component and Composition Statement

<u>Ingredient</u>	Proposed Formulation Ibuprofen 200 mg. Gelatin Caplets <u>mg/Gelatin Caplet</u>
<u>Core</u>	
Ibuprofen USP	200.00
Pregelatinized Starch NF	(b)(4)(TS)
Silicon Dioxide NF	[REDACTED]
Stearic Acid NF	[REDACTED]
Povidone USP	[REDACTED]
Croscarmellose Sodium NF	[REDACTED]
Microcrystalline Cellulose NF	[REDACTED]
Sodium Starch Glycolate NF	[REDACTED]

### Capsule

(b)(4)(TS)

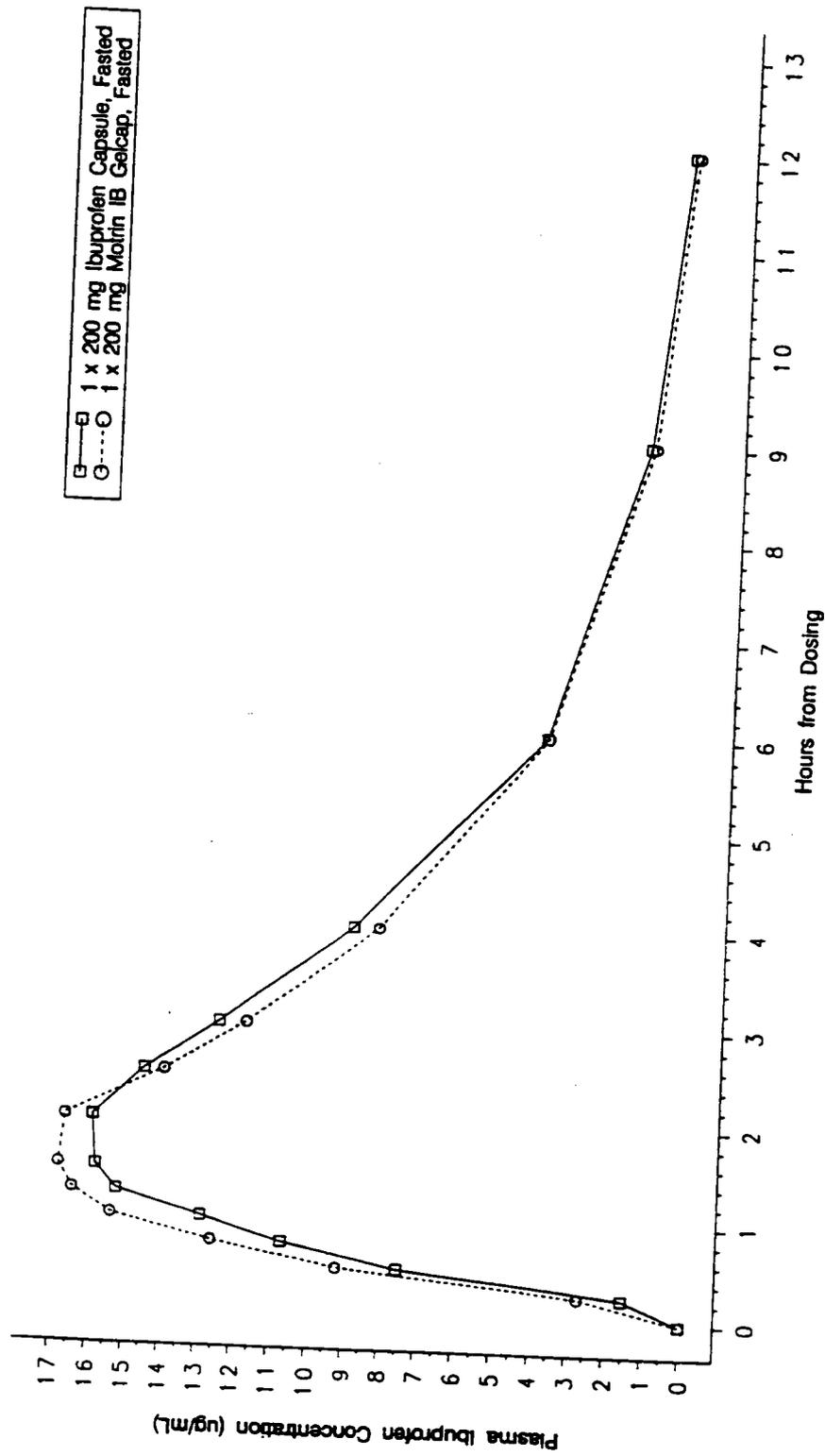
### Band

(b)(4)(TS)

\* Added as manufacturing aides to the gelatin.

000016

Figure 2  
Mean Plasma Ibuprofen Concentrations Versus Time  
Linear Scale



MAR 31 1997

Ibuprofen Capsules  
200 mg  
ANDA #74-782  
Reviewer: Moheb H. Makary  
WP 74782SD.N95

Private Formulations, Inc.  
Edison, NJ.  
Submission date:  
November 10, 1995

### Review of Bioequivalence Studies

#### I. Objective:

The firm has submitted two bioequivalence studies under fasting and nonfasting conditions on its Ibuprofen 200 mg Capsules (Hard Gelatin Capsule, solid filled) to compare the test product relative to Nuprin<sup>R</sup> (Bristol-Myers) 200 mg tablets for review. On February 13, 1994 the firm requested for the reference listed drug for Ibuprofen Capsules, 200 mg. In response to the firm request, OGD provided the remarks described below:

As listed in the Approved Drug Products with Therapeutic Equivalence Evaluations, 14th ed, 1994; (The orange Book), Midol<sup>R</sup> Capsules, manufactured by Winthrop Pharmaceuticals should be used as the reference listed drug (RLD) for bioequivalence comparison. If the RLD (Midol<sup>R</sup>) is not available in the market place, then Nuprin<sup>R</sup> Tablets manufactured by Bristol Myers could be used as the RLD for bioequivalence comparisons, unless the RLD as designated in the Orange Book become available before the bioequivalence studies are dose. Nuprin<sup>R</sup> was the listed drug upon which the petition to file Midol<sup>R</sup> Capsules was approved.

In this submission the firm included a letter dated February 10, 1995, from Sterling Winthrop Inc., which indicated that Winthrop did in fact have an approved NDA for Ibuprofen capsules 200 mg. Sterling Winthrop Inc., did not market the product nor has plans to do so; as a result, the product is not available.

It should be noted that the reference listed drug (RLD) Provel<sup>R</sup> Capsules, manufactured by Sandoz and Midol<sup>R</sup> Capsules, manufactured by Winthrop Pharmaceuticals for Ibuprofen Capsules, 200 mg are listed under the Discontinued Drug Product List in the Approved Drug Products with Therapeutic Equivalence Evaluations, 16th ed, 1996; (The orange Book).

#### II. Introduction:

Ibuprofen is a propionic acid derivative with analgesic, antipyretic and anti-inflammatory activities. Peak serum ibuprofen levels are generally attained one to two hours after administration. With single doses up to 800 mg, a linear relationship exists between amount of drug administered and the integrated area under the serum drug concentration vs time curve.

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. Nuprin<sup>R</sup> (Bristol-Myers) is an OTC product containing ibuprofen 200 mg and is indicated for the temporary relief of minor aches and pains associated with the common cold. The usual adult dosage is 1 tablet every 4 to 6 hours, and may be increased to 2 tablets but not exceeding 6 tablets in 24 hours.

III. Study-068-46 For Single Dose Fasting Bioequivalence Of Private Formulations's Ibuprofen 200 mg Capsules

Study site:

(b)(4)(CC)

Investigators:

Principal Investigator

Study date:

February 18-26, 1995

Sample analysis:

Sample analysis began on February 28, 1995 through March 10, 1995.

Study design:

A single-dose, randomized, Two-treatment, Two-period crossover design.

Subjects:

Twenty-six (26) healthy male subjects enrolled and completed the study.

Selection criteria: Subjects selected for the study met the following acceptance criteria:

1. Ages 19 - 44 years,  $\pm$  15% of the ideal weight for his height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983.
2. Healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests (blood chemistry, hematology, urinalysis).
3. No concurrent illness, acute or chronic diseases or history of serious cardiovascular, pulmonary, endocrine, immunologic, dermatologic, renal, G.I., hepatic, hematologic, neurologic, or psychiatric disease.
4. No history of hypersensitivity to ibuprofen or other nonsteroidal anti-inflammatory drugs.

- Restrictions:
1. No ingestion of any alcohol, caffeine or xanthine-containing food or beverage within the 48 hours prior to initial dose of study medication.
  2. No Rx or OTC drugs beginning 72 days prior to the study.
  3. No concomitant use of prescription medication during the study.

Dose and treatment: All subjects completed an overnight fast (at least ten hours) before any of the following drug treatments:

Test Products: a) 1x200 mg Ibuprofen Capsule (Private Formulations), lot #G49136, batch size not reported, Manufacturing Date not provided, potency not provided, content uniformity not provided.

Reference Product: b) 1x200 mg Nuprin<sup>R</sup> Tablet (Bristol-Myers Squibb), Exp. July 99, lot #409161, potency not provided.

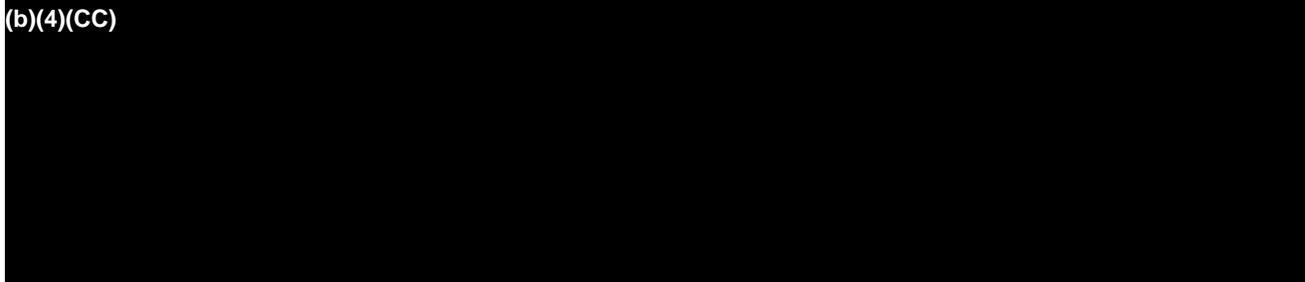
Washout period: One week

Food and fluid intake: A 200 mg ibuprofen capsule or tablet of the test or the reference product, respectively, was administered with 240 mL of water following a 10 hour fast. Subjects continued fasting for 4 hours post-dose. Water intake was not permitted from 1 hour before and until 1 hour after the dose.

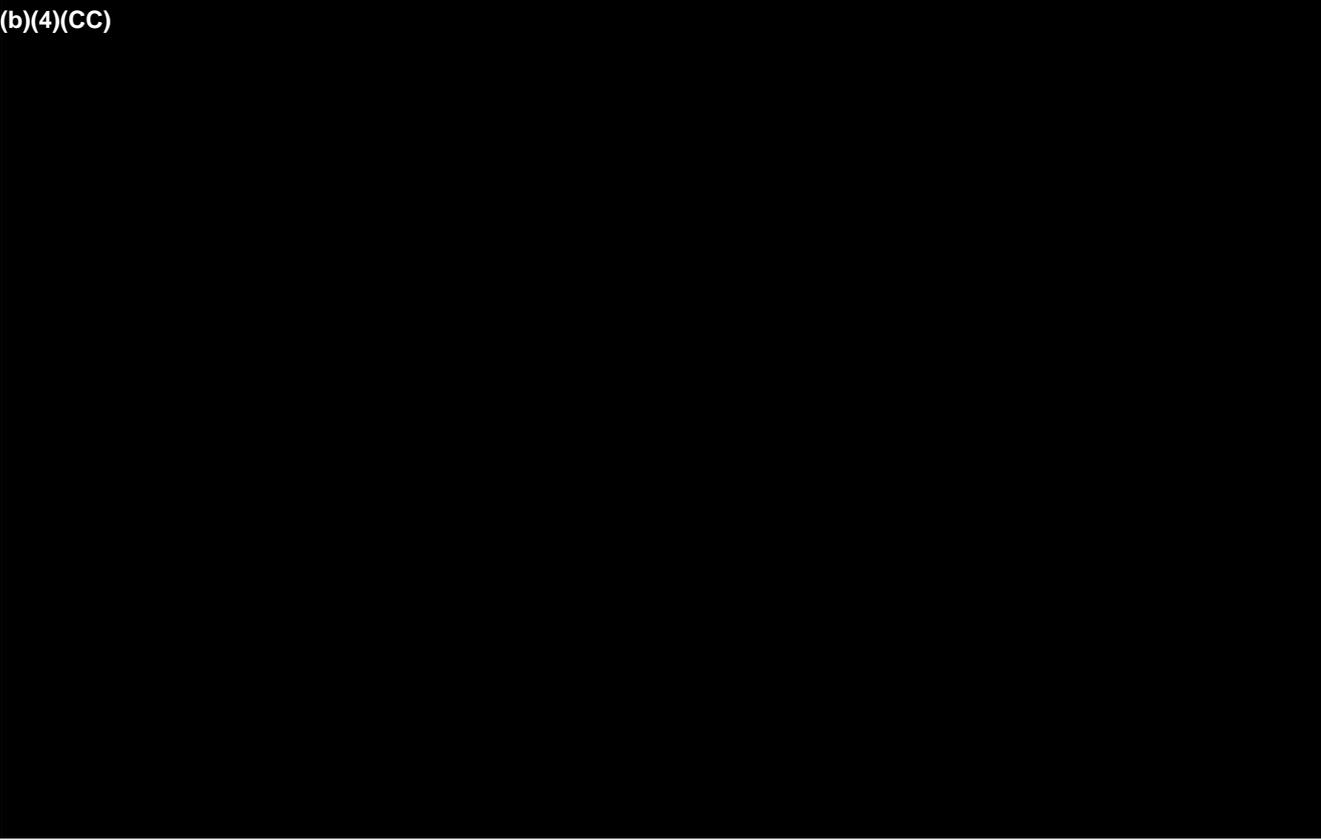
Blood samples: Blood samples were collected at: 0 (prior to dosing), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 9 and 12 hours after dosing. Plasma was extracted and stored in labeled tubes at -12°C pending assay.

#### Assay Methodology

(b)(4)(CC)



(b)(4)(CC)



#### Statistical Methods

AUC(0-t), AUCinf, Cmax, Tmax, Ke and T1/2 were calculated from the individual concentration versus time data for ibuprofen. An analysis of variance (ANOVA) was applied to log-transformed bioequivalence parameters to determine any statistically significant differences between the drug formulations. The 90% confidence intervals were calculated for each bioequivalence parameter.

#### IV. In Vivo Results:

The study was conducted at (b)(4)(CC) during the period of February 18 to 26, 1995. Twenty-six (26) male subjects enrolled and completed the study. No serious or unexpected adverse experience occurred during the conduct of the study.

The plasma concentrations for ibuprofen are summarized in Table I.

Table I

Mean Ibuprofen Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x200 mg Ibuprofen Capsule/Tablet Under Fasting Conditions  
(N=26)

Time hr	A	B
	Private Formulations <u>Test Product</u> Lot #G49136 ug/mL (CV%)	Bristol-Myers Squibb <u>Reference Product</u> Lot #409161 ug/mL (CV%)
0	0.00	0.00
0.25	0.64 (142.5)	3.72 (134 )
0.50	5.09 ( 81.0)	10.35 (84.5)
0.75	9.96 ( 64.4)	13.30 (56.4)
1.00	12.90 ( 55.4)	15.68 (44.0)
1.25	14.41 ( 45.5)	16.32 (27.2)
1.50	14.43 ( 39.8)	16.12 (31.3)
2.00	13.97 ( 23.3)	14.45 (21.1)
2.50	12.91 ( 21.0)	12.51 (24.1)
3.00	11.55 ( 25.8)	10.54 (25.8)
4.00	8.66 ( 27.8)	7.79 (28.9)
6.00	3.76 ( 36.0)	3.49 (44.6)
9	1.34 ( 45.0)	1.31 (57.1)
12	0.47 ( 72.5)	0.45 (88.3)

Pharmacokinetic Parameters

	A	B	90% CI
	<u>Test</u>	<u>Reference</u>	log-transf
AUC(0-t) (ug.hr/mL)	65.37(16)	66.32(17)	96.2-101.2
AUCinf (ug.hr/mL)	67.02(17)	68.05(18)	96.2-101.2
Cmax (ug/mL)	17.87(21)	20.93(18)	79.1-90.5
Tmax (hr)	1.74	1.20	
Kel(1/hr)	0.366	0.365	
t1/2 (hr)	1.92	1.94	

1. For Private Formulations test product, the means AUC(0-t), AUCinf and Cmax values are 1.43%, 1.51% and 14.6 lower, respectively, than those for the reference product values. The difference is statistically significant for Cmax. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t) and AUCinf. The 90% confidence interval for Cmax is 79.1 to 90.5% of the reference parameter for log transformed data, which is outside the acceptable range of 80-125%.

2. The ibuprofen plasma levels peaked at 1.25 and 1.50 hours for the reference and test products, respectively, following their administration under fasting conditions.

V. Study #068-47 For Single Dose post-prandial Bioequivalence Study

Objective: The objective of the study is to compare the relative bioavailability of Ibuprofen 200 mg Capsules (Private Formulations Inc.) with that of Nuprin<sup>R</sup> 200 mg Tablets (Bristol-Myers Squibb) in healthy male volunteers under nonfasting conditions, and to compare the difference in plasma levels after dosing with the test product when dosed with and without food.

Study site: Same as Study #068-46 above

Study date: February 17 to March 4, 1995

Study design: A single-dose, randomized, three-treatment, three-period, six-sequence crossover design.

Subjects: Eighteen (18) healthy male subjects entered and completed the study.

Selection criteria: Same as Study #068-46 above.

Washout period: One week

Dose and treatment: Treatment A:  
1x200 mg Ibuprofen Capsule (Private Formulations Inc.), lot #G49136 administered following a standard meal preceded by an overnight fast.

Treatment B:  
1x200 mg Nuprin<sup>R</sup> Tablet (Bristol-Myers Squibb), lot #409161 administered following a standard meal preceded by an overnight fast.

Treatment C:  
1x200 mg Ibuprofen Capsule (Private Formulations Inc.), lot#G49136, administered after an overnight fast.

Food and fluid intake: Subjects were required to fast overnight for 10 hours prior to dosing in each treatment phase. Subjects on regimen C ingested the capsule with 180 mL of water. Subjects on regimen A and B ingested the capsule and tablet, respectively, with 180 mL of water within 5 minutes after completing 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). At 4 hours post-drug, standardized xanthine-free meals were provided to the subjects. Water intake was not permitted for 1 hour before and 1 hour after dosing, but was allowed at all other times.

Blood samples: Same as in Study #068-46

Assay Methodology Same as in Study #068-46.

Statistical Methods Same as in Study #068-46.

VI. In Vivo Results:

The study was conducted at (b)(4)(CC) during the period of February 17 and March 4, 1995. Eighteen (18) male subjects entered and completed the study. No serious or unexpected adverse experience occurred during the conduct of the study.

The plasma concentrations for ibuprofen are summarized in Table II.

Table II

Mean Ibuprofen Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x200 mg Ibuprofen Capsule/Tablet Under Fasting and Nonfasting Conditions (N=18)

Time hr	A Private Formulations		B Bristol-Myers		C Private Formulations	
	<u>Test Product</u>		<u>Reference Product</u>		<u>Test Product</u>	
	Lot #G49136		Lot #409161		Lot #G49136	
	Nonfasting		Nonfasting		Fasting	
	ug/mL (CV%)		ug/mL (CV%)		ug/mL (CV%)	
0	0.00		0.00		0.0	
0.25	0.04 (303.2)		0.02 (424.3)		0.59 (163 )	
0.50	0.68 (275.6)		0.94 (152.3)		7.13 (69.5)	
0.75	1.50 (226.1)		4.09 ( 87.4)		11.56 (48.3)	
1.00	2.63 (161.1)		7.26 ( 67.6)		12.49 (42.4)	
1.25	4.30 (120.7)		9.70 ( 52.2)		12.88 (34.8)	
1.50	5.92 ( 88.2)		10.86 ( 43.6)		13.31 (33.4)	
2.00	9.22 ( 63.7)		11.37 ( 34.9)		12.63 (35.0)	
2.50	10.26 ( 41.3)		10.35 ( 33.3)		11.08 (37.7)	
3.00	10.29 ( 27.6)		9.77 ( 32.9)		10.48 (34.7)	
4.00	9.58 ( 25.1)		8.01 ( 33.4)		7.32 (41.3)	

6.00	4.82 ( 30.3)	4.15 ( 45.8)	3.26 (45.5)
9	1.63 ( 47.7)	1.32 ( 52.1)	1.11 (56.4)
12	0.66 ( 69.3)	0.54 ( 77.9)	0.43 (87.8)

Pharmacokinetic Parameters

	<u>A</u> <u>Test</u>	<u>B</u> <u>Reference</u>	<u>C</u> <u>Test</u>	<u>A/B</u>
AUC(0-t) (ug.hr/mL)	54.27(21)	54.91(25)	58.96(29)	0.99
AUCinf (ug.hr/mL)	56.33(23)	56.75(27)	60.32(31)	0.99
Cmax (ug/mL)	12.75(28)	13.66(19)	16.22(19)	0.93
Tmax (hr)	2.94	2.03	1.54	
Kel(1/hr)	0.358	0.352	0.359	
t1/2 (hr)	1.99	2.02	1.96	

1. For Private Formulations Inc., test product, the means AUC(0-t), AUCinf and Cmax values are 1.2%, 0.74% and 6.7% lower, respectively, than those for 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-t), AUCinf and Cmax. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf and Cmax.

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

3. The mean Cmax of the test product was reduced by 21%, when dosed under nonfasting conditions compared to fasting conditions. This reduction in Cmax value is in agreement with the reference product's labeling which indicated that food intake, reduces the rate of absorption.

VII. Formulations:

Private's formulation for its Ibuprofen 200 mg capsule is shown in Table III.

VIII. Dissolution:

Dissolution testing is not reported by the firm.

IX. Deficiency Comments:

1. For the single-dose bioequivalence study under fasting conditions, the 90% confidence interval for LnCmax is 79.1-90.5%,

which is outside the acceptable range of 80-125%.

2. The size of the biobatch and the potency and content uniformity for the test and reference products should be submitted.

3. Comparative dissolution testing should be submitted.

X. Recommendations:

1. The bioequivalence study under fasting (study #068-46) conditions conducted by Private Formulations Inc., on its Ibuprofen Capsule 200 mg, lot #G49136, comparing it to Bristol-Myers's Nuprin<sup>R</sup> Tablet 200 mg, has been found unacceptable by the Division of Bioequivalence for the reasons given in deficiency comments 1-3.

2. The bioequivalence study under fasting and nonfasting (study #068-47) conditions conducted by Private Formulations Inc., on its Ibuprofen Capsule 200 mg, lot #G49136, comparing it to Bristol-Myers's Nuprin<sup>R</sup> Tablet 200 mg, has been found incomplete by the Division of Bioequivalence for the reasons given in deficiency comments 2 and 3.

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

/s/ [redacted]

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

/s/ [redacted]

RD INITIALLED RMHATRE  
FT INITIALLED RMHATRE

Date: 3/21/97

/s/ [redacted]

Concur: [redacted]

3/31/97  
Nicholas Fleischer, Ph.D.  
Director  
Division of Bioequivalence

MMakary/3-21-97/wp 74782SD.N95

cc: ANDA # 74-782, original, HFD-658 (Makary), Drug File.



Figure 1  
Mean (S.D.) Plasma Ibuprofen Concentrations Versus Time  
Linear Scale

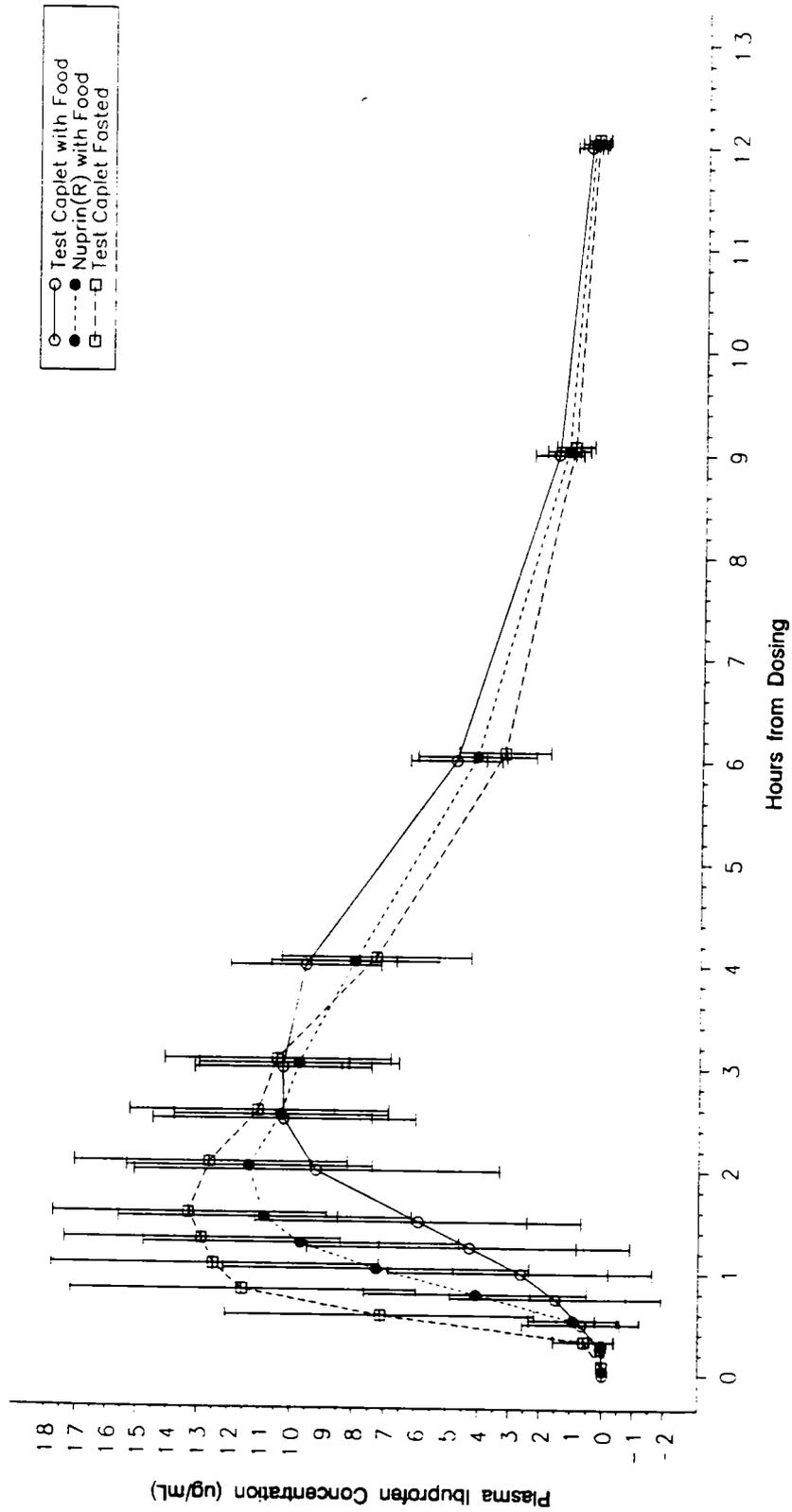
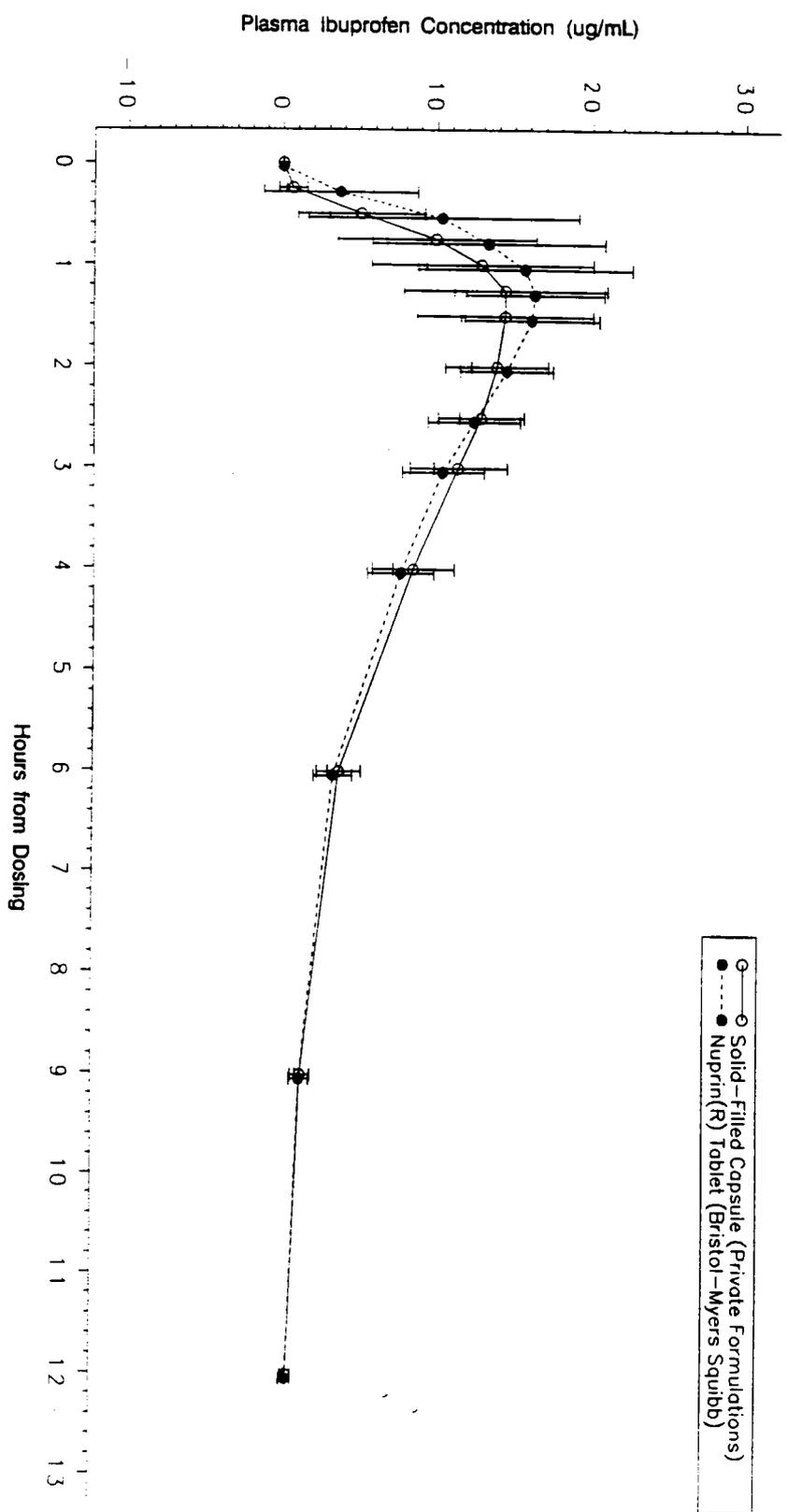


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Study dates  
2-18-95