CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75588

BIOEQUIVALENCY REVIEW(S)

(1)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-588 SPONSOR : Pharmaceutical Formulations, Inc.

DRUG AND DOSAGE FORM : Ibuprofen/Pseudoephedrine HCl Tablets

STRENGTH(S) : 200 mg/30 mg

TYPES OF STUDIES : Fasting and non-fasting

CLINICAL STUDY SITE(S) (

ANALYTICAL SITE(S) (

STUDY SUMMARY : Single-dose fasting and non-fasting studies are acceptable.

DISSOLUTION : Dissolution study is acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic __No__ New facility __No_ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : S. P. Shrivastava, Ph.D. BRANCH : II

INITIAL : _____ DATE : 5/14/99_____

TEAM LEADER : S. Nerurkar, Ph.D. BRANCH : II

INITIAL : /S/ DATE : 5/26/99

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : _____ DATE : 5/26/99

CC: ANDA 75-588
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/SShrivastava

Printed in final on 5/7/99

Endorsements: (Final with Dates)
HFD-655/ SShrivastava 5/26/99
HFD-655/ SNerurkar 5/26/97
HFD-650/ D. Conner for 5/26/99

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF)
   Clinical:
   Analytical:
   Submission date: 2/19/99
   Strengths: 200 mg/30 mg
   Outcome: AC

2. Amendment
   FOOD STUDY (STP)
   Clinical:
   Analytical:
   Submission date: 2/19/99
   Strengths: 200 mg/30 mg
   Outcome: AC

3. **Other (Diskette)**
   Submission date: 4/26/99
   Strengths: 200 mg/30 mg
   Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments: Studies acceptable.

Ibuprofen 200 mg and
Pseudoephedrine HCl 30 mg Tablets
ANDA 75-588
Reviewer: S.P. Shrivastava

Pharmaceut. Formulations, Inc.
Edison, NJ
Submission Date:
February 19, 1999
April 26, 1999

REVIEW OF TWO BIOEQUIVALENCE STUDIES

The firm has submitted an ANDA application for the OTC drug product mentioned above. It has conducted studies and submitted data for single-dose fasting study, single-dose nonfasting study, and dissolution testing.

The drug is indicated for temporary relief of symptoms associated with the common cold, sinusitis or flu including nasal congestion, headache, fever, body aches and pains. The reference listed drug for this product is Advil® Cold and Sinus, manufactured by Whitehall Laboratories, Inc.

II. BIOEQUIVALENCE STUDY UNDER FASTING CONDITIONS

A. Study Information

Protocol #	299-05; 4/17/98
IRB approval	R. Kilgore; 5/13//98
Consent Form Signed	Yes
Clinical Site	(
Principal Investigator	(
Clinical Manager	(
Analytical Facility	(
Analytical Manager	(
Study Dates	May 16 - May 25, 1998
Analysis Dates	May 28, 98-June 17, 1998
Storage Period	32 Days
Study Design	Randomized, two-way crossover design
Wash-out Period	7 Days between dosing
Subjects Enrolled	30 subjects enrolled; Age 18-43 years
Subjects: Sequence	AB: 1, 4, 6, 8, 10, 11, 14, 15, 17, 19, 21, 24, 27, 30, 31

Subjects: Sequence	BA: 2, 3, 5, 7, 9, 12, 13, 18, 20, 22, 23, 25, 28, 29, 32
Drop-outs:	29 completed the study
Treatment: Test	**A:** 2 x 200/30 mg; Lot #H79293; Lot size: 226,667; Private Formulations; Exp. Date:4/00; Assay: %; Content Uniformity: 100.4%
Treatment: Ref	**B:** 2 x 200/30 mg; Lot #3971328; Expiry Date: 3/1/99; Whitehall Labs., Assay: ; Content Unif: 101.
Formulation	See Section IV
Housing	Evening before dosing until last sampling (24 Hrs.)
Dosing	2 x 200/30 mg Dose after overnight fast, with 240 mL of water.
Sample Collection Time	Predose, and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 18 and 24 hours post-dose
Sample Storage Temp.	-20 ^{0} C
Method/Analyte(s)	
Internal Standard	
Protocol Deviations	None significant

B. Pre-Study Methods Validation: Ibuprofen

Linearity/No. Stds.	
Regression	
QC Samples	
Accuracy	
Precision (%CV)	
Recovery (%)	
Stability (%)	
Criteria for Rejection of Stds	
Batch Accept. Criteria	

C. Within Study Methods Validation:Ibuprofen

QC Samples	
Calibration Curves	
Reassays:	

D. Pre-Study Methods Validation: Pseudoephedrine

Linearity/No. Stds.	
Regression	
QC Samples	
Accuracy	
Precision (%CV)	
Recovery (%)	
Stability (%)	
Criteria for Rejection of Stds	
Batch Accept. Criteria	

E. Within Study Methods Validation: Pseudoephedrine

QC Samples	
Calibration Curves	
Reassays:	

Conclusion: Assay validation is acceptable.

F. Pharmacokinetics/Statistics: **Ibuprofen and Pseudoephedrine**

Mean plasma concentrations: Attachments 1-2 and Tables 1-2.
Pharmacokinetic parameters: Tables 3 and 4.

90% Confidence Intervals:	Ibuprofen	Pseudoephedrine
$LAUC_{0-t}$	96.92-104.1%	92.2-103.87
$LAUC_{0-inf}$	96.93-104.09%	91.62-103.38
LC_{max}	81.32-94.55%	91.6-101.65

G. Adverse Reactions: Following adverse reactions (number of subjects) were observed:

	Test	Ref
Sleepy	1	1
Lightheaded	1	1

H. Comments

1. The reviewer recalculated the pharmacokinetic parameters and 90% confidence intervals. The reported values are in good agreement with those obtained by the reviewer.

2. The elimination constants were calculated for all subjects appropriately.

3. There were no subjects with 0 hour drug level, no subjects with first scheduled post-dose time point as T_{max}, and no subjects with first measurable drug concentration as C_{max}.

4. The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits of 80-125%. There were no statistically significant period, sequence or treatment effects for any of these parameters (Tables 3, 4).

I. Conclusion: The fasting study is acceptable.

TABLE 1. MEAN PLASMA IBUPROFEN LEVELS FOR TEST AND REFERENCE PRODUCTS

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0,0	0.02,	0.12,	0.03,	0.14,	0.85,
,0.25	3.65,	5.14,	7.95,	7.89,	0.46,
,0.5	12.15,	9.95,	17.29,	12.41,	0.70,
,0.75	18.62,	10.87,	23.35,	12.28,	0.80,
,1	20.79,	9.96,	24.99,	11.81,	0.83,
,1.25	22.56,	10.44,	26.37,	10.75,	0.86,
,1.5	23.39,	10.75,	25.98,	9.24,	0.90,
,1.75	23.55,	11.13,	24.73,	7.66,	0.95,
,2	22.75,	10.04,	24.57,	7.48,	0.93,
,2.5	23.00,	6.33,	22.98,	7.22,	1.00,
,3	22.44,	5.65,	20.79,	6.12,	1.08,
,4	17.65,	5.27,	16.85,	6.87,	1.05,
,6	8.50,	3.64,	7.35,	3.10,	1.16,
,8	4.55,	2.21,	3.90,	1.91,	1.16,
,10	2.69,	1.78,	2.29,	1.29,	1.18,
,12	1.42,	1.04,	1.26,	0.91,	1.12,
,18	0.28,	0.47,	0.23,	0.37,	1.22,
,24	0.06,	0.20,	0.06,	0.20,	1.02,

TABLE 2. MEAN PLASMA PSEUDOEPHEDRINE LEVELS FOR TEST AND REFERENCE PRODUCTS

,	MEAN1	SD1	MEAN2	SD2	RMEAN12
,TIME HR					
,0	0.00,	0.00,	0.00,	0.00,	.,
,0.25	3.82,	9.23,	11.06,	17.86,	0.35,
,0.5	47.00,	40.54,	82.40,	49.30,	0.57,
,0.75	102.09,	56.43,	129.07,	42.46,	0.79,
,1	128.90,	61.11,	154.71,	36.04,	0.83,
,1.25	154.20,	60.56,	171.12,	31.34,	0.90,
,1.5	158.68,	54.89,	175.04,	24.10,	0.91,
,1.75	156.36,	48.94,	173.69,	26.14,	0.90,
,2	163.02,	47.96,	173.24,	25.47,	0.94,
,2.5	157.41,	35.28,	167.12,	27.98,	0.94,
,3	158.92,	26.89,	162.13,	24.31,	0.98,
,4	150.30,	23.93,	151.31,	29.66,	0.99,
,6	121.04,	24.99,	119.59,	23.76,	1.01,
,8	100.82,	20.08,	99.31,	23.76,	1.02,
,10	81.18,	19.37,	81.64,	24.79,	0.99,
,12	65.80,	18.28,	66.96,	21.49,	0.98,
,18	34.76,	12.77,	34.92,	15.40,	1.00,
,24	16.71,	9.91,	17.60,	11.09,	0.95,

Mean1/SD1= Test; Mean2/SD2= Reference

Table 3. General Linear Models Procedure
Least Squares Means: Ibuprofen PK Parameters
[A=Test, B=Ref]

TRT	AUC LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1 =LSMEAN2	90% CI
A	119.566670	4.585070	0.0001	0.9039	
B	119.189807	4.210467	0.0001		

TRT	CMAX LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1 =LSMEAN2	
A	31.9405662	2.1297426	0.0001	0.0083	
B	36.0299538	1.9557414	0.0001		

TRT	LAUC LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1 =LSMEAN2	
A	4.76024294	0.03226472	0.0001	0.8403	96.9-104.1
B	4.75581807	0.02962868	0.0001		

TRT	LCMAX LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1 =LSMEAN2	
A	3.44262987	0.06809373	0.0001	0.0080	81.3-94.6
B	3.57405813	0.06253043	0.0001		

TRT	AUCI LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1 =LSMEAN2	
A	121.181029	4.711985	0.0001	0.9151	
B	120.836499	4.275997	0.0001		

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1 =LSMEAN2	
A	4.77372946	0.03260892	0.0001	0.8420	96.9-104.1
B	4.76927111	0.02959170	0.0001		

Table 4. General Linear Models Procedure
Least Squares Means: Pseudoephedrine PK Data
[A=Test, B=Ref]

TRT	AUC LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	90% CI
A	1979.54130	95.06343	0.0001	0.4509	
B	2028.57192	87.29670	0.0001		

TRT	AUCI LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1 =LSMEAN2
A	2174.64245	109.83619	0.0001	0.3877
B	2239.65945	100.86251	0.0001	

TRT	CMAX LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1 =LSMEAN2
A	201.562254	9.098284	0.0001	0.4937
B	205.818063	8.354949	0.0001	

TRT	LAUC LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1 =LSMEAN2	
A	7.56774700	0.05381999	0.0001	0.5569	92.2-103.9
B	7.58933153	0.04942287	0.0001		

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1 =LSMEAN2	
A	7.66012606	0.05449844	0.0001	0.4665	91.6-103.4
B	7.68726145	0.05004589	0.0001		

TRT	LCMAX LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1 =LSMEAN2	
A	5.27923520	0.04698972	0.0001	0.2701	91.6-101.7
B	5.31490348	0.04315063	0.0001		

III. BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS

A. Study Information

Protocol #	299-04; 9/9/97
IRB approval	Constance M Johnson; 1/21/98
Consent Form Signed	Yes
Clinical Site	
Principal Investigator	
Clinical Manager	
Analytical Facility	
Analytical Manager	
Study Dates	10/8/97 - 10/16/97
Analysis Dates	November 5, 1997 - November 25, 1997
Storage Period	48 Days
Study Design	Randomized, three-way crossover design
Wash-out Period	7 Days between dosing
Subjects Enrolled	18 subjects enrolled; Age 20-52 years
Subjects: Sequence	ABC: 2, 9, 15; ACB: 6, 16; BAC: 3, 11, 14; BCA: 4, 8, 13: CAB: 5, 10, 17; CBA: 1, 7, 18
Drop-outs:	17 completed the study
Treatment: Test Fed	**A:** 2 x 200/30 mg; Lot #22453F/H79293; Lot size: 226,667; Exp. Private Formulations; Date:4/00; %; Content Uniformity: 100.4%
Treatment: Ref Fed	**B**: 2 x 200/30 mg; Lot #3971328; Expiry Date: 3/1/99; Whitehall Labs., Assay: %; Content Unif: 101.
Treatment: Test Fast	**B**: 2 x 200/30 mg; Lot #22453F/H79293; Expiry Date: None Private Formulations, Assay: Content Unif:
Formulation	See Section IV
Housing	Evening before dosing until last sampling (24 Hrs.)
Dosing	2 x 200/30 mg Dose after overnight fast, with 240 mL of water.
Sample Collection Time	Predose, and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 18 and 24 hours post-dose
Sample Storage Temp.	-20 ^{0} C

Method/Analyte(s)	
Internal Standard	
Protocol Deviations	None significant

B. Pre-Study Methods Validation: Ibuprofen

Linearity/No. Stds.	
Regression	
QC Samples	
Accuracy	
Precision (%CV)	
Recovery (%)	
Stability (%)	
Criteria for Rejection of Stds	
Batch Acceptance Criteria	

C. Within Study Methods Validation:Ibuprofen

QC Samples	
Calibration Curves	
Reassays:	

D. Pre-Study Methods Validation: Pseudoephedrine

Linearity/No. Stds.	
Regression	
QC Samples	

Accuracy	
Precision (%CV)	
Recovery (%)	
Stability (%)	
Criteria for Rejection of Stds	
Batch Acceptance Criteria	

Conclusion: Methods validation is acceptable.

E. Within Study Methods Validation: Pseudoephedrine

QC Samples	
Calibration Curves	
Reassays:	

F. Pharmacokinetics/Statistics

Mean plasma concentrations: Attachments 3-4 and Tables 5-6.
Pharmacokinetic parameters: Tables 7 and 8.

LS Mean Ratios (Nonfasting):	**Ibuprofen**	**Pseudoephedrine**
$LAUC_{0-t}$	1.005	1.038
$LAUC_{0-inf}$	1.004	1.044
LC_{max}	1.039	1.036

TABLE 5. MEAN PLASMA IBUPROFEN LEVELS FOR TEST AND REFERENCE PRODUCTS (N =17)

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12	RMEAN13	RMEAN23
,0	0.00,	0.00,	0.00,	0.00,	0.07,	0.29,	0.00 .,	0.00,	0.00,
,0.25	1.45,	3.29,	3.20,	8.65,	2.79,	4.09,	0.45,	0.52,	1.15,
,0.5	5.02,	8.67,	7.73,	11.38,	14.54,	9.66,	0.65,	0.35,	0.53,
,0.75	7.79,	10.78,	10.81,	11.43,	22.23,	13.49,	0.72,	0.35,	0.49,
,1	11.15,	12.58,	13.55,	11.64,	25.25,	14.57,	0.82,	0.44,	0.54,
,1.25	14.33,	12.04,	15.79,	11.14,	25.99,	13.35,	0.91,	0.55,	0.61,
,1.5	16.63,	11.53,	18.24,	9.55,	25.79,	12.26,	0.91,	0.64,	0.71,
,1.75	18.08,	9.62,	19.60,	9.01,	25.14,	11.08,	0.92,	0.72	0.78,
,2	20.56,	8.85,	20.64,	9.04,	23.83,	10.11,	1.00,	0.86,	0.87,
,2.5	20.41,	7.26,	19.74,	7.11,	21.41,	8.47,	1.03,	0.95,	0.92,
,3	19.89,	6.22,	19.34,	5.83,	20.74,	6.96,	1.03,	0.96,	0.93,
,4	18.73,	5.10,	16.98,	4.48,	16.53,	6.23,	1.10,	1.13,	1.03,
,6	10.28,	2.95,	10.19,	4.09,	8.72,	4.50,	1.01,	1.18,	1.17,
,8	5.22,	2.04,	5.22,	2.52,	4.41,	2.12,	1.00,	1.18,	1.18,
,10	3.22,	1.81,	3.22,	1.88,	2.56,	1.53,	1.00,	1.26,	1.26,
,12	1.71,	1.09,	1.73,	1.03,	2.24,	4.15,	0.99,	0.76,	0.77,
,18	0.36,	0.41,	0.40,	0.49,	0.37,	0.78,	0.90,	0.96,	1.07,
,24	0.04,	0.12,	0.05,	0.14,	0.07,	0.24,	0.94,	0.59,	0.63,

TABLE 6. MEAN PLASMA PSEUDOEPHEDRINE LEVELS FOR TEST AND REFERENCE PRODUCTS (N=17)

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12	RMEAN13	RMEAN23
0,0	0.00,	0.00,	0.00,	0.00,	0.00,	0.00,	0.00	0.00	0.00
,0.25	3.55,	8.08,	4.35,	13.64,	0.93,	3.83,	0.82,	3.82,	4.68,
,0.5	17.15,	30.98,	28.62,	42.06,	56.83,	36.71,	0.60,	0.30,	0.50,
,0.75	45.94,	47.62,	57.93,	47.80,	134.87,	57.70,	0.79,	0.34,	0.43,
,1	73.27,	62.93,	88.69,	56.13,	163.47,	56.59,	0.83,	0.45,	0.54,
,1.25	101.11,	67.15,	111.66,	61.37,	183.55,	52.69,	0.91,	0.55,	0.61,
,1.5	118.24,	64.60,	134.11,	57.80,	188.06,	43.71,	0.88,	0.63,	0.71,
,1.75	139.51,	63.81,	159.51,	49.31,	191.86,	37.42,	0.87,	0.73,	0.83,
,2	155.25,	55.57,	173.64,	45.41,	196.13,	30.42,	0.89,	0.79,	0.89,
,2.5	186.31,	49.49,	193.92,	37.26,	197.61,	26.48,	0.96,	0.94,	0.98,
,3	200.29,	41.82,	195.70,	34.86,	195.88,	24.01,	1.02,	1.02,	1.00,
,4	205.17,	32.25,	189.44,	35.55,	184.03,	26.19,	1.08,	1.11,	1.03,
,6	166.94,	34.26,	157.16,	33.51,	151.79,	26.35,	1.06,	1.10,	1.04,
,8	140.22,	35.12,	132.13,	36.71,	134.09,	32.64,	1.06,	1.05,	0.99,
,10	121.52,	34.20,	116.80,	39.30,	117.99,	33.79,	1.04,	1.03,	0.99,
,12	94.38,	30.59,	90.23,	33.03,	96.23,	33.68,	1.05,	0.98,	0.94,
,18	48.33,	20.97,	46.31,	21.68,	47.81,	20.39,	1.04,	1.01,	0.97,
,24	24.41,	15.79,	21.74,	15.13,	24.39,	15.58,	1.12,	1.00,	0.89,

Mean1/SD1= Test fed; Mean2/SD2=Reference Fed; Mean3/SD3=TestFast

Table 7. General Linear Models Procedure
Least Squares Means: Ibuprofen

[A=Test Fed, B=Ref. Fed, C=Test Fast]

TRT	AUC LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3	Ratio A/B
A	123.172119	2.159685	0.0001	1	.	0.9625	0.0003	1.000
B	123.316582	2.159685	0.0001	2	0.9625	.	0.0004	
C	135.489582	2.159685	0.0001	3	0.0003	0.0004	.	

TRT	AUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3	
A	125.349209	2.198240	0.0001	1	.	0.9373	0.0005	0.998
B	125.594933	2.198240	0.0001	2	0.9373	.	0.0007	
C	137.376484	2.198240	0.0001	3	0.0005	0.0007	.	

TRT	CMAX LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3	
A	26.4456944	1.4439510	0.0001	1	.	0.7714	0.0126	1.023
B	25.8490278	1.4439510	0.0001	2	0.7714	.	0.0061	
C	31.8486111	1.4439510	0.0001	3	0.0126	0.0061	.	

TRT	LAUC LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3	
A	4.79812314	0.01724615	0.0001	1	.	0.8394	0.0005	1.005
B	4.79315386	0.01724615	0.0001	2	0.8394	.	0.0003	
C	4.89273580	0.01724615	0.0001	3	0.0005	0.0003	.	

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3	
A	4.81605138	0.01721365	0.0001	1	.	0.8631	0.0008	1.004
B	4.81183121	0.01721365	0.0001	2	0.8631	.	0.0005	
C	4.90667702	0.01721365	0.0001	3	0.0008	0.0005	.	

TRT	LCMAX LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3	
A	3.23496778	0.05220671	0.0001	1	.	0.6095	0.0174	1.039
B	3.19697550	0.05220671	0.0001	2	0.6095	.	0.0049	
C	3.42029853	0.05220671	0.0001	3	0.0174	0.0049	.	

Table 8. General Linear Models Procedure
Least Squares Means: Pseudoephedrine
[A=Test Fed, B=Ref. Fed, C=Test Fast]

TRT	AUC LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3	Ratio A/B
A	2315.36397	53.05350	0.0001	1	.	0.3474	0.5221	1.032
B	2243.97100	53.05350	0.0001	2	0.3474	.	0.1195	
C	2363.80616	53.05350	0.0001	3	0.5221	0.1195	.	

TRT	AUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3	
A	2568.15369	60.76027	0.0001	1	.	0.2746	0.6594	1.039
B	2472.83360	60.76027	0.0001	2	0.2746	.	0.1297	
C	2606.28065	60.76027	0.0001	3	0.6594	0.1297	.	

TRT	CMAX LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3	
A	216.177315	3.797208	0.0001	1	.	0.1812	0.9173	1.035
B	208.850231	3.797208	0.0001	2	0.1812	.	0.2159	
C	215.616898	3.797208	0.0001	3	0.9173	0.2159	.	

TRT	LAUC LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3	
A	7.72402928	0.02249150	0.0001	1	.	0.2467	0.5084	1.038
B	7.68656792	0.02249150	0.0001	2	0.2467	.	0.0740	
C	7.74525146	0.02249150	0.0001	3	0.5084	0.0740	.	

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3	
A	7.82143533	0.02292492	0.0001	1	.	0.1918	0.6784	1.044
B	7.77828423	0.02292492	0.0001	2	0.1918	.	0.0896	
C	7.83496576	0.02292492	0.0001	3	0.6784	0.0896	.	

TRT	LCMAX LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3	
A	5.36867472	0.01828276	0.0001	1	.	0.1841	0.9051	1.036
B	5.33364030	0.01828276	0.0001	2	0.1841	.	0.2249	
C	5.36557454	0.01828276	0.0001	3	0.9051	0.2249	.	

G. Adverse Reactions: Following adverse reactions (number of subjects) were observed:

	A (Test Fed)	Ref Fed	Test Fast
Tired	0	2	0

H. Comments

1. The reviewer ran ANOVA on pharmacokinetic parameters. The reported values are in good agreement with those obtained by the reviewer.

2. The elimination constants were calculated for all subjects appropriately.

3. There were no subjects with 0 hour drug level, no subjects with first scheduled post-dose time point as T_{max}, and no subjects with first measurable drug concentration as C_{max}.

4. The Test/Reference ratios for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits of 80-120%. The were no statistically significant period, sequence or treatment effects for any of these parameters (Tables 7, 8)

I. Conclusion: The non-fasting study is acceptable.

IV. FORMULATION

Table 9. Test Product Formulation (mg/Tablet)

Ingredients/Strength	**200 mg**
Core:	
Ibuprofen, USP	
Pseudoephedrine, USP	
Pregelatinized starch, NF	
Silicone Dioxide, NF	
Stearic Acid, NF	
Microcrystalline Cellulose, NF 101	
Total (weights added)	**376.4**
Coating:	
Carnauba wax, NF	
G. Total (Weights added)	**388.5**

Tablet Appearance: Red, oval/round (details about scoring and imprint not available).

V. *IN VITRO* DISSOLUTION TESTING

The dissolution testing was done by USP method as follows (Tables 10-13).

DISSOLUTION INFORMATION

ANALYTE:	Ibuprofen/Pseudoephedrine HCl
STRENGTH AND UNIT:	200/30 mg 12 each
DISSOLUTION METHOD:	USP
DISSOLUTION MEDIUM:	Phosphate Buffer, pH 7.2
VOLUME:	900 mL
DISSOLUTION APPARATUS:	2
RPM:	50
ASSAY METHOD:	

[1]Used in granulation of the product, but is not present in the finished product.

[2]Used in coating of the product, but is not present in the finished product.

DISSOLUTION SPECIFICATION: NLT [illegible]% (Q) in 30 and 45 minutes, respectively for Ibuprofen and Pseudoephedrine

Conclusion: Product meets the *in vitro* dissolution specifications.

Ibuprofen **TABLE 10**

	Test Lot #H79292 (9/30/97)			Ref Lot #3971328 (1/29/99)		
Time(MIN)	MEAN	RANGE	CV%	MEAN	RANGE	CV%
10	95.4		3.3	85.4		2.3
20	97.2		1.8	91.5		3.1
30	95.8		1.6	93.9		1.9
45	94.4		1.5	96.4		1.3

Similarity Factor (F2) = 61.1

Pseudoephedrine **TABLE 11**

	Test Lot Round #H79292 (Test Date 9/29/97)			Ref Lot #3971328 (1/29/99)		
Time(MIN)	MEAN	RANGE	CV%	MEAN	RANGE	CV%
10	102		3.9	90.0		6.4
20	99.4		3.3	96.5		5.4
30	99.9		3.8	98.9		3.1
45	98.6		3.2	100.9		2.8

Similarity Factor (F2) = 59.8

Ibuprofen **TABLE 12**

	Test Lot Oval #H79293 (Test Date 9/29/97)			Ref Lot #3981283 (2/1/99)		
Time(MIN)	MEAN	RANGE	CV%	MEAN	RANGE	CV%
10	93.6		6.0	74.7		5.3
20	97.6		1.2	92.5		2.3
30	96.4		1.3	94.9		1.0
45	94.8		1.1	96.9		1.1

Similarity Factor (F2) = 50.2

Pseudoephedrine **TABLE 13**

	Test Lot Round #H79293 (Test Date 9/29/97)			Ref Lot #3981283 (2/1/99)		
Time(MIN)	MEAN	RANGE	CV%	MEAN	RANGE	CV%
10	105.1		2.9	96.0		3.9
20	102.9		1.7	100.2		2.7
30	104.7		2.0	100.7		2.7
45	105.7		3.6	102.0		2.6

Similarity Factor (F2) = 62.7

VI. RECOMMENDATIONS

1. The bioequivalence study conducted under fasting conditions by Pharmaceutical Formulations on its ibuprofen 200 mg/pseudoephedrine HCl 30 mg tablets, Lot #H79293 comparing it to Advil® Cold and Sinus tablets, 200 mg/30 mg, Lot #3971328 manufactured by Whitehall Laboratories, is acceptable to the Division of Bioequivalence. The study demonstrates that Pharmaceutical Formulations' ibuprofen/pseudoephedrine HCl, 200 mg/30 mg tablets, is bioequivalent to the reference product, Advil®, 200 mg/30 mg tablets manufactured by Whitehall Labs.

2. The bioequivalence study conducted under non-fasting conditions by Pharmaceutical Formulations on its ibuprofen 200 mg/pseudoephedrine HCl 30 mg tablets, Lot #H79293/22452F comparing it to Advil® Cold and Sinus tablets, 200 mg/30 mg, Lot #3971328 manufactured by Whitehall Laboratories, is acceptable to the Division of Bioequivalence. The study demonstrates that Pharmaceutical Formulations' ibuprofen/pseudoephedrine HCl, 200 mg/30 mg tablets, is similar to the reference product, Advil®, 200 mg/30 mg tablets manufactured by Whitehall Labs.

3. The dissolution testing conducted by the firm on its ibuprofen 200 mg/pseudoephedrine HCl 30 mg tablets, Lot #H79293/22452F comparing it to Advil® Cold and Sinus tablets, 200 mg/30 mg, Lot #3971328 manufactured by Whitehall Laboratories, is acceptable

4. From bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing, and the application is acceptable.

5. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of

phosphate buffer, pH 7.2 at 37^{0}C using apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

Not less than ' % of the labeled amount of ibuprofen and pseudoephedrine hydrochloride in the dosage form are dissolved in 30 and 45 minutes, respectively.

/S/

S.P. Shrivastava, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NURKAR
FT INITIALED S.NURKAR /S/ Date 5/26/99

Concur: /S/ Date 5/26/99

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

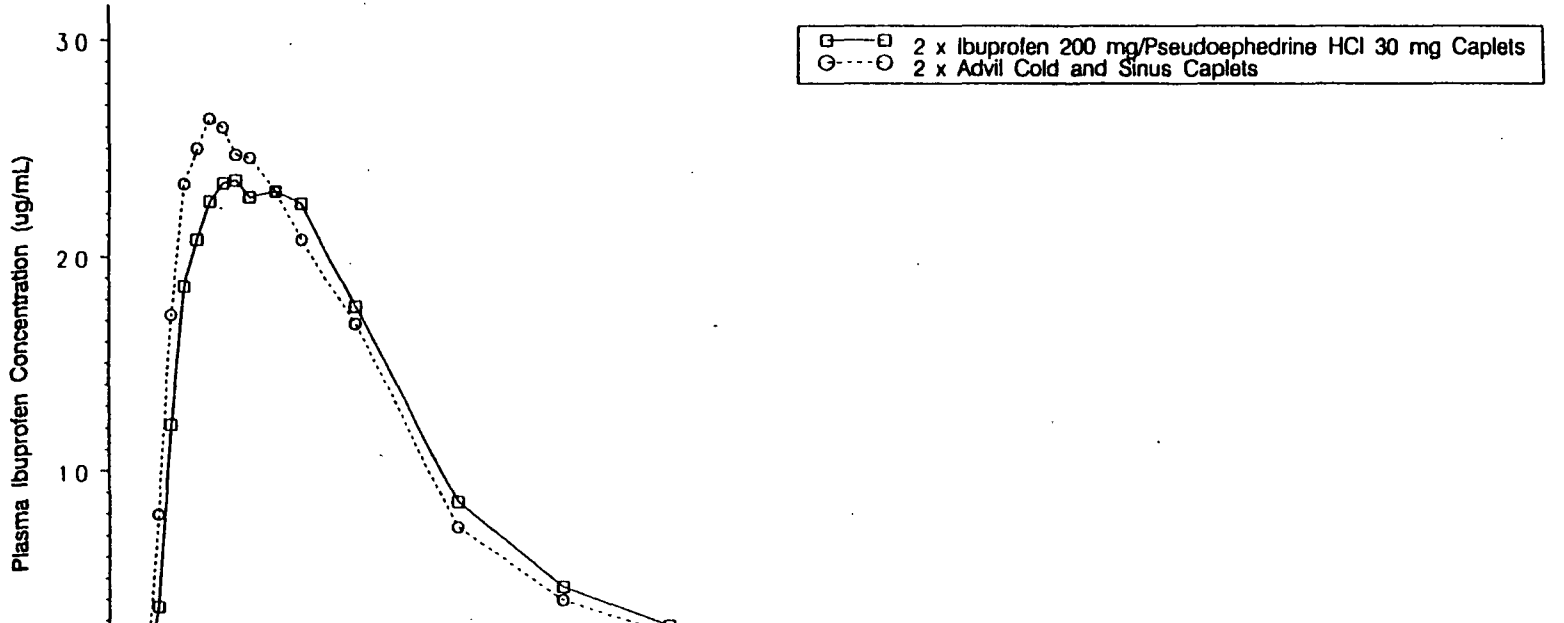
Attachments-4
SPS/sps/5-7-99/75588SDW.299

cc: ANDA #75588 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

Figure 2

Mean Plasma Ibuprofen Concentrations Versus Time

Linear Scale



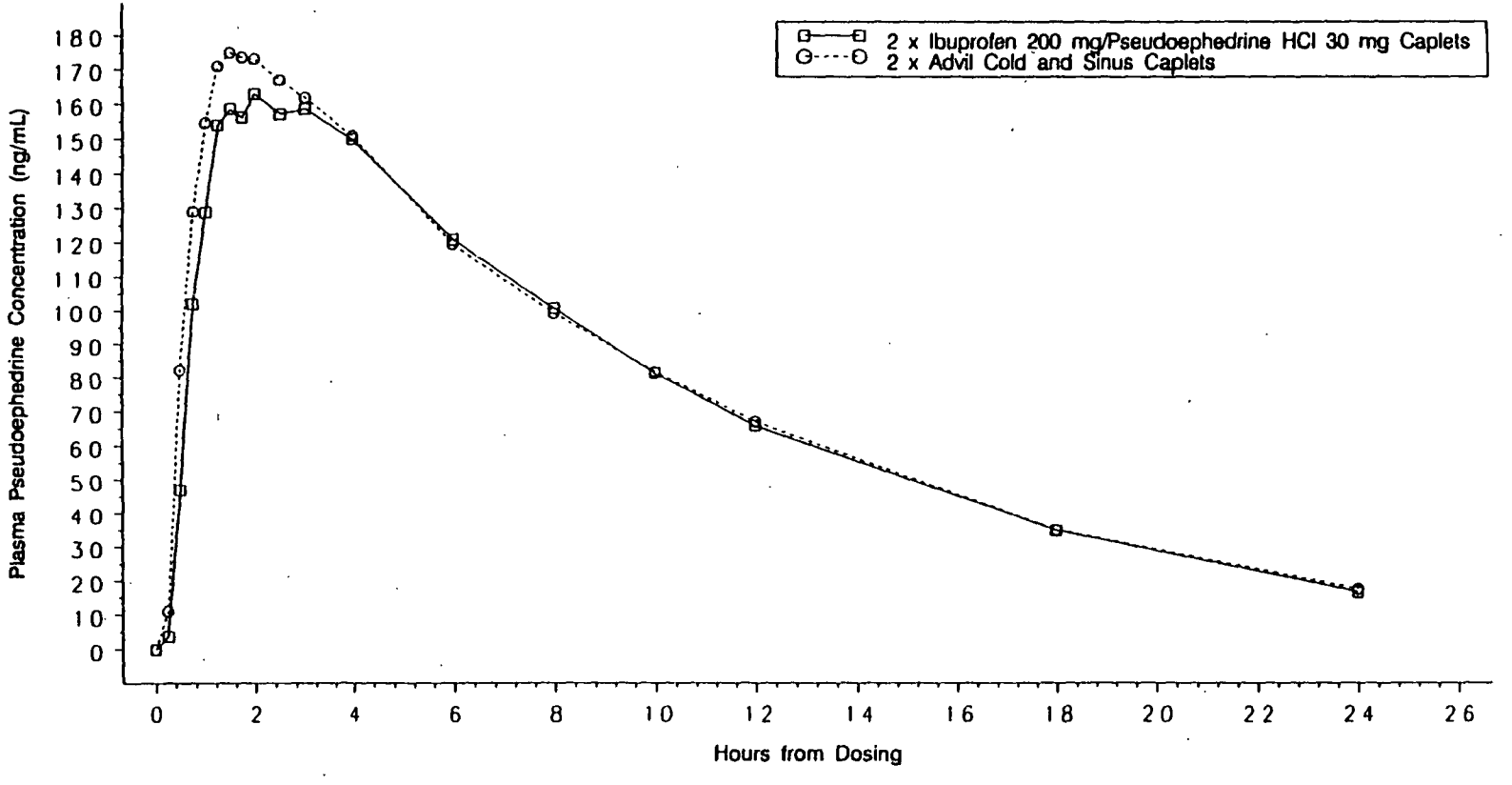
000724

Attachment-1

Figure 35

Mean Plasma Pseudoephedrine Concentrations Versus Time

Linear Scale



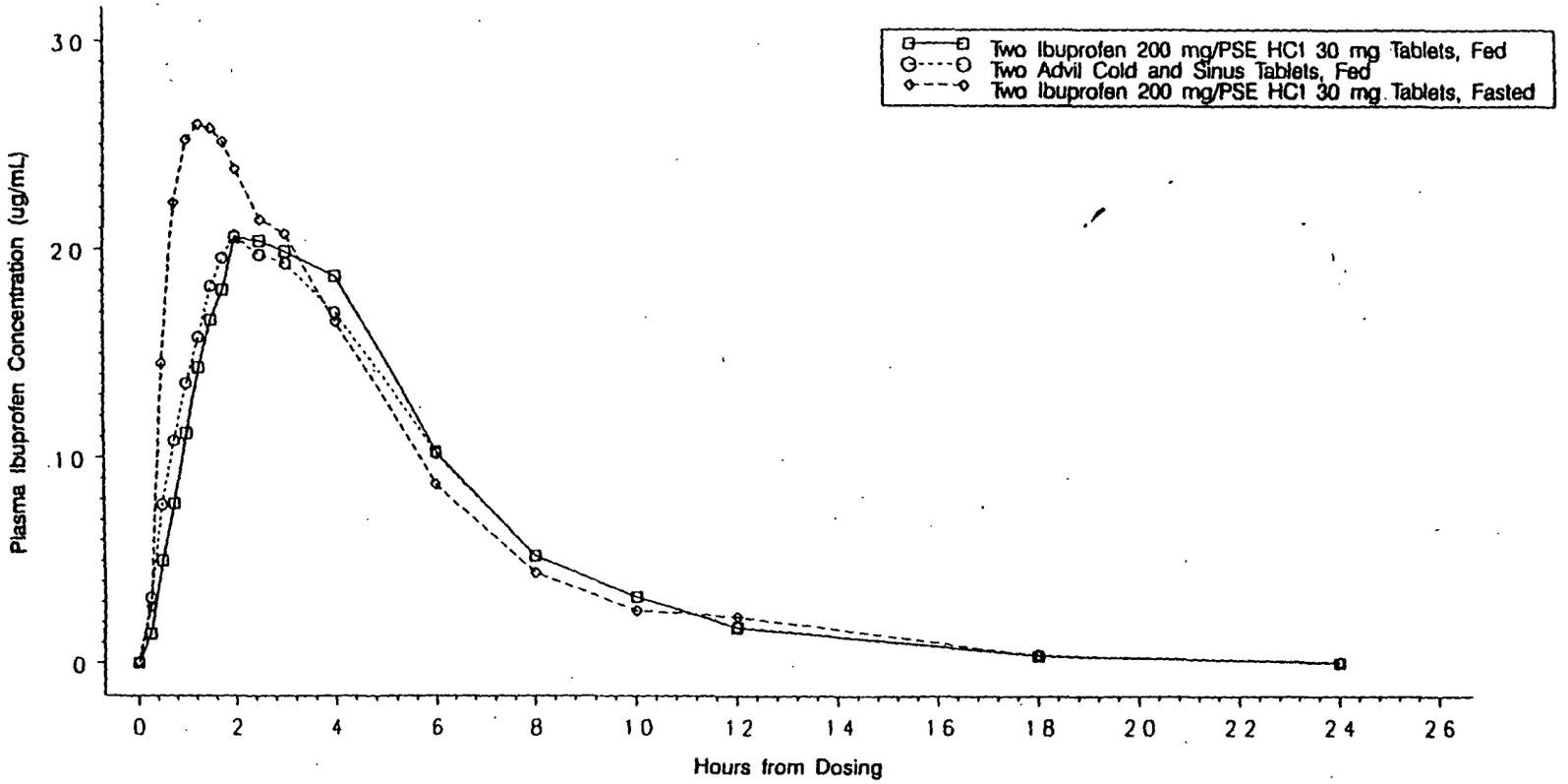
000757

Attachment - 2

Figure 2

Mean Plasma Ibuprofen Concentrations Versus Time

Linear Scale



000123

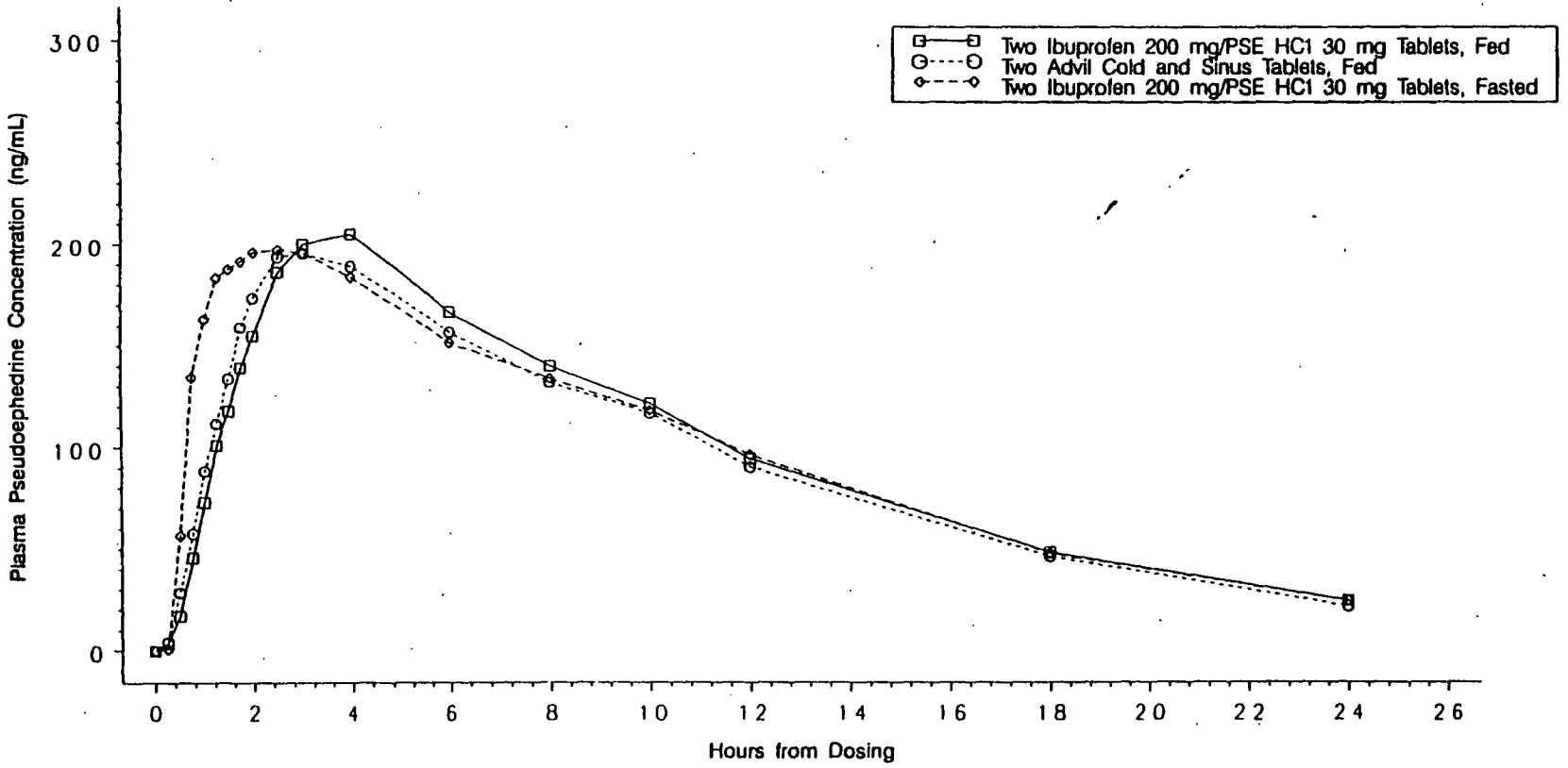
Attachment - 3

Pharmaceutical Formulations
Ibuprofen/Pseudoephedrine Protocol No. 229-04
Harris Laboratories Project MDS Harris Project 19747

Figure 22

Mean Plasma Pseudoephedrine Concentrations Versus Time

Linear Scale



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Attachment - 4

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-588 APPLICANT: Pharmaceutical Formulations

DRUG PRODUCT: Ibuprofen/Pseudoephedrine Tablets, 200 mg/30 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23, Supplement 3, 1995.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision aft 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/

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