CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75203

BIOEQUIVALENCY REVIEW(S)

Propafenone HCl
150, 225 and 300 mg Tablets
ANDA #75-203
Reviewer: Moheb H. Makary
W. 75203SDW.D98

Watson Laboratories, Inc.
Corona, CA
Submission Date:
December 28, 1998
March 16, 1999

Review of an Amendment

I. Objective:

The firm has submitted a bioequivalence study under fasting conditions on its Propafenone HCl 225 mg Tablet comparing the test product to Knoll's Rythmol^{R} 225 mg Tablets.

II. Background:

The firm has submitted a second in vivo bioequivalence study under fasting conditions on its Propafenone HCl 225 mg Tablet as a response to the Agency's letter dated August 19, 1998.

In the original ANDA (submission dated September 11, 1997), the single-dose bioequivalence study under fasting conditions, conducted on the firm's Propafenone HCl 300 mg Tablet was found unacceptable by the Division of Bioequivalence. The 90% confidence interval for log-transformed Cmax was %, which is outside the acceptable 80-125% range. The single-dose bioequivalence study of Propafenone HCl 225 mg Tablets administered under fasting and nonfasting conditions was found acceptable.

In the Agency's letter dated August 19, 1998, the Division of Bioequivalence agreed with the firm to conduct the second bioequivalence study under fasting conditions on the lower strength of Propafenone HCl Tablets, 225 mg, for safety reasons.

The same lot of Propafenone HCl 225 mg Tablet that was given in the fasting and nonfasting study was also administered in the new fasting study.

III. Study #98091 for Single-Dose, 4-way Crossover Study Replicate Design of Propafenone HCl Tablets, 225 mg, Under Fasting Conditions

Objective: The objective of the study was to determine the bioequivalence of the test product Propafenone HCl 225 mg Tablet versus Knoll's Rythmol^{R} 225 mg Tablet, under fasting conditions.

Clinical site:

Analytical site:

Sponsor:	Watson Laboratories, Inc.
Study design:	Open-label, single-dose, fasted, randomized, four-period crossover replicate design. Subjects were randomized into two dosing sequences ABAB and BABA. Sequence 1: ABAB, subjects #3, 4, 5, 8, 9, 13, 14, 15, 17, 22, 24, 26, 29, 30, 32, 33, 34, 36 Sequence 2: BABA, subjects #1, 2, 6, 7, 10, 11, 12, 16, 18, 19, 20, 21, 23, 25, 27, 28, 31, 35 A = Test product B = Reference product
Dosing dates:	August 1, 1998 August 8, 1998 August 15, 1998 August 22, 1998
Analytical Date:	From September 2 to October 13, 1998
Subjects selection:	Thirty-six (36) male subjects were enrolled in the study. A total of thirty-four subjects completed the study. Selection criteria listed in Vol. 3.1, page 044.

Dose and treatment: A. 1 x 225 mg Propafenone HCl Tablet, lot #R77096, lot size Tablets, potency 98.9%, content uniformity 99.4% (%CV=1.4), manufactured by Watson Laboratories, under fasting conditions.

B. 1 x 225 mg Rythmol Tablet, lot #23000076, potency 97.8%, content uniformity 99.6% (%CV=1.3), Exp. 9/2000, manufactured by Knoll, under fasting conditions.

Food and fluid intake: Subjects were required to fast overnight prior to and 4 hours after drug administration. Subjects received identical standardized meals for lunch at 4 hours post-dose, supper at 10 hours post-dose, a snack at 14 hours post-dose and breakfast at 24 hours post-dose. Water was allowed ad lib. from 1 hour before dosing until 2 hours after dosing except for 240 mL water administered with the dose.

Safety Monitoring: Vital signs including blood pressure and heart rate were obtained prior to drug administration and at 1, 2, 3, 4, 6, 8, 12 and 36 hours following dose administration.
Electrocardiograms were obtained on each subject within one hour prior to dosing, and within 30 minutes prior to, or post, blood draw at post-dose hours 6, 12 and 24.

Blood samples: Blood samples were collected at 0 (pre-dose) and at 0.33, 0.66, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 30, 36, 48, 60 and 72 hours post-dose. Whole blood samples were centrifuged at room temperature for 15 minutes at 3400 rpm, and the resultant plasma from each tube was decanted into an individual pre-labeled polypropylene screw cap tube. Plasma samples were immediately frozen at -20 ^{o}C until shipment to the

Analytical Methodology

Statistical Analysis:

Statistical analysis was performed on propafenone and its metabolites 5-hydroxypropafenone and N-depropylpropafenone data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The two one-sided test was used to estimate the 90% confidence intervals.

IV. In Vivo Results:

A total of 36 subjects were entered and 34 subjects completed the study. Subject #14 dropped prior to period II dosing, subject #28 dropped prior to period IV dosing. All of the adverse events which occurred during the study are summarized in page 021, Vol. 3.1. All adverse events were mild or moderate. No serious adverse events occurred during the study.

The mean plasma concentrations and pharmacokinetic parameters for propafenone, 5-hydroxypropafenone and N-depropylpropafenone are summarized in Tables I, II and III, respectively.

Table I. Mean Plasma Propafenone Concentrations (CV%)

Time (hours)	Reference Treatment B1 Mean (ng/ml)	Reference Treatment B1 CV (%)	Reference Treatment B2 Mean (ng/ml)	Reference Treatment B2 CV (%)	Test Treatment A1 Mean (ng/ml)	Test Treatment A1 CV (%)	Test Treatment A2 Mean (ng/ml)	Test Treatment A2 CV (%)	Ratio (A1+A2/B1+B2)
0.00	0.000	0%	0.000	0%	0.000	0%	0.000	0%	
0.33	2.94	255.9%	2.13	148.2%	3.49	147.9%	5.66	193.4%	1.80
0.66	35.1	147.7%	38.3	109.5%	34.4	104.1%	49.9	139.7%	1.15
1.00	85.5	104.5%	99.5	102.7%	105	83.2%	111	90.7%	1.16
1.25	123	92.1%	133	84.9%	142	84.8%	153	77.0%	1.15
1.50	143	80.5%	150	77.8%	151	84.2%	158	76.3%	1.06
2.00	159	62.0%	176	73.1%	185	101.80%	194	93.2%	1.13
2.50	156	61.1%	179	77.9%	172	86.3%	191	105.6%	1.08
3.00	170	86.4%	184	91.9%	154	90.0%	187	102.7%	0.96
3.50	149	98.2%	171	100.6%	142	92.4%	176	97.5%	1.00
4.00	143	110.8%	163	106.6%	126	94.1%	162	106.4%	0.94
5.00	118	134.3%	127	121.6%	117	129.0%	131	118.9%	1.01
6.00	93.9	150.5%	95.7	134.3%	106	174.3%	98.2	133.1%	1.08
8.00	66.0	184.7%	69.8	161.8%	73.4	187.3%	72.4	161.7%	1.07
12.0	35.4	239.5%	32.6	219.9%	36.9	229.7%	32.8	208.1%	1.03
16.0	22.0	263.1%	22.8	253.0%	23.9	246.5%	21.1	228.4%	1.00
24.0	11.0	335.7%	12.2	329.3%	10.7	308.6%	10.5	310.1%	0.91
30.0	7.69	366.8%	8.06	360.3%	7.23	351.5%	7.07	336.2%	0.91
36.0	4.78	398.2%	5.74	387.4%	4.75	382.4%	4.55	362.6%	0.88
48.0	2.40	432.8%	2.36	419.6%	1.99	417.9%	2.46	424.7%	0.94
60.0	1.05	427.6%	1.20	418.0%	0.91	415.7%	1.05	409.9%	0.87
72.0	0.646	462.8%	0.619	437.3%	0.54	443.6%	0.574	417.2%	0.88

	Test A	Reference B	T/R	90% CI
AUC(0-t) (ng.hr/mL)	1560 (147)	1530 (154)	1.02	
AUCinf (ng.hr/mL)	1580 (147)	1550 (154)	1.02	
Cmax(ng/mL)	249 (87)	237 (74)	1.05	
Tmax(hr)	3.49	2.34		
T1/2 (hr)	2.98	3.31		
Kel (1/hr)	0.25	0.28		
LnAUC(0-t)				93.3-115.0%
LnAUCinf				93.9-115.0%
LnCmax				89.3-114.0%

1. For propafenone, means for AUC(0-t), AUCinf and Cmax values were 2.0%, 1.9% and 5.1% higher, respectively, for the test product than for the reference product. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data.

2. The mean propafenone plasma levels peaked at 2 hours for the test product in both treatments (A1&A2) and at 3 hours

for the reference product in both treatments (B1&B2), following their administration under fasting conditions.

3. Additional analysis of variance was performed by Shan Sun, Ph.D. (Mathematical Statistician, QMR), after employing the following model using SAS^R Proc Mixed:

Y = sequence period treat/ddfm =satterth;

The results of Dr. Sun's analysis are very close to that of the sponsor for propafenone, 5-hydroxypropafenone and N-depropylpropafenone (plesea see the statistical report attached).

Table II. Mean Plasma 5-Hydroxypropafenone Concentrations (CV%)

Time (hours)	Reference Treatment B1		Reference Treatment B2		Test Treatment AI		Test Treatment A2		Ratio (AI+A2/BI+B2)
	Mean (ng/ml)	CV (%)	Mean (ng/ml)	CV (%)	Mean (ng/ml)	CV (%)	Mean (ng/ml)	CV (%)	
0.00	0.000	0%	0.000	0%	0.000	0%	0.000	0%	
0.33	2.19	273.5%	2.16	166.9%	3.30	186.3%	6.11	191.6%	2.16
0.66	39.2	113.1%	45.3	93.6%	42.3	95.5%	57.3	107.4%	1.18
1.00	85.6	84.7%	94.0	80.0%	97.1	67.5%	104	76.9%	1.12
1.25	111	79.5%	111	69.6%	113	59.1%	119	66.5%	1.05
1.50	121	68.1%	117	59.8%	114	55.6%	118	58.8%	0.97
2.00	121	51.4%	116	51.3%	118	46.4%	121	49.9%	1.01
2.50	111	42.7%	106	52.8%	106	52.3%	105	49.2%	0.97
3.00	97.2	44.9%	95.9	52.8%	88.5	48.8%	97.7	49.2%	0.96
3.50	75.8	44.0%	81.1	51.1%	76.2	46.9%	89.0	47.6%	1.05
4.00	66.2	47.7%	73.8	49.1%	65.8	51.3%	76.9	49.4%	1.02
5.00	54.7	49.4%	59.4	51.3%	54.8	51.5%	62.4	50.0%	1.03
6.00	42.2	60.0%	43.4	60.5%	43.1	66.8%	46.5	62.8%	1.05
8.00	29.8	67.8%	32.2	63.6%	31.2	74.6%	34.1	69.8%	1.05
12.0	16.7	98.0%	16.6	82.8%	18.3	115.8%	17.1	95.1%	1.06
16.0	11.6	96.7%	12.2	100.5%	12.8	110.9%	12.5	96.6%	1.06
24.0	6.05	115.6%	6.45	100.3%	6.51	117.9%	6.67	93.5%	1.05
30.0	3.98	154.8%	3.95	137.6%	4.45	136.1%	4.15	139.5%	1.09
36.0	1.62	233.4%	1.97	194.0%	1.98	206.1%	1.88	188.3%	1.07
48.0	0.67	260.7%	0.60	258.1%	0.63	259.8%	0.69	255.3%	1.04
60.0	0.15	410.2%	0. 16	408.3%	0.22	333.5%	0.15	408.6%	1 19
72.0	0.060	583.1%	0.00	0%	0.00	0%	0.00	0%	0.00

	Test A	Reference B	T/R	90% CI
AUC(0-t) (ng.hr/mL)	832 (52)	803 (51)	1.04	
AUCinf (ng.hr/mL)	870 (50)	839 (49)	1.04	
Cmax(ng/mL)	160 (41)	159 (42)	1.01	
Tmax(hr)	2.18	2.16		

T1/2 (hr)	8.93	8.80	
Kel (1/hr)	0.082	0.085	
LnAUC(0-t)			99.0-109%
LnAUCinf			99.3-109%
LnCmax			93.6-109%

1. For 5-hydroxypropafenone, means for AUC(0-t), AUCinf and Cmax values were 3.6%, 3.7% and 0.6% higher, respectively, for the test product than for the reference product. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data.

2. The mean 5-hydroxypropafenone plasma levels peaked at 1.5 hours for the reference product in both treatments (B1&B2) and at 2 hours for the test product in both treatments (A1&A2), following administration of propafenone tablet, 225 mg, under fasting conditions.

Table III. Mean Plasma N-Depropylpropafenone Concentrations (CV%)

Time (hours)	Reference Treatment B1		Reference Treatment B2		Test Treatment AI		Test Treatment A2		Ratio (AI+A2/BI+B2)
	Mean (ng/ml)	CV (%)	Mean (ng/ml)	CV (%)	Mean (ng/ml)	CV (%)	Mean (ng/ml)	CV (%)	
0.00	0.000	0%	0.000	0%	0.000	0%	0.000	0%	
0.33	0.000	0%	0.000	0%	0.0380	406.3%	0.0651	412.6%	
0.66	1.13	157.3%	1.30	108.8%	1.24	117.9%	1.69	136.0%	1.21
1.00	3.82	114.9%	4.44	106.7%	4.59	84.1%	5.00	90.1%	1.16
1.25	5.43	96.5%	5.97	84.5%	6.49	72.7%	6.77	77.1%	1.16
1.50	6.89	78.2%	7.34	74.1%	6.90	63.4%	7.33	60.8%	1.00
2.00	8.18	49.0%	8.59	53.7%	8.59	55.5%	8.94	53.2%	1.05
2.50	8.65	37.3%	9.13	56.1%	9.25	54.7%	9.43	55.8%	1.05
3.00	9.19	36.4%	9.78	54.8%	9.18	53.9%	9.78	50.1%	1.00
3.50	8.74	39.1%	9.21	58.6%	8.74	46.3%	10.06	51.3%	1.05
4.00	8.39	45.1%	9.24	55.6%	8.35	51.4%	9.39	55.5%	1.01
5.00	7.97	50.5%	8.85	60.7%	7.79	56.6%	8.99	63.6%	1.00
6.00	7.16	63.5%	7.68	75.2%	7.31	65.9%	7.82	75.4%	1.02
8.00	5.87	83.2%	6.82	83.3%	6.30	83.4%	6.81	84.0%	1.03
12.0	3.68	121.9%	3.93	112.4%	4.02	118.6%	3.92	112.0%	1.04
16.0	2.98	134.8%	3.24	141.9%	3.12	145.2%	3.01	131.6%	0.99
24.0	1.52	178.5%	1.77	187.7%	1.57	171.3%	1.55	159.4%	0.95
30.0	0.924	231.5%	0.997	219.4%	0.942	223.3%	0.955	219.0%	0.99
36.0	0.439	320.9%	0.563	285.4%	0.527	280.7%	0.536	259.6%	1.06
48.0	0.184	367.1%	0.207	355.3%	0.218	280.5%	0.182	360.8%	1.02
60.0	0.079	409.2%	0.108	355.6%	0.0598	415 .4%	0.078	410.2%	0.74
72.0	0.033	583.1%	0.0229	583.1%	0.0183	583.1%	0.000	0%	0.33

	Test A	Reference B	T/R	90% CI
AUC(0-t) (ng.hr/mL)	126 (101)	125 (105)	1.01	
AUCinf (ng.hr/mL)	136 (96)	135 (100)	1.01	
Cmax(ng/mL)	12.6 (46)	12.2 (45)	1.03	
Tmax(hr)	3.10	3.45		
T1/2 (hr)	7.37	7.66		
Kel (1/hr)	0.11	0.11		
LnAUC(0-t)				97.0-109%
LnAUCinf				97.3-108%
LnCmax				95.6-110%

1. For N-depropylpropafenone, means for AUC(0-t), AUCinf and Cmax values were 0.8%, 0.7% and 3.3% higher, respectively, for the test product than for the reference product. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data.

2. The mean N-depropylpropafenone plasma levels peaked at 3 hours for the reference product in both treatments (B1&B2), and at 2.5 and 3.5 hours for for the test product in the first and the second treatments (A1&A2), respectively, following administration of propafenone tablet, 225 mg, under fasting conditions.

V. Comments:

1. The firm's single-dose bioequivalence study #98091 under fasting conditions, conducted on its 225 mg propafenone HCl tablet is acceptable. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% for propafenone, 5-hydroxypropafenone and N-depropylpropafenone.

2. The firm had previously submitted an acceptable single-dose bioequivalence study under fasting and nonfasting conditions conducted on its propafenone HCl 225 mg Tablet.

XI. Recommendations:

1. The single-dose bioequivalence study #98091, conducted by Watson Laboratories, Inc., on its Propafenone HCl 225 mg Tablet, lot #R77096, comparing it to Rythmol^{R} 225 mg Tablet,

manufactured by Knoll, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Watson's Propafenone Tablet, 225 mg, is bioequivalent to Knoll's Rythmol[R] Tablet, 225 mg, under fasting conditions.

2. The single-dose post-prandial bioequivalence study #96043, conducted by Watson Laboratories Inc., on its Propafenone HCl 225 mg Tablet, lot #R77096, comparing it to Rythmol[R] 225 mg Tablet, manufactured by Knoll, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Watson's Propafenone Tablet, 225 mg, is bioequivalent to Knoll's Rythmol[R] Tablet, 225 mg, under fasting and nonfasting conditions.

3. The dissolution testing conducting by Watson Laboratories Inc., on its Propafenone HCl 300 mg, 225 mg and 150 mg Tablets, lot #R69296, R77096 and R76996, respectively, is acceptable. The formulations for Propafenone HCl Tablets, 150 mg and 300 mg are proportionally similar to the 225 mg strength, which underwent acceptable bioequivalence testing. Waivers of in vivo bioequivalence study requirements for the 150 mg and 300 mg strengths of the test products are granted.

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 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

> Not less than % (Q) of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations.

/S/

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

Date: 5/4/99

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-203 SPONSOR : Watson Laboratories, Inc.
DRUG AND DOSAGE FORM : Propafenone HCl Tablets
STRENGTH(S) : 150 mg and 225 mg
TYPES OF STUDIES : Single-dose, Fasting/Fed bioequivalence study
CLINICAL STUDY SITE(S) :
ANALYTICAL SITE(S) :

STUDY SUMMARY : The audit of the bioequivalence study conducted By DSI, on Propafenone HCl Tablet, 225 mg, ANDA #75-203 of Watson Laboratories, Inc., did not reveal findings which would invalidate the study. Therefore, the recommendations by the Division of Bioequivalence for this study stay unchanged. The study was reviewed and found acceptable by the Division of Bioequivalence. See review dated March 11, 1998.

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic Yes New facility No For cause ____ other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Moheb H. Makary BRANCH : III

INITIAL : MHM DATE : 10/19/00

for TEAM LEADER : Barbara M. Davit BRANCH : III

INITIAL : CL for DATE : 10/19/00

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

INITIAL : BMD **DATE :** 10/19/00

Propafenone HCl
150, 225 and 300 mg Tablets
ANDA #75-203
Reviewer: Moheb H. Makary
W. 75203sdw.000

Watson Laboratories, Inc.
Corona, CA

October 12, 2000

Review of an Establishment Inspection Report

I. Background:

At the request of the Division of Bioequivalence (DBE), the Division of Scientific Investigation (DSI) HFD-48 conducted an audit on Watson's Propafenone HCl, 225 mg, post-prandial bioequivalence study (Protocol 96043). The clinical portion of the study was conducted at The analytical part of the study was performed at the

Following the inspection at , no Form FDA-483 was issued and no significant objectionable findings were identified. After the inspection at FDA Form-483 was issued.

The study was reviewed and found acceptable to the DBE. The final determination as to the acceptability of the study was pending in part on the outcome of the audit report.

II. Inspector's Findings:

The following subject samples in study 96043 (Food study) were re-injected due to unacceptable QC results. These samples should have been re-assayed according to SOP 2D-11.2.

Propafenone Assay:

Subject #15 - all samples in periods II and III
Subject #17 - 12, 16, 24 hours samples in period III

5-Hydroxypropafenone Assay:

Subject #12 - All samples in period III
Subject #13 - All samples in period I
Subject #15 - All samples in Periods II and III

Subject #16 - All samples in period III
Subject #17 - All samples in periods III

The inspector indicated that the above subject data should have been re-assayed due to unacceptable QC results. The inspector recommends that these subject data should be excluded from the statistical analysis of the study since these data are questionable.

III. Reviewer's Comments:

The reviewer agrees with the inspector that the above subject data are questionable.

Additional analysis of variance was performed by the reviewer after excluding these subjects. The ratios of the arithmetic and geometric means are as following:

Propafenone	B/C Arithmetic Mean	B/C Geometric Mean
AUC(0-t)	1.02	1.12
AUCinf	1.03	1.14
Cmax	1.06	1.12

5-Hydroxypropafenone	B/C Arithmetic Mean	B/C Geometric Mean
AUC(0-t)	1.02	1.02
AUCinf	1.02	1.02
Cmax	0.91	0.99

The ratios of the arithmetic and geometric means remain within the acceptable range of 0.80-1.25 range for AUC(0-t), AUCinf and Cmax for Propafenone and 5-Hydroxy-propafenone.

IV. Recommendation:

The audit of the bioequivalence study conducted By DSI, on Propafenone HCl Tablet, 225 mg, ANDA #75-203 of Watson Laboratories, Inc., did not reveal findings which would invalidate the study. Therefore, the recommendations by the Division of Bioequivalence for this study stay unchanged.

The study was reviewed and found acceptable by the Division of Bioequivalence. See review dated March 11, 1998.

/S/

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

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT /S/ Date: 10/19/00

Concur: /S/ Date: 10/19/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/10-19-2000, 75203SDW.000
cc: ANDA #75-203, original, HFD-658 (Makary), Drug File, Division File.

(5)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-203 SPONSOR : Watson Laboratories, Inc.

DRUG AND DOSAGE FORM : Propafenone HCl Tablets

STRENGTH(S) : 150 mg, 225 mg and ~~300 mg~~ MHM BPV

TYPES OF STUDIES : Single-dose, Fasting/Fed bioequivalence studies

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S) :

STUDY SUMMARY : The bioequivalence studies are acceptable

DISSOLUTION : Dissolution testing is acceptable

DSI INSPECTION STATUS

Inspection needed: (YES) / NO	Inspection status:	Inspection results:
First Generic Yes New facility No For cause ____ other ____	Inspection requested: (date) Inspection completed: (date) Application submitted prior to April 1, 1999 - not holding for DSI results.	

PRIMARY REVIEWER : Moheb H. Makary BRANCH : III MHM 6/26/00

INITIAL : MHM DATE : 5-4-99

TEAM LEADER : Barbara M. Davit BRANCH : III

INITIAL : BMD DATE : 5/4/99

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

INITIAL : DPC DPC DATE : 6/7/99 6/26/00

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-203 APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Propafenone HCl Tablets, 150, 225 and 300 mg

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

1. The Orange Book identifies the 300 mg tablet as the reference strength on which bioequivalence determinations should be based.

2. There were no safety issues identified during the fasting study on the Propafenone HCl Tablet, 300 mg (study #96040) that would justify the use of the lower dosage strength (i.e., 225 mg).

Based upon the reasons outlined above, you have two options:

1. You are advised to either withdraw the 300 mg strength and seek approval of the 225 mg and 150 mg tablets, since the data submitted in the ANDA support the approval for these two strengths and/or

2. You may conduct a new single-dose fasting bioequivalence study on the 300 mg strength to support the approval of the Propafenone HCl Tablet, 300 mg. It is your responsibility to enroll a sufficient number of subjects to power your study appropriately to meet the current bioequivalence criteria.

Sincerely yours,

/S/

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

CC: ANDA #75-203
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-658 /Reviewer M. makary MHM
HFD-658 /Bio Team Leader B. Davit BD
HFD-617/Project Manager 3/7/00
HFD-650/Dale Conner 3/7/00

BIOEQUIVALENCY - DEFICIENCIES Submission Date:

1. **OTHER** (OTH) Strengths: 300 mg
Outcome: UN

Outcome Decisions:
UN - Unacceptable

U2 Document.

Propafenone HCl
150, 225 and 300 mg Tablets
ANDA #75-203
Reviewer: Moheb H. Makary
W 75203sdw.200

Watson Laboratories, Inc.
Corona, CA

Addendum to the Review

The Division of Bioequivalence has determined that the waiver of *in vivo* study requirements for Watson's Propafenone HCl, 300 mg, should be denied for the following reasons:

a. The Orange Book identified the 300 mg tablet as the reference strength on which bioequivalence determinations should be based.

b. There were no safety issues identified during the fasting study on the Propafenone HCl Tablet, 300 mg (study #96040) that would justify the use of the lower dosage strength (i.e., 225 mg).

Based upon the reasons outlined above, it is the opinion of the Division of Bioequivalence that an *in vivo* single dose fasting bioequivalence study will be needed to support the approval of the Propafenone HCl Tablet, 300 mg for this specific ANDA. See the attached minutes of teleconference from 3/2/00. Also see attached Medical Officer Review of 1/21/00.

/S/

Moheb H. Makary, Ph.D. Date: 3/3/00
Review Branch III
Division of Bioequivalence

RD INITIALLED BDAVIT BMD 2/3/00 /S/
FT INITIALLED BDAVIT_____ Date: 3/3/00

Concur: /S/ Date: 3/7/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/ 2-3-00, 3-3-00, 75203sdw.200
cc: ANDA #75-203, original, HFD-658 (Makary), Drug File, Division File.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-203 APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Propafenone HCl Tablets, 300 mg, 225 mg and 150 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 0.1N HCl, at 37°C using USP Apparatus II(paddle) at 75 rpm. The test product should meet the following specifications:
>
> Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 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 P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #75-203
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary MMM
HFD-658/ Bio team Leader B. Davit

Printed in final on 5/4/99

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit BMD 5/14/99
HFD-650/ D. Conner 5/17/99

BIOEQUIVALENCY - ACCEPTABLE submission date: December 28, 1998

all OK BMD 5/14/99

✓ 1. **FASTING STUDY** (STF) Strengths: 225 mg
Clinical: **Outcome: AC**
Analytical:

✓ 2. **DISSOLUTION WAIVER** (DIW) Strengths: 150 mg and 300 mg

✓ 3. **STUDY AMENDMENT** (STA) Strengths: 225 mg
March 16, 1999 **Outcome: AC**

Outcome Decisions: **AC** - Acceptable

FIGURE 5.

N-Depropylpropafenone Mean Plasma Concentration Profiles

Watson Laboratories, Inc.
Study Drug: Propafenone (Protocol No. 98091)

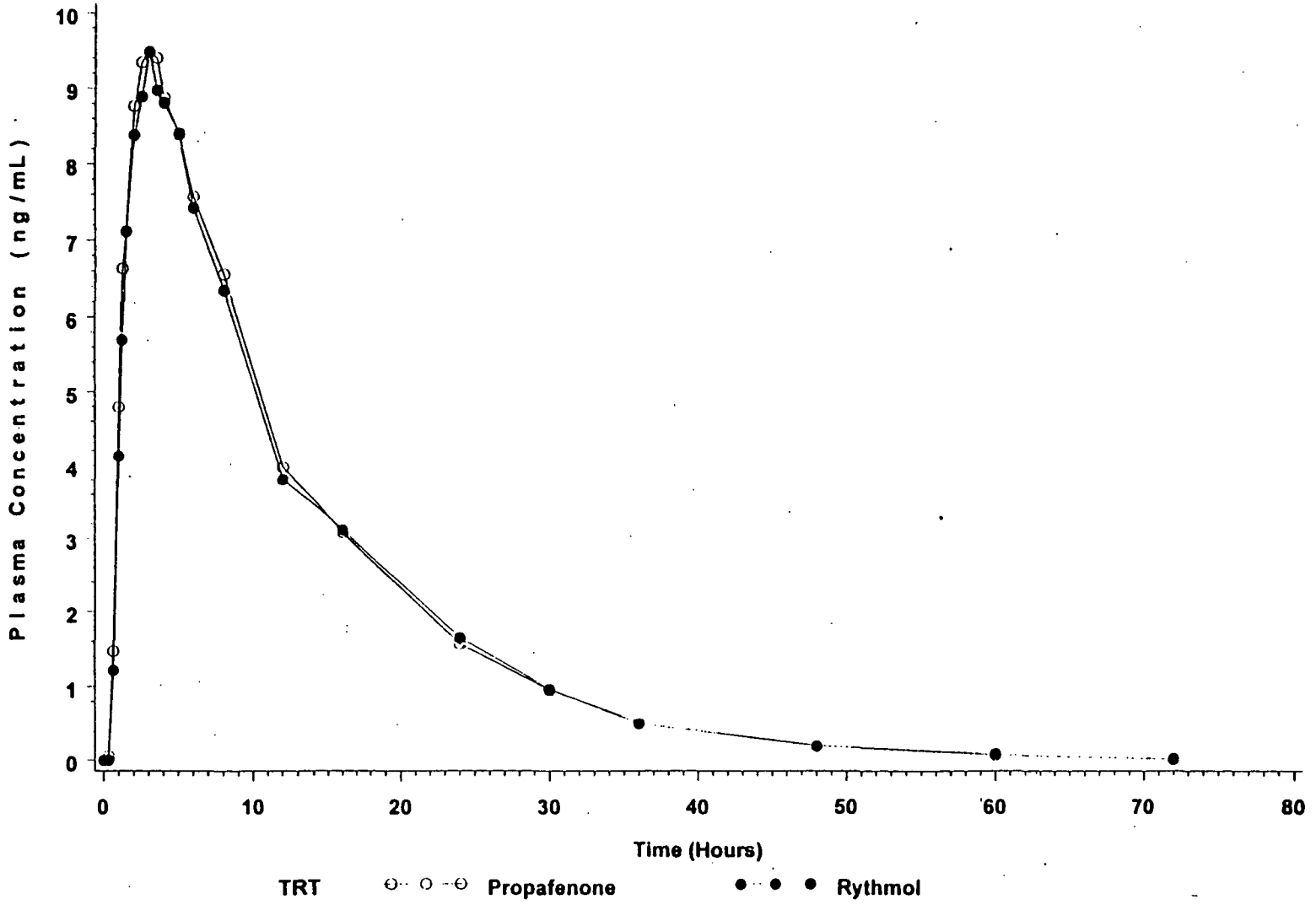


FIGURE 3.

5-Hydroxypropafenone Mean Plasma Concentration Profiles

Watson Laboratories, Inc.
Study Drug: Propafenone (Protocol No. 98091)

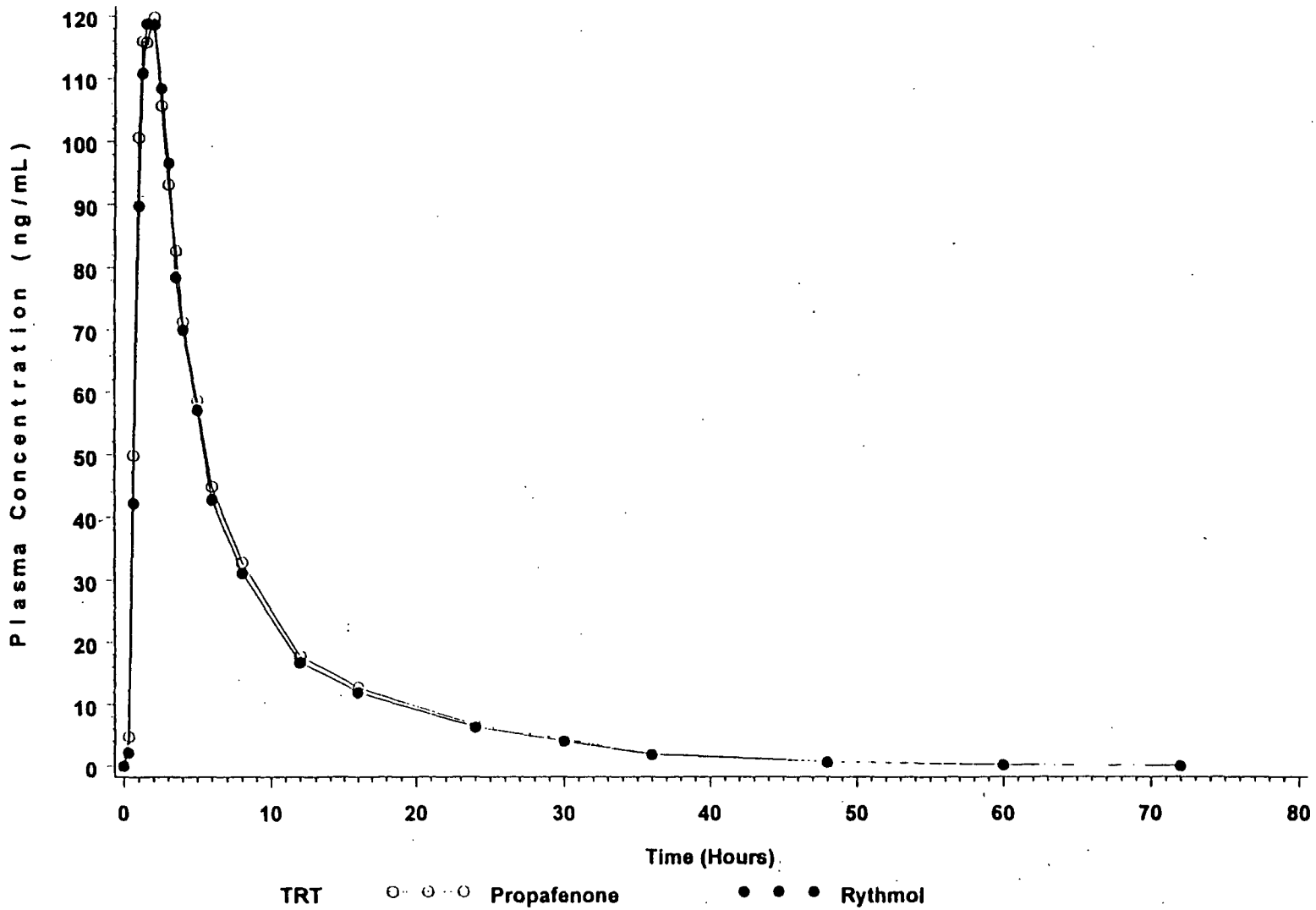
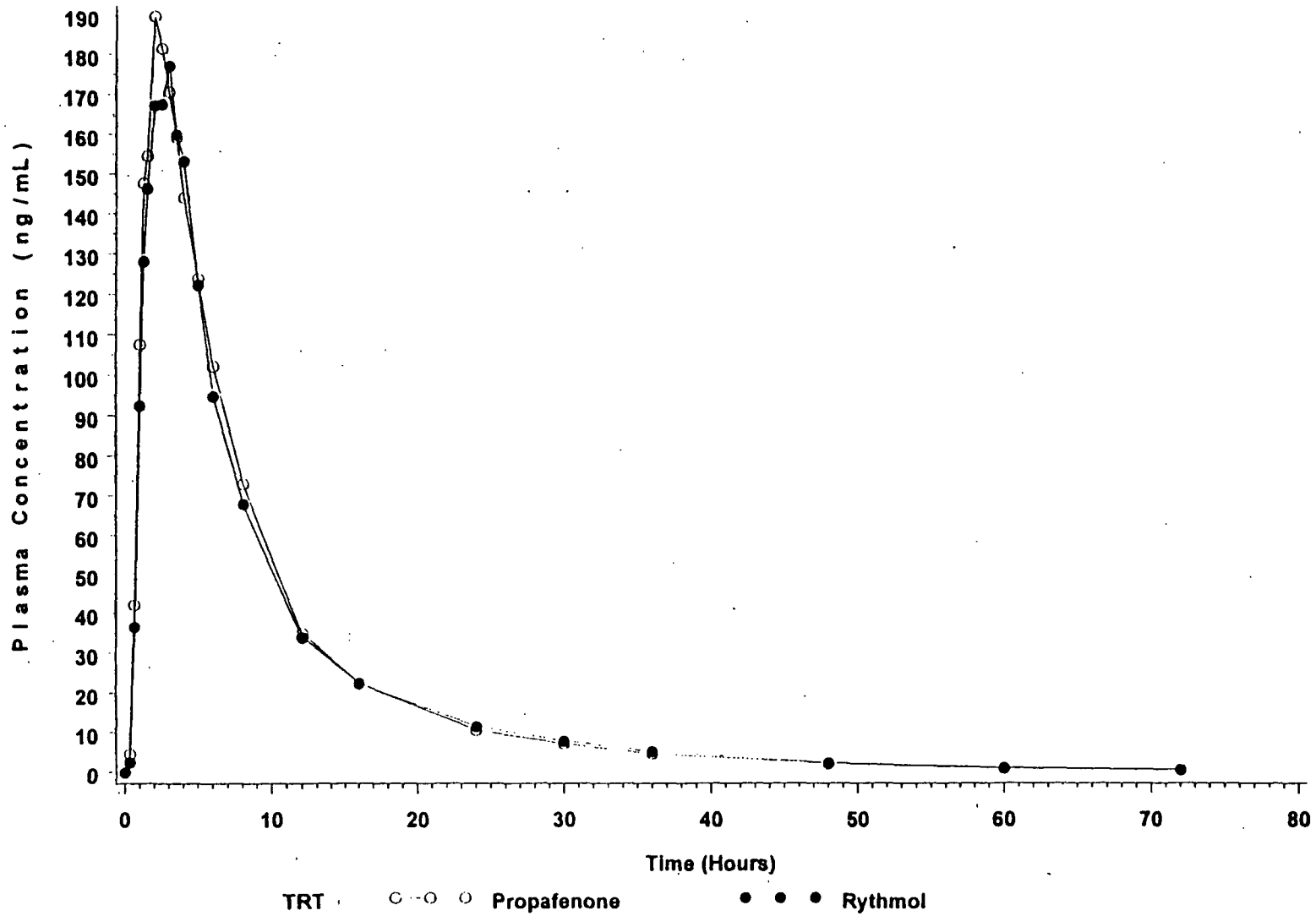


FIGURE 1.

Propafenone Mean Plasma Concentration Profiles

Watson Laboratories, Inc.
Study Drug: Propafenone (Protocol No. 98091)



AUG 19 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-203 APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Propafenone HCl Tablets, 150 mg, 225 mg and 300 mg

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

1. The Division has no further questions on your food-effect study and dissolution testing. However, your application remains incomplete pending the submission of an acceptable fasting study on the 225 mg strength of your Propafenone HCl product.

2. 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 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

   Not less than 1% (Q) of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

Sincerely yours,

/S/

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

CC: ANDA #75-203
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-658/Reviewer M. Makary MHM
HFD-658/Bio Team Leader B. Davit BZD
HFD-617/Project Manager
HFD-650/Dale Conner DAC 8/11/98

BIOEQUIVALENCY - DEFICIENCIES Submission Date: 4-29-98

1. **FOOD STUDY** (STP) Strengths: 225

Clinical:
Analytical: **Outcome: AC**

2. **STUDY AMENDMENT** (STA) Strengths: 150 mg, 225 mg and 300 mg
Outcome: IC

Outcome Decisions:
IC - Incomplete

WinBio Comments: ANDA is incomplete- fasting study is needed

Propafenone HCl	Watson Laboratories, Inc.
150, 225 and 300 mg Tablets	Corona, CA
ANDA #75-203	Submission Date:
Reviewer: Moheb H. Makary	April 29, 1998

Review of an Amendment

I. Objective:

The firm has replied to the reviewer's comments made in the review of the September 11, 1997 submission (bioequivalence studies on Propafenone HCl Tablets 300 mg and 225 mg, dissolution data and waiver requests).

Comment #I

The firm was informed that excluding subject #25 from the statistical analysis of the study is not justified. After including the subject in the statistical analysis of the study, the resulting 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are as following:

Propafenone	
LnAUC(0-t)	85.6-123.6%
LnAUCinf	83.0-118.4%
LnCmax	85.3-130.0%

Th 90% confidence interval for Cmax is 85% to 130% of the reference parameter for log-transformed data, which is outside the acceptable 80-125% range. Therefore, the study is unacceptable

The firm acknowledged the Agency's comments regarding the study above (study #96040). The firm plans to conduct another bioequivalence study with a replicate design of a two-way crossover, single-dose, open-label under fasting conditions on the lower 225 mg strength instead of the 300 mg as in the original ANDA (submission dated September 11, 1997), due to safety reasons. In addition, request for a bioequivalence waiver for the 150 mg and 300 mg strengths drug product will be included with the study amendment.

Conducting the bioequivalence study under fasting conditions on Propafenone HCl Tablets, 300 mg, might cause significant adverse events to the subject in the study (please see OGD letter attached). In addition, the firm's formulations for Propafenone HCl Tablets, 150 mg and 300 mg are proportionally (quantitively and qualitatively) similar to the 225 mg which underwent bioequivalence testing under nonfasting conditions. The Division of bioequivalence

agrees with the firm to conduct the bioequivalence study under fasting conditions on the lower strength i.e., Propafenone HCl Tablets, 225 mg.

Reply to Comment #I

The firm's response to the comment is acceptable.

Comment #II

The firm was asked to explain the reason for not including subject #18 in the repeated study (study #97107). Subject #18 exhibited below quantitative limit (BQL) plasma levels for propafenone and its metabolites 5-hydroxypropafenone and N-depropylpropafenone during period II (Reference product) in the original study (study #96040).

The firm indicated that subject #18 was not available for inclusion in the repeated study due to other personal time commitments.

Reply to Comment #II

The firm's response to the comment is acceptable.

Comment #III

For the single-dose food-effect study #96043, in the randomly selected chromatograms of subject #3 for determination of 5-hydroxypropafenone, the title on the pages stated 5-hydroxypropafenone but the mass scanning mode was 342-116 m/z propafenone. The firm was asked to explain this discrepancy.

The firm indicated that the incorrect chromatograms of 5-hydroxypropafenone for subject #3 for study #96043 were inadvertently included in the report. The firm has attached the correct chromatograms with the same page numbers as in the ANDA for review.

Reply to Comment #III

The firm's response to the comment is acceptable.

Comment #IV

The firm was advised to use the following dissolution testing method instead of the method reported by the firm in the submission:

In Vitro Dissolution Testing

Method: USP 23 apparatus II (paddle) at 75 rpm

Medium:	900 mL of 0.1N HCl at 37°c
Number of Tablets:	12
Specification:	NLT %(Q) in 30 minutes

The firm repeated the dissolution testing for all three strengths of the drug product, using the above method. The dissolution testing results are shown in Table I.

Reply to Comment #IV

The firm's response to the comment is acceptable.

II. Recommendations:

1. The single-dose bioequivalence study #96040, conducted by Watson Laboratories, Inc., on its Propafenone HCl 300 mg Tablet, lot #R69296, comparing it to Rythmol[R] 300 mg tablet, manufactured by Knoll, has been found unacceptable by the Division of Bioequivalence.

2. The single-dose post-prandial bioequivalence study #96043, conducted by Watson Laboratories Inc., on its Propafenone HCl 225 mg Tablet, lot #R77096, comparing it to Rythmol[R] 225 mg Tablet, manufactured by Knoll, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Watson's Propafenone HCl Tablet, 225 mg, is bioequivalent to the reference product, Rythmol[R] Tablet, 225 mg, manufactured by Knoll under nonfasting conditions.

3. The dissolution testing conducting by Watson Laboratories Inc., on its Propafenone HCl 300 mg, 225 mg and 150 mg Tablets, lot #R69296, R77096 and R76996, respectively, is acceptable.

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 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

> Not less than %(Q) of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

5. From the bioequivalence point of view, the firm has not met the requirements of *in vivo* bioavailability and the application is incomplete.

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

Date: 8-5-98

RD INITIALLED BDAVIT B.D 8/5/98
FT INITIALLED BDAVIT /S/ Date: 8/5/98

Concur: /S/ Date: 8/11/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/8-5-98, wp 75203SDW.498
cc: ANDA #75-203, original, HFD-658(Makary), Drug File, Division File.

Table I. In Vitro Dissolution Testing

Drug (Generic Name): Propafenone HCl Tablets
Dose Strength: 300 mg, 225 mg and 150 mg
ANDA No.: 75-203
Firm: Watson Laboratories, Inc.
Submission Date: April 29, 1998
File Name: 75203SDW.498

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:X RPM: 75
No. Units Tested: 12
Medium: 900 mL of 0.1N HCl
Specifications: NLT % (Q) in 30 minutes
Reference Drug: Rythmol
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # R76996 Strength(mg) 150			Reference Product Lot # 21400246 Strength(mg) 150		
	Mean %	Range	%CV	Mean %	Range	%CV
5	34.9		25.5	6.0		44.5
10	92.2		2.6	57.5		15.7
20	100.8		1.4	97.7		1.6
30	101.4		1.4	99.6		1.2

Sampling Times (Minutes)	Test Product Lot # R77096 Strength(mg) 225			Reference Product Lot # 23000076 Strength(mg) 225		
	Mean %	Range	%CV	Mean %	Range	%CV
5	48.1		14.5	10.9		41.8
10	93.0		3.2	74.2		7.1
20	100.4		1.4	97.1		0.8
30	101.4		1.6	98.7		0.9

Sampling Times (Minutes)	Test Product Lot # R69296 Strength(mg) 300			Reference Product Lot # 21450085 Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
5	54.4		6.2	7.9		45.7
10	84.0		1.6	60.6		16.2
20	93.2		1.4	93.9		3.0
30	95.3		1.5	94.8		2.9

Propafenone HCl
150, 225 and 300 mg Tablets
ANDA #75-203
Reviewer: Moheb H. Makary
Wp. 75203sdw.997

Watson Laboratories, Inc.
Corona, CA
Submission Date:
September 11, 1997

Review of in vivo Bioequivalence Studies, Dissolution Data and Waiver requests

I. Objective:

The firm has submitted two bioequivalence studies under fasting and nonfasting conditions. The fasted study was conducted on propafenone HCl Tablet 300 mg dosage strength while the food effect study was conducted on the 225 mg dosage strength due to safety reasons (the DBE agreed with the firm's request to conduct the bioequivalence study under nonfasting conditions on the lower strength, i.e., propafenone HCl Tablet 225 mg, letter dated August 18, 1997). The firm requested waivers of in vivo bioequivalence study requirements for its 150 mg strength, fasting study for its 225 mg strength and food-effect study on its 300 mg strength. Dissolution profiles comparing Watson's 150 mg, 225 mg and 300 mg tablets and Rythmol^{R} Tablets were submitted. Comparative compositions were also submitted.

II. Background:

Propafenone is rapidly absorbed from the gastrointestinal tract with a T_{max} of about 3.5 hours in most subjects. Propafenone follows a nonlinear pharmacokinetic disposition presumably due to saturation first pass hepatic metabolism. As the liver is exposed to higher concentrations of propafenone its bioavailability increases; e.g., a 150 mg tablet of Rythmol^{R} had an absolute bioavailability of 3.4% while a 300 mg tablet had an absolute bioavailability of 10.6% and at higher doses the bioavailability increases still further. A very high degree of interindividual variability in the pharmacokinetics is observed.

In over 90% of the patients treated with propafenone HCl the drug is rapidly and extensively metabolized to two metabolites, 5-hydroxypropafenone and N-depropylpropafenone. In these fast metabolizers the elimination half-life is 2 to 10 hours. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is minimally formed if formed at all. In these patients the propafenone elimination half-life ranges from 10 to 32 hours. Slow metabolizers achieve propafenone concentrations 1.5 to 2 times those of the extensive metabolizers at daily doses of 675-900 mg/day. At lower doses the differences are greater, with slow metabolizers attaining concentrations more than five times that of the extensive metabolizers.

Coadministration of propafenone with food increases its bioavailability although the mechanism of this phenomenon is uncertain. Also in the presence of food Cmax is more rapidly attained. It is interesting that such enhancement of propafenone bioavailablility by food could only be demonstrated in subjects with the extensive metabolizer phenotype. The mean increase in area under the concentration-time curve (AUC) was 147% when only extensive metabolizer phenotype subjects were used in the calculation, and 120% when all subjects data were incorporated.

The reference listed drug is Rythmol^{R} supplied in scored tablets of 150 mg, 225 mg and 300 mg, manufactured by Knoll Pharmaceuticals.

III. Propafenone HCl's Protocol #96040 for a Single-Dose 2-Way Crossover Study Under Fasting Conditions:

Objective: The objective of the study was to determine the bioequivalence of the test product Propafenone HCl 300 mg tablet versus Knoll's Rythmol^{R} 300 mg tablet, under fasting conditions.

Clinical site:

Investigators:

Analytical site:

Sponsor: Watson Laboratories, Inc.

Study design: Single-dose, randomized, 2-way crossover, open-label, under fasting conditions.

Subjects eligibility: Thirty-eight (38) male volunteers were enrolled in the study and 33 subjects completed the study. They were judged to be healthy based on medical history, physical examination and clinical laboratory tests within 21 days prior to period 1 dosing. A 12-lead electrocardiogram was obtained for all subjects. PR intervals were within normal range for heart rate, and were not exceeded 190 msec upon screening. All subjects were within 18 to 39 years of age and were within ± 10% of their IBW.

This study was conducted in two groups. Group 1 consisted of subjects numbered 01 through 30 (no subjects numbered 05, and 06). Group 2

consisted of subjects numbered 31 through 40. Study period I was initiated on August 3, 1996 (Group 1), and September 14, 1996 (Group 2); study period II was initiated on August 17, 1996 (Group 1), and September 28, 1996 (Group 2). The subjects were randomized into two dosing sequences.
Sequence AB subjects #3, 4, 6, 7, 10, 11, 13, 16, 18, 21, 22, 23, 26, 28, 29, 31, 32, 34, 37, 39 Sequence BA subjects #1, 2, 5, 8, 9, 12, 14, 15, 17, 19, 20, 24, 25, 27, 30, 33, 35, 36, 38, 40

Exclusion Criteria: Subjects meeting any of the following criteria were excluded:

* Known history of hypersensitivity to the class of drug being tested.
* Known history or presence of cardiac, pulmonary, gastrointestinal, endocrine, neuromuscular, neurological, hematological, liver or kidney disease, or any condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.
* Known history of asthma, chronic bronchitis or other bronchospastic condition.
* Any subject requiring maintenance therapy with any drug, or a history of drug dependency, or serious psychological disease.
* Regular use of medication, abuse of alcoholic beverages, or participation in a clinical trial with an investigational drug within 30 days preceding this study.
* Use of enzyme-inducing and enzyme-inhibiting drugs such as phenobarbital, carbamazepine and cimetidine within 30 days prior to entry into the study.
* Use of any drugs similar to the one under study or administered of any medication (including over-the-counter preparations) within 14 days preceding entry into this study.
* History of conditions which might contraindicate or require that caution be used in the administration of propafenone, including:

a. Sick sinus syndrome.
B. Sitting systolic blood pressure below 100 mm Hg, or diastolic pressure below 60 mm Hg.
C. PR interval greater than 190 msec.
D. Sinus bradycardia (heart rate less than 60

beats per minute after a 5-minute rest in a seated position).
E. History of heart failure.
F. Pre-existing cardiac arrhythmias associated with tachycardia.
G. Hypersensitivity to propafenone, or any antiarrhythmic drug.

Dose and treatment: Test product
A. 1 x 300 mg Propafenone HCl Tablet (Watson) lot #R69296, lot size tablets, potency 96.8%, content uniformity 97.5% (%CV=2.9), following an overnight fast.
Reference products:
B. 1 x 300 mg Rythmol[R] Tablet (Knoll), lot #21450085, Exp. 11/99, potency 97.3%, content uniformity 98.1% (%CV=1.7), following an overnight fast.

Food and fluid intake: Subjects were required to fast overnight prior to and 4 hours after drug administration. Subjects received identical standardized meals for lunch at 4 hours post-dose, supper at 10 hours post-dose, a snack at 14 hours post-dose and breakfast at 24 hours post-dose. Water was allowed ad lib. until 1 hour before dosing and 2 hours after dosing except for 240 mL water administered with the dose.

Safety Monitoring: Vital signs including blood pressure and heart rate were obtained prior to drug administration and at 1, 2, 3, 4, 6, 8, 12 and 36 hours following dose administration. Electrocardiograms were obtained on each subject within one hour prior to dosing, and within 30 minutes prior to, or post, blood draw at post-dose hours 6, 12 and 24.

Washout period: Two weeks

Blood samples: Blood samples were collected at 0 (pre-dose) and at 0.33, 0.66, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 30, 36, 48, 60 and 72 hours post-dose. Whole blood samples were centrifuged at room temperature for 15 minutes at 3400 rpm, and the resultant plasma from each tube was decanted into an individual pre-labeled polypropylene screw cap tube. Plasma samples were immediately frozen at -20

°C until shipment to the analytical facility (University of California San Francisco, Drug Studies Unit, San Francisco, CA).

Analytical Methodology

Statistical Analysis:

Statistical analysis was performed on propafenone and its metabolites 5-hydroxypropafenone and N-depropylpropafenone data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The statistical model included two and/or four period to accommodate the two groups. There was no significant period effect detected in the study. The two one-sided test was used to estimate the 90% confidence intervals.

IV. In Vivo Results:

A total of 38 subjects were entered and 33 subjects completed the study. This study was initiated with 28 of required 30 subjects. One subject failed to report to the clinic on check-in day for period I, and one subject had a baseline PR interval above the inclusive limit of 190 msec (subjects #5 and #6). After initial dosing, three subjects discontinued their participation in the study for the following reasons: subject #09 withdrew from the study after 24 hours in period I, due to flu-like symptoms and subjects #13 and #29 withdrew from the study after 8 and 5 hours, respectively, in period I with no reason given. The sponsor made the decision to start a second group of 10 subjects (subject #31-40) to ensure that the data pool was large enough to produce statistically significant results. In addition to the above, two additional subjects' participation in the study was discontinued for the following reasons: subject #4 withdrew from the study at one hour post-dose in period II, due to flu-like symptoms and subject #22 had baseline PR interval in period II exceed the inclusion maximum limit of 190 msec. Therefore, the principal investigator dropped the subject from further participation in this study. Eighteen adverse events were reported in six of thirty-three subjects dosed and included the following events: phlebitis left arm, headache , dizziness, lightheadedness, flu symptoms, congestion, syncope and hot flashes There were no serious adverse events or any events which required terminating any subject from study participation.

The firm indicated that subjects #18 and #25 were considered as statistical outliers, and whose plasma concentration data were not appropriate to include in the data pool. Subject #18 dosed with reference product, in period II, exhibited below quantitative limit (BQL) plasma levels for propafenone and its metabolites 5-hydroxypropafenone and N-depropylpropafenone (i.e., did not have detectable drug level after dosing). Subject #25 dosed with

reference product, in period I, exhibited low plasma concentrations for both propafenone and 5-hydroxypropafenone compared to period II when dosed with the test product.

The mean plasma concentrations and pharmacokinetic parameters for propafenone, 5-hydroxypropafenone and N-depropylpropafenone after excluding subjects #18 and #25 are summarized in Tables I, II and III, respectively.

Table I

Mean Plasma Propafenone Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 300 mg Propafenone (1x300 mg Tablet) under Fasting Conditions
(N=31)

Time hr	Treatment A Watson Lot #R69296 ng/mL (± SD)	Treatment B Knoll Lot #21450085 ng/mL (± SD)
0	0.00 (0.0)	0.00 (0.0)
0.33	8.71 (16.1)	4.95 (12.6)
0.66	71.47 (121.0)	51.60 (85.1)
1	160.12 (208.7)	127.58 (142.2)
1.25	187.87 (236.9)	190.29 (224.3)
1.5	201.77 (226.0)	209.04 (215.5)
2	203.85 (185.3)	236.91 (260.5)
2.5	242.71 (237.7)	247.37 (261.2)
3	238.83 (287.4)	232.20 (222.8)
3.5	194.02 (171.3)	222.45 (209.5)
4	181.52 (151.5)	203.59 (181.0)
5	125.83 (111.5)	156.41 (158.2)
6	94.91 (114.2)	118.13 (163.2)
8	51.58 (65.5)	64.26 (82.6)
12	17.63 (23.3)	18.69 (25.9)
16	5.76 (8.4)	6.72 (10.6)
24	1.48 (2.8)	1.76 (3.5)
30	0.29 (1.2)	0.22 (0.9)
36	0.08 (0.5)	bql*
48	bql	bql
60	bql	bql
72	bql	bql

*below quanifiable limits

			90% CI
AUC(0-t) (ng.hr/mL)	1302.8 (1193)	1447.5 (1392)	
AUCinf (ng.hr/mL)	1317.0 (1196)	1511.7 (1395)	

Cmax(ng/mL)	325.6 (335)	323.7 (280)	
Tmax(hr)	2.2	2.6	
T1/2 (hr)	2.98	2.95	
Kel (1/hr)	0.26	0.27	
LnAUC(0-t)			83.2-116.4%
LnAUCinf			80.9-111.4%
LnCmax			82.5-121.5%

1. None of the subjects reached Cmax at the first sampling time point (0.33 hr). The reviewer has verified the AUC and AUCinf values to be accurate.

2. For propafenone, after excluding subjects #18 and #25 from the statistical analysis of the study, the least squares means for AUC(0-t), AUCinf and Cmax values were 11.1%, 12.1% and 0.12% lower and higher, respectively, for the test product than for the reference product. The differences were not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

3. The mean propafenone plasma levels peaked at 2.5 hours for both the test and the reference products, following their administration under fasting conditions.

4. It should be noted that subject #18 exhibited below quantitative limit (BQL) plasma levels for propafenone and its metabolites 5-hydroxypropafenone and N-depropylpropafenone during period II (Reference product), for this reason, excluding subject #18 from the statistical analysis of the study may be justified.

5. Subject #25 exhibited low plasma concentrations for both propafenone and 5-hydroxypropafenone during period I (Reference product) compared to period II (Test product).

6. Subject #25 was not the only subject in the study exhibiting low plasma propafenone concentrations when dosed with reference product. The plasma propafenone concentration values for subjects #10, 16 and 17 were also low when dosed with the reference product. The Cmax, AUC(0-t) and AUCinf values for subjects 10, 16, 17 and 25 dosed the reference product in the study are shown below:

	Cmax (ng/mL)	AUC(0-T) (ng.hr/mL)	AUCinf (ng.hr/mL)
Subject #10	33.5	92.9	103.1
Subject #16	9.2	41.1	*
Subject #17	10.5	47.1	56.0
Subject #25	18.3	52.2	57.5

* AUCinf and kel for subject #16 could not be estimated.

In addition, subject #25 revealed no clinical abnormalities. Excluding this subject from the statistical analysis of the study is not justified. After including subject #25 in the statistical analysis of the study, the resulting 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are as following:

Propafenone	
LnAUC(0-t)	85.6-123.6%
LnAUCinf	83.0-118.4%
LnCmax	85.3-130.0%

Th 90% confidence interval for Cmax is 85 to 130% of the reference parameter for log-transformed data, which is outside the acceptable 80-125% range.

Table II

Mean Plasma 5-Hydroxypropafenone Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 300 mg Propafenone (1x300 mg Tablet) under Fasting Conditions

(N=31)

Time hr	Treatment A Watson Lot #R69296 ng/mL (± SD)	Treatment B Knoll Lot #21450085 ng/mL (± SD)
0	0.00 (0.0)	0.00 (0.0)
0.33	12.29 (21.4)	5.61 (12.0)
0.66	84.17 (83.2)	59.83 (75.0)
1	143.37 (104.2)	136.45 (124.5)
1.25	162.98 (96.7)	160.03 (97.2)
1.5	167.77 (89.7)	176.50 (110.4)
2	162.13 (71.4)	163.71 (74.9)
2.5	159.18 (66.5)	148.80 (73.2)
3	135.95 (62.5)	134.49 (66.6)
3.5	125.73 (60.6)	120.65 (57.6)
4	119.81 (65.3)	116.27 (64.1)
5	92.74 (49.1)	93.37 (56.8)
6	68.55 (36.0)	69.42 (42.4)
8	47.86 (27.2)	48.98 (33.6)
12	23.19 (13.7)	24.38 (17.6)
16	12.64 (7.7)	13.46 (11.3)
24	6.75 (3.7)	7.31 (5.9)
30	3.81 (3.1)	4.25 (3.7)
36	2.16 (2.2)	2.11 (2.5)
48	0.44 (1.0)	0.34 (1.1)

60	bql*	0.09 (0.5)
72	bql	bql

* below quantifiable limits

			90% CI
AUC(0-t) (ng.hr/mL)	1147.85 (469)	1149.34 (564)	
AUCinf (ng.hr/mL)	1207.11 (483)	1184.97 (567)	
Cmax(ng/mL)	226.21 (81)	225.51 (107)	
Tmax(hr)	2.1	2.1	
T1/2 (hr)	9.53	8.97	
Kel (1/hr)	0.08	0.08	
LnAUC(0-t)			97.6-109.5%
LnAUCinf			97.1-109.6%
LnCmax			93.4-113.7%

1. None of the subjects reached Cmax at the first sampling time point (0.33 hr). The reviewer has verified the AUC and AUCinf values to be accurate.

2. For 5-hydroxypropafenone, after excluding subjects #18 and #25 from the statistical analysis of the study, the least squares means for AUC(0-t), AUCinf and Cmax values were 0.44%, 0.35% and 0.47% lower and higher, respectively, for the test product than for the reference product. The differences were not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

3. The mean 5-hydroxypropafenone plasma levels peaked at 1.5 hours for both the test and the reference products, following their administration under fasting conditions.

4. It should be noted that subject #18 exhibited below quantitative limit (BQL) plasma levels for propafenone and its metabolites 5-hydroxypropafenone and N-depropylpropafenone during period II (dosed with reference product), for this reason, excluding subject #18 from the statistical analysis of the study may be justified. Subject #25 exhibited low plasma concentrations for both propafenone and 5-hydroxypropafenone during period I (Reference product) compared to period II (dosed with test product). Excluding this subject from the statistical analysis of the study is not justified. After including subject #25 in the statistical analysis of the study, the resulting 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are as following:

5-Hydroxypropafenone	
LnAUC(0-t)	98.4-112.6%
LnAUCinf	98.3-112.8%

LnCmax 95.2-118.9%

All confidence intervals remained within the acceptable 80-125% range.

Table III

Mean Plasma N-Depropylpropafenone Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 300 mg Propafenone (1x300 mg Tablet) under Fasting Conditions

(N=31)

Time hr	Treatment A Watson Lot #R69296 ng/mL (± SD)	Treatment B Knoll Lot #21450085 ng/mL (± SD)
0	0.00 (0.0)	0.00 (0.0)
0.33	0.18 (0.5)	0.05 (0.3)
0.66	3.25 (5.1)	2.10 (3.8)
1	7.79 (8.9)	5.32 (5.5)
1.25	9.16 (8.5)	7.62 (6.4)
1.5	10.95 (9.6)	9.48 (7.0)
2	11.79 (8.3)	11.22 (7.3)
2.5	12.24 (8.2)	12.53 (8.1)
3	13.74 (10.3)	12.25 (7.4)
3.5	13.26 (7.9)	12.96 (8.0)
4	12.69 (7.6)	12.82 (7.8)
5	11.39 (7.0)	12.13 (7.4)
6	10.00 (6.8)	10.63 (7.8)
8	7.45 (5.5)	8.10 (6.3)
12	4.17 (3.5)	4.23 (3.8)
16	2.27 (1.9)	2.55 (2.4)
24	0.94 (1.0)	1.16 (1.1)
30	0.34 (0.6)	0.32 (0.6)
36	0.11 (0.3)	0.14 (0.3)
48	bql*	bql
60	bql	bql
72	bql	bql

* below quantifiable limits

			90% CI
AUC(0-t) (ng.hr/mL)	130.04 (92)	134.24 (96)	
AUCinf (ng.hr/mL)	138.18 (94)	145.35 (100)	
Cmax(ng/mL)	17.48 (11)	16.02 (8)	
Tmax(hr)	2.9	3.1	
T1/2 (hr)	6.2	6.75	
Kel (1/hr)	0.12	0.11	

LnAUC(0-t)	90.1-108.9%
LnAUCinf	89.3-105.6%
LnCmax	93.3-117.2%

1. None of the subjects reached Cmax at the first sampling time point (0.33 hr). The reviewer has verified the AUC and AUCinf values to be accurate.

2. For N-depropylpropafenone, after excluding subjects #18 and #25 from the statistical analysis of the study, the least squares means for AUC(0-t), AUCinf and Cmax values were 3.84%, 5.1% and 7.77% lower and higher, respectively, for the test product than for the reference product. The differences were not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

3. The mean N-depropylpropafenone plasma levels peaked at 3 and 3.5 hours for the test and the reference products, respectively, following their administration under fasting conditions.

4. It should be noted that subject #18 exhibited below quantitative limit (BQL) plasma levels for propafenone and its metabolites 5-hydroxypropafenone and N-depropylpropafenone during period II (dosed with reference product), for this reason, excluding subject #18 from the statistical analysis of the study may be justified. Subject #25 exhibited low plasma concentrations for propafenone, 5-hydroxypropafenone and N-depropylpropafenone during period I (dosed with reference product) compared to period II (Test product). Excluding this subject from the statistical analysis of the study is not justified. After including subject #25 in the statistical analysis of the study, the resulting 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are as following:

N-Depropylypropafenone	
LnAUC(0-t)	91.4-110.2%
LnAUCinf	90.0-116.2%
LnCmax	94.8-119.1%

All confidence intervals remained within the acceptable 80-125% range.

V. Propafenone HCl's Protocol #97107 for a Single-Dose 2-Way Crossover Repeated Study Under Fasting Conditions (5 Subjects):

Objective: The primary objective of this single-dose, two-way crossover study was to re-evaluate the aberrant pharmacokinetic performance of subject #25 from the previous pivotal bioequivalence study (protocol #96040). In order to provide a control group, subject #25 and an additional five subjects

(subjects #2, 4, 11, 23 and 40) from the same study were chosen at random. Additionally, the study procedures, and study drug lot numbers were identical between Study #96040 and this repeated study #97107.

In Vivo Results:

Six (6) subjects were enrolled in the study, five (5) subjects completed the entire study. Subject #4 was unable to participate in study period II, because he was unable to comply with the change in schedule, necessitated by the illness of subject #25. The original washout phase between study periods was to have been three weeks in order to accommodate study participant work /personal schedules. However, at post-dose hour 416, subject #25 developed flu-like symptoms which required a three-week delay to allow prescribed medication to wash-out of his system (please see Adverse Events Table IV).

Comparison of results obtained from studies #96040 and #97107 for propafenone and 5-hydroxypropafenone are shown in Tables V and VI.

1. Among the five subjects in the repeated study #97107, subject #25 exhibited the highest T/R ratios for the three pharmacokinetic parameters AUC(0-t), AUCinf and Cmax for propafenone and 5-hydroxypropafenone. The results were consistent with those of the original pivotal study #96040.

2. For propafenone, the Cmax ratios (T/R) for subject #25 were 6.17 and 3.87 in the original study (96040) and in the repeated study (study #97107), respectively. The ratio of 3.87 in the repeated study was close to the ratio of 3.395 for Cmax (T/R) for subject #16 in the original study (96040). The high ratio (T/R) for Cmax for subject #25 in the original and the repeated study was because of the high variability of the drug.

3. These high parameter ratios (T/R) for subject #25 in the two studies, can be explained by the high variability of this drug. For example, the Cmax, AUC(0-t) and AUCinf values for subject #2 dosed with the test product in the original study (#96040) were 1208.0 ng/mL, 4056.8 (ng.hr/mL) and 4077.9 (ng.hr/mL), respectively, and in the repeated study (#97107), the values were 297.0 ng/mL, 1264.2 (ng.hr/mL) and 1276.0 (ng.hr/mL), respectively (Table V). The parameter ratios for the two studies (T/T, study #96040/study #97107) were 4.06 , 3.20 and 3.20 for Cmax, AUC(0-t) and AUCinf, respectively, for subject #2.

4. The firm did not include subject #18 in the repeated study #97107. Subject #18 exhibited below quantitative limit (BQL) plasma levels for propafenone and its metabolites 5-hydroxypropafenone and N-depropylpropafenone during period II (dosed with reference product) in the original study (study #96040). The firm should

explain the reason for not including the subject in the study.

5. In addition, the potency and content uniformity for the reference product were 97.3% and 98.1% (%CV=1.7), which might rule out product failure.

7. Based on the above, subject #25 should be included in the statistical analysis of the study.

VI. Study #96043 for Single-Dose, 3-way Crossover Study of Propafenone HCl Tablets, 225 mg, Under Fasting and Nonfasting Conditions

Objective: The objective of this study was to compare the bioavailability of a single-dose of Watson's Propafenone HCl Tablet, 225 mg with Knoll's Rythmol^{R} Tablet, 225 mg, under fasting and nonfasting conditions.

Clinical site:

Investigators:

Analytical site:

Sponsor:	Watson Laboratories, Inc.
Study design:	Single-dose, randomized, 3-way crossover, open-label, under fasting and nonfasting conditions.
Dosing dates:	February 1, 1997, Period I February 15, 1997, Period II March 1, 1997, Period III
Subjects:	Twenty-four (24) subjects entered and twenty-two (22) subjects successfully completed the study. The subjects were randomized into six dosing sequences. Sequence ABC, subjects #2, 8, 13, 23 Sequence BCA, subjects #4, 7, 18, 24 Sequence CAB, subjects #1, 9, 17, 22 Sequence ACB, subjects #3, 10, 14, 19 Sequence BAC, subjects #6, 11, 16, 21 Sequence CBA, subjects #5, 12, 15, 20
Subjects eligibility:	Twenty-four (24) healthy male subjects (ages 19-39 years), within ±10% of their IBW were

enrolled in the study. Each subject received a complete physical examination, laboratory tests of hematology, clinical chemistry and urinalysis. Only medically healthy subjects with normal laboratory profiles were enrolled in the study.

Selection criteria: Same as the study above.

Dose and treatment: A. 1 x 225 mg Propafenone HCl Tablet, lot #77096, lot size Tablets, potency 98.9%, content uniformity 99.4% (%CV=1.4), manufactured by Watson Laboratories under fasting conditions

B. 1 x 225 mg Propafenone HCl Tablet, lot #77096, manufactured by Watson Laboratories following a standard breakfast.

C. 1 x 225 mg Rythmol Tablet, lot #23000076, potency 97.8%, content uniformity 99.6% (%CV=1.3), Exp. 9/2000, manufactured by Knoll following a standard breakfast.

Food and fluid intake: Subjects on regimens B and C were required to fast overnight until 15 minutes prior to their scheduled dosing times, when they were administered 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). Subjects on regimen A were required to fast overnight for 10 hours before dosing and for 4 hours thereafter. Water was not permitted for one hour before and two hours after dosing except for water (240 mL) administered with the dose.

Washout period: Two weeks

Blood samples: Blood samples were collected at 0 (pre-dose) and at 0.33, 0.66, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 30, 36, 48, 60 and 72 hours post-dose.

Analytical Methodology

Data Analysis

ANOVA was performed with subjects within sequence, period, drug (i.e. formulations), and sequence as factors for AUC(0-t), AUCinf, Cmax and Tmax. Areas under the curve was determined using linear trapezoidal method. The geometric mean for each formulation was calculated for AUC(0-t), AUCinf and Cmax, and is defined as the anti-log of the estimate from the ANOVA of the log-transformed data.

VII. In Vivo Results:

Twenty-four (24) normal, healthy subjects enrolled in the study. Twenty (22) subjects successfully completed the study. Subject #2 withdrew from the study after period 2 and subject #21 withdrew from the study after period 1. Nine adverse events (headache and lightheadedness, possibly drug related) were reported in two subjects dosed over the course of the study. There were no serious adverse events or any events which required terminating any subjects from the study.

The mean plasma concentrations and pharmacokinetic parameters for propafenone, 5-hydroxypropafenone and N-depropylpropafenone are summarized in Tables VII, VIII and IX, respectively.

Table VII

Mean Plasma Propafenone Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 225 mg Propafenone (1x225 mg Tablet) under Fasting and Nonfasting Conditions
(N=22)

Time hr	Treatment A Watson Fasting Lot #R77096 ng/mL (± SD)	Treatment B Watson Nonfasting Lot #R77096 ng/mL (± SD)	Treatment C Knoll Nonfasting Lot #23000076 ng/mL (± SD)
0	0.00 (0.0)	0.00 (0.0)	0.00 (0.0)
0.33	2.52 (5.5)	9.23 (33.0)	4.88 (10.5)
0.66	34.43 (39.0)	57.97 (121.5)	65.45 (113.4)
1	93.83 (79.9)	119.28 (186.4)	142.20 (196.7)
1.25	149.90 (135.5)	151.14 (211.4)	160.17 (190.0)
1.5	179.15 (165.4)	169.83 (232.3)	171.57 (196.9)
2	164.72 (125.9)	191.26 (236.3)	190.24 (211.5)

2.5	164.76 (153.5)	202.86 (239.6)	197.31 (210.9)
3	148.63 (142.7)	194.99 (220.6)	178.75 (204.7)
3.5	137.58 (143.4)	177.82 (193.1)	159.46 (199.2)
4	128.02 (144.6)	162.84 (187.0)	143.60 (188.9)
5	100.09 (150.1)	123.45 (158.1)	110.96 (170.6)
6	79.75 (131.0)	93.65 (145.5)	84.70 (151.0)
8	49.97 (94.3)	64.89 (110.7)	57.86 (112.7)
12	24.28 (57.6)	27.07 (54.3)	26.77 (58.6)
16	14.53 (42.8)	16.34 (42.0)	16.91 (44.1)
24	7.31 (27.5)	7.46 (25.8)	7.28 (25.0)
30	4.54 (19.8)	4.34 (18.1)	4.60 (18.2)
36	2.98 (14.0)	2.70 (12.7)	2.67 (11.9)
48	1.22 (5.7)	1.08 (5.1)	0.95 (4.4)
60	0.78 (3.6)	0.60 (2.8)	0.61 (2.9)
72	0.29 (1.4)	0.39 (1.8)	0.31 (1.5)

AUC(0-t) (ng.hr/mL)	1221.9 (1968)	1443.3 (2231)	1374.4 (2312)
AUCinf (ng.hr/mL)	1242.5(1988)	1467.6(2262)	1392.3(2335)
Cmax(ng/mL)	215.5(184)	259.6(258)	230.0(219)
Tmax(hr)	2.0	2.3	2.2
T1/2 (hr)	3.16	3.64	3.21
Kel (1/hr)	0.26	0.25	0.27

	B/C Arithmetic Mean	B/C Geometric Mean
AUC(0-t)	1.05	1.15
AUCinf	1.05	1.16
Cmax	1.13	1.14

Propafenone

1. None of the subjects reached Cmax at the first sampling time point (0.33 hr). The reviewer has verified the AUC and AUCinf values to be accurate.

2. The propafenone plasma levels peaked at 2.5 hours for both the test and reference products, under nonfasting condition and at 1.50 hour for the test product under fasting condition.

3. For Watson's test product, the mean AUC(0-t), AUCinf and Cmax values were 5.0%, 5.5% and 12.9% higher, respectively, than the reference product values under nonfasting condition. The ratios of the arithmetic and geometric means for propafenone are within the acceptable range of 0.8-1.2 and 0.8-1.25, respectively, under

nonfasting conditions for the above parameters. The reviewer's calculations are similar to those submitted by the firm.

4. For the test product, the mean AUC(0-t) and Cmax values after dosing with food increased by 18.1% and 20.5%, respectively, of the values reported in the fasting state. This is in agreement with PDR (1995). Also, after feeding the mean Tmax was delayed about 0.5 hour relative to the fasting mean Tmax.

Table VIII

Mean Plasma 5-Hydroxypropafenone Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 225 mg Propafenone (1x225 mg Tablet) under Fasting and Nonfasting Conditions
(N=22)

Time hr	Treatment A Watson Fasting Lot #R77096 ng/mL (± SD)	Treatment B Watson Nonfasting Lot #R77096 ng/mL (± SD)	Treatment C Knoll Nonfasting Lot #23000076 ng/mL (± SD)
0	0.00 (0.0)	0.00 (0.0)	0.00 (0.0)
0.33	3.03 (8.2)	6.39 (20.0)	6.59 (10.6)
0.66	45.47 (49.1)	42.33 (68.1)	52.11 (68.4)
1	98.98 (66.1)	78.68 (103.0)	95.55 (106.7)
1.25	127.76 (78.4)	89.39 (99.8)	103.19 (102.3)
1.5	134.40 (72.5)	90.16 (82.2)	113.39 (82.3)
2	123.77 (60.6)	108.06 (60.2)	117.08 (60.0)
2.5	105.76 (51.9)	113.10 (71.3)	113.79 (68.0)
3	87.28 (39.5)	108.18 (68.9)	97.41 (67.2)
3.5	71.61 (30.1)	90.46 (48.6)	77.27 (40.6)
4	62.78 (25.3)	77.54 (39.1)	69.07 (31.9)
5	49.30 (23.1)	61.51 (37.7)	52.27 (25.0)
6	39.88 (20.1)	42.19 (23.5)	37.26 (19.4)
8	26.66 (15.8)	30.71 (18.8)	26.10 (15.5)
12	14.46 (10.4)	16.54 (12.6)	14.44 (11.6)
16	9.19 (6.8)	10.26 (8.2)	9.40 (8.2)
24	4.41 (4.2)	5.48 (4.6)	4.83 (4.4)
30	3.02 (2.8)	3.31 (2.9)	3.27 (3.0)
36	1.40 (2.1)	1.49 (2.0)	1.36 (2.0)
48	0.24 (0.8)	0.35 (0.9)	0.22 (0.7)
60	bql*	bql	bql
72	bql	bql	bql
AUC(0-t) (ng.hr/mL)	723.9 (297)	773.0 (354)	728.8 (353)
AUCinf			

* below quantifiable limit

(ng.hr/mL)	764.1 (299)	810.9 (357)	765.4 (356)
Cmax(ng/mL)	155.1(69)	169.8 (84)	165.6 (96)
Tmax(hr)	1.8	2.1	1.7
T1/2 (hr)	10.52	10.21	9.97
Kel (1/hr)	0.077	0.076	0.079

	B/C Arithmetic Mean	B/C Geometric Mean
AUC(0-t)	1.06	1.09
AUCinf	1.06	1.09
Cmax	1.02	1.09

1. None of the subjects reached Cmax at the first sampling time point (0.33 hr). The reviewer has verified the AUC and AUCinf values to be accurate.

2. The 5-hydroxypropafenone plasma levels peaked at 2 hours for both the test and the reference products under nonfasting condition and at 1.50 hour for the test product under fasting condition.

3. For Watson's test product, the mean AUC(0-t), AUCinf and Cmax values were 6.1%, 6.0% and 2.5% higher, respectively, than the reference product values under nonfasting condition. The ratios of the arithmetic and geometric means for 5-hydroxypropafenone are within the acceptable range of 0.8-1.2 and 0.8-1.25, respectively, under nonfasting conditions for the above parameters. The reviewer's calculations are similar to those submitted by the firm.

4. For the test product, the mean AUC(0-t) and Cmax values after dosing with food increased by 6.8% and 9.5%, respectively, of the values reported in the fasting state.

Table IX

Mean Plasma N-Depropylpropafenone Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 225 mg Propafenone (1x225 mg Tablet) under Fasting and Nonfasting Conditions
(N=22)

Time hr	Treatment A Watson Fasting Lot #R77096 ng/mL (± SD)	Treatment B Watson Nonfasting Lot #R77096 ng/mL (± SD)	Treatment C Knoll Nonfasting Lot #23000076 ng/mL (± SD)
0	0.00 (0.0)	0.00 (0.0)	0.10 (0.3)
0.33	0.07 (0.2)	1.92 (3.4)	1.94 (2.8)

0.66	1.28 (1.6)	4.76 (7.3)	5.49 (8.5)
1	4.22 (3.6)	6.25 (8.2)	5.96 (7.2)
1.25	7.48 (6.7)	7.60 (9.6)	6.97 (7.3)
1.5	8.88 (6.6)	8.43 (7.0)	8.67 (8.3)
2	10.11 (7.9)	9.30 (6.9)	9.30 (8.1)
2.5	10.33 (7.5)	9.80 (6.7)	9.25 (7.8)
3	10.27 (6.9)	9.40 (6.4)	8.38 (7.2)
3.5	9.66 (6.5)	9.34 (7.1)	8.17 (7.6)
4	9.15 (6.1)	8.27 (7.2)	7.58 (8.2)
5	8.46 (6.8)	7.20 (7.2)	6.54 (8.1)
6	7.71 (7.2)	6.10 (7.2)	5.27 (7.7)
8	6.19 (6.9)	3.90 (6.2)	3.29 (5.4)
12	4.12 (6.7)	2.78 (5.4)	2.58 (5.6)
16	2.94 (5.6)	1.47 (3.6)	1.40 (3.8)
24	1.48 (3.6)	0.88 (2.6)	0.80 (2.8)
30	0.85 (2.6)	0.53 (1.8)	0.50 (1.8)
36	0.52 (1.9)	0.18 (0.7)	0.15 (0.5)
48	0.17 (0.6)	0.08 (0.4)	0.07 (0.3)
60	0.09 (0.4)	0.04 (0.2)	0.04 (0.2)
72	0.04 (0.2)	0.04 (0.2)	0.04 (0.2)

AUC(0-t) (ng.hr/mL)	127.3 (187)	122.7 (188)	111.7 (195)
AUCinf (ng.hr/mL)	134.5 (299)	129.9 (190)	118.6 (198)
Cmax(ng/mL)	12.0(8)	12.4 (8)	10.7 (8)
Tmax(hr)	2.5	2.7	2.7
T1/2 (hr)	6.79	6.93	6.54
Kel (1/hr)	0.11	0.11	0.12

	B/C Arithmetic Mean	B/C Geometric Mean
AUC(0-t)	1.10	1.20
AUCinf	1.10	1.18
Cmax	1.16	1.19

1. None of the subjects reached Cmax at the first sampling time point (0.33 hr). The reviewer has verified the AUC and AUCinf values to be accurate.

2. The N-depropylpropafenone plasma levels peaked at 2 and 2.5 hours for the reference and the test and reference products, respectively, under nonfasting condition and at 2.50 hour for the test product under fasting condition.

3. For Watson's test product, the mean AUC(0-t), AUCinf and Cmax values were 9.8%, 9.5% and 15.9% higher, respectively, than the

reference product values under nonfasting condition. The ratios of the arithmetic and geometric means for N-depropylpropafenone are within the acceptable range of 0.8-1.2 and 0.8-1.25, respectively, under nonfasting conditions for the above parameters. The reviewer's calculations are similar to those submitted by the firm.

VIII. Formulations:

Watson's formulations for its propafenone Tablets 300 mg, 225 mg and 150 mg are shown in Table X. The formulations for propafenone 225 mg and 150 mg strengths are proportionally similar to the 300 mg strength.

IX. In vitro Dissolution Testing:

The dissolution testing for the test and reference products is summarized below:

Method: USP 23 apparatus II (paddle) at 50 rpm
Medium: 900 mL of water at 37°c
Number of Tablets:12

Test product: Watson's propafenone Tablets,
150 mg, lot #R76996
225 mg, lot #R77096
300 mg, lot #R69296
Reference product: Knoll's Rythmol^{R} Tablets,
150 mg, lot #21400246
225 mg, lot #23000076
300 mg, lot #21450085

Dissolution Testing results are shown in Table XI.

X. Deficiency Comments:

1. Among the five subjects in the repeated study #97107, subject #25 exhibited the highest T/R ratios for the three pharmacokinetic parameters AUC(0-t), AUCinf and Cmax for propafenone and 5-hydroxypropafenone. The results were consistent with those of the original pivotal study #96040. These high ratios(T/R) of subject #25 in the original and repeated study were the result of the high variability of the drug.

In addition, the subject revealed no clinical abnormalities. Excluding this subject from the statistical analysis of the study is not justified. After including subject #25 in the statistical analysis of the study, the resulting 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are as following:

Propafenone
LnAUC(0-t) 85.6-123.6%

LnAUCinf	83.0-118.4%
LnCmax	85.3-130.0%

Th 90% confidence interval for Cmax is 85% to 130% of the reference parameter for log-transformed data, which is outside the acceptable 80-125% range. Therefore, the study is unacceptable

2. The firm should explain the reason for not including subject #18 in the repeated study (study #97107). Subject #18 exhibited below quantitative limit (BQL) plasma levels for propafenone and its metabolites 5-hydroxypropafenone and N-depropylpropafenone during period II (Reference product) in the original study (study #96040).

3. For the single-dose food-effect study #96043, in the randomly selected chromatograms of subject #3 for determination of 5-hydroxypropafenone, the title on the pages stated 5-hydroxypropafenone but the mass scanning mode was 342-116 m/z propafenone. The firm should explain this discrepancy.

4. The firm should be informed of the following FDA dissolution method instead of the method reported by the firm in the submission:

IN Vitro Dissolution Testing

Method:	USP 23 apparatus II (paddle) at 75 rpm
Medium:	900 mL of 0.1N HCl at 37°c
Number of Tablets:	12
Specification:	NLT % in 30 minutes

XI. Recommendations:

1. The single-dose bioequivalence study #96040, conducted by Watson Laboratories, Inc., on its Propafenone HCl 300 mg Tablet, lot #R69296, comparing it to Rythmol[R] 300 mg tablet, manufactured by Knoll, has been found unacceptable by the Division of Bioequivalence for the reasons given in deficiency comments #1 and 2.

2. The single-dose post-prandial bioequivalence study #96043, conducted by Watson Laboratories Inc., on its Propafenone HCl 225 mg Tablet, lot #R77096, comparing it to Rythmol[R] 225 mg Tablet, manufactured by Knoll, has been found incomplete by the Division of Bioequivalence for the reason given in deficiency comment #3.

3. The dissolution testing conducting by Watson Laboratories Inc., on its Propafenone HCl 300 mg, 225 mg and 150 mg Tablets, lot #R69296, R77096 and R76996, respectively, is unacceptable for the reason given in deficiency comment #4. Waivers of in vivo bioequivalence study requirements for the 225 mg and 150 mg

strengths of the test products can not be granted since the bioequivalence study for Propafenone HCl 300 mg Tablet under fasting condition is unacceptable.

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 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than . % of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

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

/S/

Moheb H. Makary, Ph.D. Date: 2/25/98
Review Branch III
Division of Bioequivalence

/S/

RD INITIALLED SNERURKAR
FT INITIALLED SNERURKAR Date: 2/27/1998

/S/

Concur: Date: 3/11/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/2-17-98, 2-25-98 wp 75203SDW.996
cc: ANDA #75-203, original, HFD-658(Makary), Drug File, Division File.

Table XI

Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Propafenone HCl Lot #R76996 Tablet Strength(mg) 150			Reference Product Rythmol Lot #21400246 Tablet Strength(mg) 150		
	Mean %	Range	%CV	Mean %	Range	%CV
5	59.6		46.1	36.8		32.5
10	92.8		4.0	88.2		4.8
20	95.5		2.7	92.7		3.6
30	96.0		2.1	93		3.3
Sampling Times (Minutes)	Test Product Propafenone HCl Lot #R77096 Tablet Strength(mg) 225			Reference Product Rythmol Lot #23000076 Tablet Strength(mg) 225		
	Mean %	Range	%CV	Mean %	Range	%CV
5	74.9		9.3	48.4		17.7
10	94.5		2.8	87.9		2.9
20	96.3		1.8	92.1		2.7
30	96.8		1.77	93.1		2.6
Sampling Times (Minutes)	Test Product Propafenone HCl Lot #R69296 Tablet Strength(mg) 300 ✓			Reference Product Rythmol Lot #21450085 Tablet Strength(mg) 300 ✓		
	Mean %	Range	%CV	Mean %	Range	%CV
5	62.7		27.1	31.9		52.7
10	86.7		5.2	84.7		9.2
15	89.5		4.2	90.0		4.4
20	90.6		3.8	91.1		3.9

25	91.3		3.5	91.7		3.5
30	91.8		3.4	92.1		3.2

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-203 APPLICANT: Watson Laboratorioes

DRUG PRODUCT: Propafenone HCl Tablets, 300 mg, 225 mg and 150 mg

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

1. Among the five subjects in the repeated study #97107, subject #25 exhibited the highest T/R ratios for the three pharmacokinetic parameters AUC(0-t), AUCinf and Cmax for propafenone and 5-hydroxypropafenone. The results were consistent with those of the original pivotal study #96040. These high ratios(T/R) in the original and repeated study were the result of high variability of the drug.

Excluding this subject from the statistical analysis of the study is not justified. After including subject #25 in the statistical analysis of the study, the resulting 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are as following:

Propafenone	
LnAUC(0-t)	85.6-123.6%
LnAUCinf	83.0-118.4%
LnCmax	85.3-130.0%

Th 90% confidence interval for Cmax is 85% to 130% of the reference parameter for log-transformed data, which is outside the acceptable 80-125% range. Therefore, the study is unacceptable

2. Please explain the reason for not including subject #18 in the repeated study (study #97107). Subject #18 exhibited below quantitative limit (BQL) plasma levels for propafenone and its metabolites 5-hydroxypropafenone and N-depropylpropafenone during period II (Reference product) in the original study (study #96040).

3. For the single-dose food-effect study #96043, in the randomly selected chromatograms of subject #3 for determination of 5-hydroxypropafenone, the title on the pages stated 5-hydroxypropafenone but the mass scanning mode was 342-116 m/z propafenone. Please explain this discrepancy.

4. The following FDA dissolution method is recommened instead of the method reported in the submission:

IN Vitro Dissolution Testing

Method:	USP 23 apparatus II (paddle) at 75 rpm
Medium:	900 mL of 0.1N HCl at 37°c
Number of Tablets:	12
Specification:	NLT % in 30 minutes

Sincerely yours,

/S/

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

CC: ANDA #75-203
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Secretary - Bio Drug File
HFD-650/ Reviewer

Endorsements: (Final with Dates)
HFD-658/ Reviewer Moheb Makary MHM
HFD-655/ Bio team Leader 3/11/98
HFD-617/ L. Sanchez or N.Chamberlin
HFD-650/ D. Conner ADK 3/11/98
nz

Printed in final on 3/11/98

BIOEQUIVALENCY - DEFICIENCIES submission date: 9-11-97

1. **FASTING STUDY** (STF) Strengths: 300 mg Tablet
Clinical: **Outcome: UN**
Analytical:

2. **FOOD STUDY** (STP) Strengths: 225
Clinical:
Analytical:

3. **DISSOLUTION WAIVER** (DIW) Strengths: 225 mg and 150 mg
Outcome: UN

OUTCOME DECISIONS: **UN** - Unacceptable

Table IV

000404 A

verse Events

During this clinical evaluation, the following side effects, or adverse events were reported by the volunteers, or elicited, or observed by the staff.

Subject	Assigned Drug*	Adverse Event	Severity	Period/ Date of Onset	Hours Post-Dose	Hours Duration	Therapy/Comments
01,	R	Nausea	Moderate	1 - 05/27/97	416.25	53	Trimethobenzamide 250 mg bid x 3 doses. Possibly drug related.
01,	R	Intermittent Vomiting	Moderate	1 - 05/27/97	416.25	18	Trimethobenzamide 250 mg bid x 3 doses. Possibly drug related.
01,	R	Diarrhea	Moderate	1 - 05/27/97	416.25	53	Amoxicillin 250 mg tid x 30 doses. Unlikely drug related.
05,	R	Shoulder Injury	Moderate	1 - 06/07/97	680.25	50	Ibuprofen 2 x 200 mg Not drug related.

*R = Reference

otocol Exceptions

This project was performed in conformance with the study protocol #97107, with the following exceptions:

- Study Timing: The original washout phase between study periods was to have been three weeks in order to accommodate study participant work/personal schedules. However, at post-dose hour 416, Subject No. 01/25 developed flu-like symptoms which required a three-week delay to allow prescribed medication to wash-out of his system.

- Of the six (6) subjects enrolled in the study, five (5) completed the study in its entirety. Subject #04, was unable to participate in Study Period II, because he was unable to comply with the change in schedule, necessitated by the illness of Subject #01.

000235

Table V

Table 1: Propafenone Pharmacokinetic Parameters

Comparison of Results Obtained from Fasting Definitive Study (#96040) and Fasting Re-confirmed Study (#97107)
Propafenone HCl 300 mg, Single Dose Fasted Study (Component: Propafenone)

#96040 Study

		Test Formulation (Lot R69296)				Reference Formulation (Lot 21450085)				Parameter Ratio (Test/Reference)			
Subject #	Sequence	Cmax (ng/mL)	AUC 0-t (ng*h/mL)	AUC 0-inf (ng*h/mL)	t 1/2 (hr)	Cmax (ng/mL)	AUC 0-t (ng*h/mL)	AUC 0-inf (ng*h/mL)	t 1/2 (hr)	Cmax	AUC 0-t	AUC 0-inf	t 1/2
(25)													
(23)													
(11)													
(40)													
(02)													
ARITH MEAN (N=5)		441.2	1638.7	1655.2	2.88	334.5	1399.6	1414.9	2.90	2.150	1.812	1.770	1.087
STD DEV		449.2	1526.8	1530.4	1.22	252.3	1086.0	1088.5	1.18	2.298	1.711	1.626	0.439
C.V. (%)		101.8	93.2	92.5	42.31	75.4	77.6	76.9	40.53	106.873	94.416	91.853	40.363
ARITH MEAN (N=32)		318.9	1269.9	1284.2	2.94	314.2	1403.9	1464.8*	2.89*	1.366	1.258	1.203*	0.983*
STD DEV		331.8	1188.3	1191.4	1.02	281.1	1391.2	1396.5*	1.18*	1.167	0.948	0.887*	0.555*
C.V. (%)		104.0	93.6	92.8	34.81	89.5	99.1	95.3*	40.78	85.386	75.353	73.763*	56.446*
LSM Ratio (N=32) Excluding Subject 18 (plasma concentrations are BQL after Reference formulation)										105.3	102.9	99.1*	—
90% CI (N=32)										84.6-131.1	85.0-124.5	82.5-119.1	—
LSM Ratio (N=31) Excluding Subjects 18 and 25										**100.1**	**98.4**	**94.9***	—
90% CI (N=31)										**82.0-122.3**	**82.7-117.1**	**80.5-112.0**	—

Note: * N may be differed due to some subjects did not have accurate half-life determination; in all cases N >= 29)

#97107 Study

		Test Formulation (Lot R69296)				Reference Formulation(Lot 21450085)				Parameter Ratio (Test/Reference)				% Change (T/R Ratio) versus #96040			
Subject #	Sequence	Cmax (ng/mL)	AUC 0-t (ng*h/mL)	AUC 0-inf (ng*h/mL)	t 1/2 (hr)	Cmax (ng/mL)	AUC 0-t (ng*h/mL)	AUC 0-inf (ng*h/mL)	t 1/2 (hr)	Cmax	AUC 0-t	AUC 0-inf	t 1/2	Cmax	AUC 0-t	AUC 0-Inf	t 1/2
01 (25)																	
02 (23)																	
03 (11)																	
05 (40)																	
06 (02)																	
ARITH MEAN (N=5)		231.6	980.7	996.3	2.30	165.9	716.6	731.4	2.35	1.826	1.732	1.688	0.994	**23.388**	**17.033**	**17.077**	**6.151**
STD DEV		146.5	713.3	716.5	0.11	115.5	506.1	512.9	0.31	1.305	1.243	1.143	0.147	**94.716**	**74.005**	**72.337**	**47.414**
C.V. (%)		63.2	72.7	71.9	4.62	69.6	70.6	70.1	13.09	71.486	71.770	67.724	14.798	**404.981**	**434.467**	**423.586**	**770.798**

000236

Table VI

Table 2: 5-Hydroxypropaferone Pharmacokinetic Parameters

Comparison of Results Obtained from Fasting Definitive Study (#96040) and Fasting Re-confirmed Study (#97107)
Propafenone HCl 300 mg, Single Dose Fasted Study (Component: 5-Hydroxypropaferone)

#96040 Study

		Test Formulation (Lot R69296)				Reference Formulation (Lot 21450085)				Parameter Ratio (Test/Reference)			
Subject #	Sequence	Cmax (ng/mL)	AUC 0-t (ng*h/mL)	AUC 0-Inf (ng*h/mL)	t 1/2 (hr)	Cmax (ng/mL)	AUC 0-t (ng*h/mL)	AUC 0-Inf (ng*h/mL)	t 1/2 (hr)	Cmax	AUC 0-t	AUC 0-Inf	t 1/2
(25)													
(23)													
(11)													
(40)													
(02)													
ARITH MEAN (N=5)		245.6	1201.1	1250.7	11.31	180.9	1048.1	1085.5	9.83	1.611	1.297	1.290	1.135
STD DEV		83.4	507.5	516.4	4.00	81.6	507.2	512.1	1.51	0.945	0.488	0.466	0.305
C.V. (%)		34.0	42.3	41.3	35.38	45.1	48.4	47.2	15.33	58.678	37.626	36.081	26.895
ARITH MEAN (N=32)		225.8	1129.4	1186.9*	9.67*	220.5	1121.5	1156.3	8.97	1.149	1.085	1.085*	1.096*
STD DEV		79.9	473.1	487.2*	3.22*	108.6	576.7	580.1	2.36	0.508	0.274	0.270*	0.296*
C.V. (%)		35.4	41.9	41.0*	33.34*	49.2	51.4	50.1	26.27	44.251	25.241	24.875*	27.032*
LSM Ratio (N=32) Excluding Subject 18 (plasma concentrations are BQL after Reference formulation)										106.4	105.3	105.3*	—
90% CI (N=32)										94.8-119.4	98.2-113.0	97.9-113.2	—
LSM Ratio (N=31) Excluding Subjects 18 and 25										**103.1**	**103.2**	**103.2***	—
90% CI (N=31)										**93.4-113.7**	**97.3-109.5**	**97.1-109.6**	—

Note: * N may be differed due to some subjects did not have accurate half-life determination; in all cases N >= 29)

#97107 Study

		Test Formulation (Lot R69296)				Reference Formulation (Lot 21450085)				Parameter Ratio (Test/Reference)				% Change (T/R Ratio) versus #96040			
Subject #	Sequence	Cmax (ng/mL)	AUC 0-t (ng*h/mL)	AUC 0-Inf (ng*h/mL)	t 1/2 (hr)	Cmax (ng/mL)	AUC 0-t (ng*h/mL)	AUC 0-Inf (ng*h/mL)	t 1/2 (hr)	Cmax	AUC 0-t	AUC 0-Inf	t 1/2	Cmax	AUC 0-t	AUC 0-Inf	t 1/2
01 (25)																	
02 (23)																	
03 (11)																	
05 (40)																	
06 (02)																	
ARITH MEAN (N=5)		188.4	959.5	1003.2	10.34	151.2	806.9	851.0	9.65	1.397	1.298	1.267	1.078	**-10.634**	**1.318**	**-0.451**	**1.204**
STD DEV		46.6	436.6	447.8	1.48	54.8	349.0	354.9	1.46	0.735	0.557	0.507	0.137	**19.258**	**31.886**	**30.437**	**31.085**
C.V. (%)		24.8	45.5	44.6	14.34	36.2	43.3	41.7	15.15	52.633	42.888	39.984	12.675	**-181.097**	**2418.880**	**-6756.077**	**2581.445**

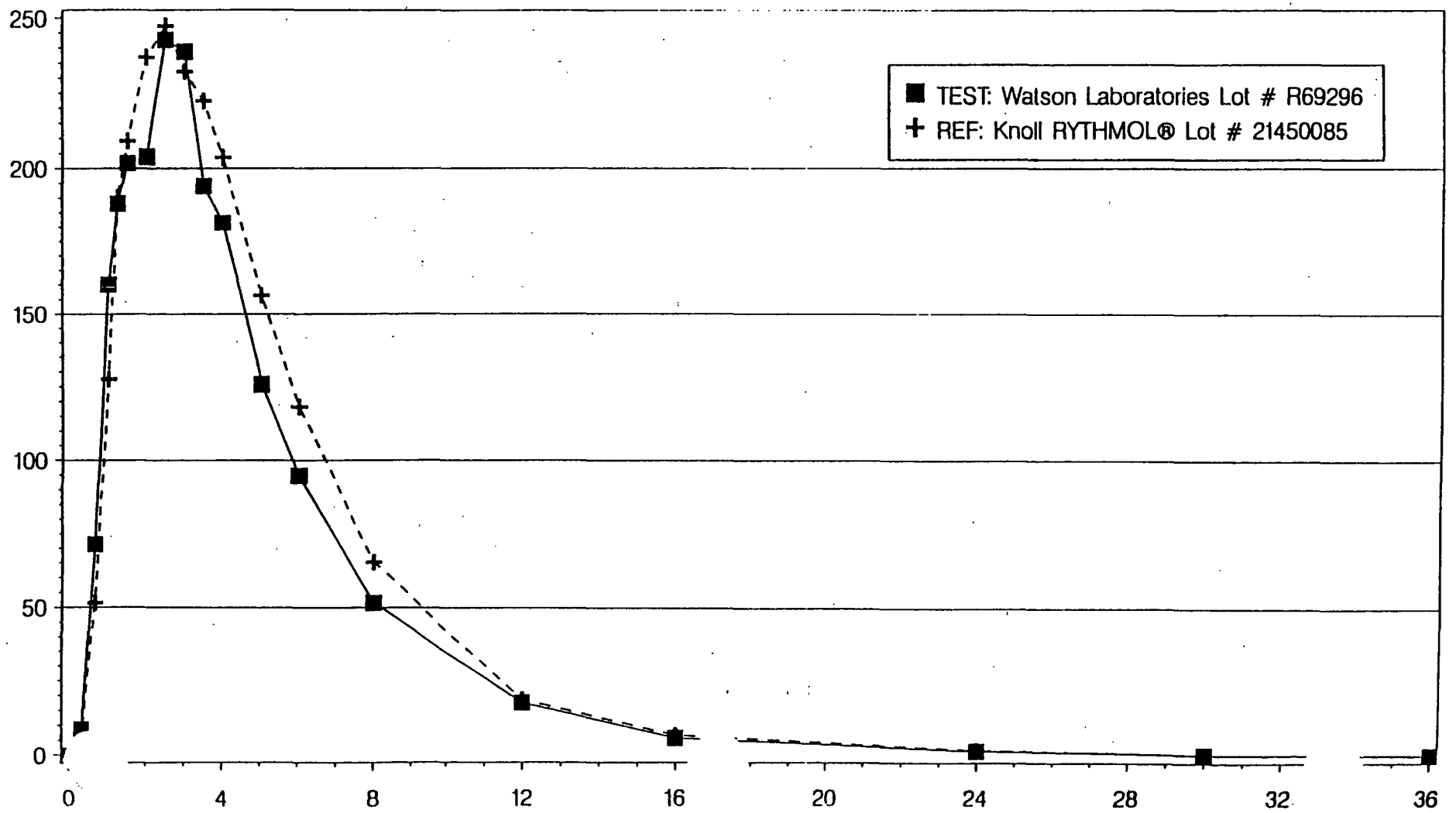
Watson Laboratories, Inc. Study 96040, Propafenone HCl 300 mg, single dose fasted, PROPAFENONE component
Comparison of Watson test lot R69296 with Knoll RYTHMOL(R) lot 21450085, excluding Subjects 18 and 25
Table 3. Cmax (ng/mL) analysis 23:02 Sunday, December 8, 1996
Sub-table 3a. DATA.

ID	SEQUENCE	TEST Cmax	REFERENCE Cmax	TEST - REF DIFFERENCE	TEST/REF RATIO	ln (TEST/REF)	TEST ln(Cmax)	REFERENCE ln(Cmax)
01								
02								
03								
07								
08								
10								
11								
12								
14								
15								
16								
17								
19								
20								
21								
23								
24								
26								
27								
28								
30								
31								
32								
33								
34								
35								
36								
37								
38								
39								
40								
MEAN		325.6	323.7	1.9	1.211	0.003	5.331	5.327
STD DEV		335.1	280.4	236.3	0.782	0.620	1.033	1.156
GEOM MEAN		206.5	205.9		1.003			
C.V. (%)		102.9	86.6		64.527		19.372	21.700

Mean Propafenone Plasma Concentration versus Time

Watson Laboratories Protocol 96040, 31 Subjects

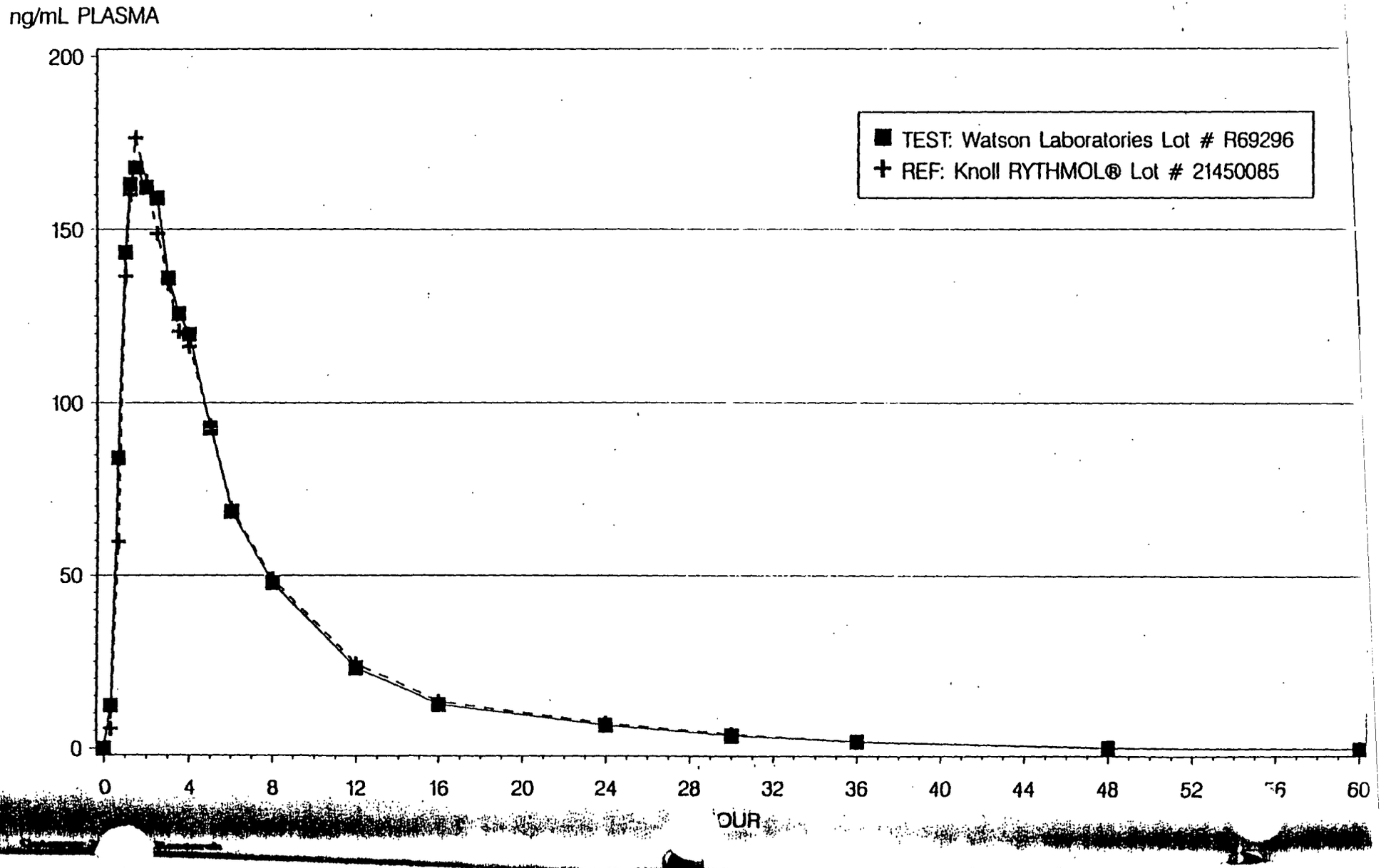
ng/mL PLASMA



000011

Mean 5-Hydroxypropafenone Plasma Concentration versus Tin

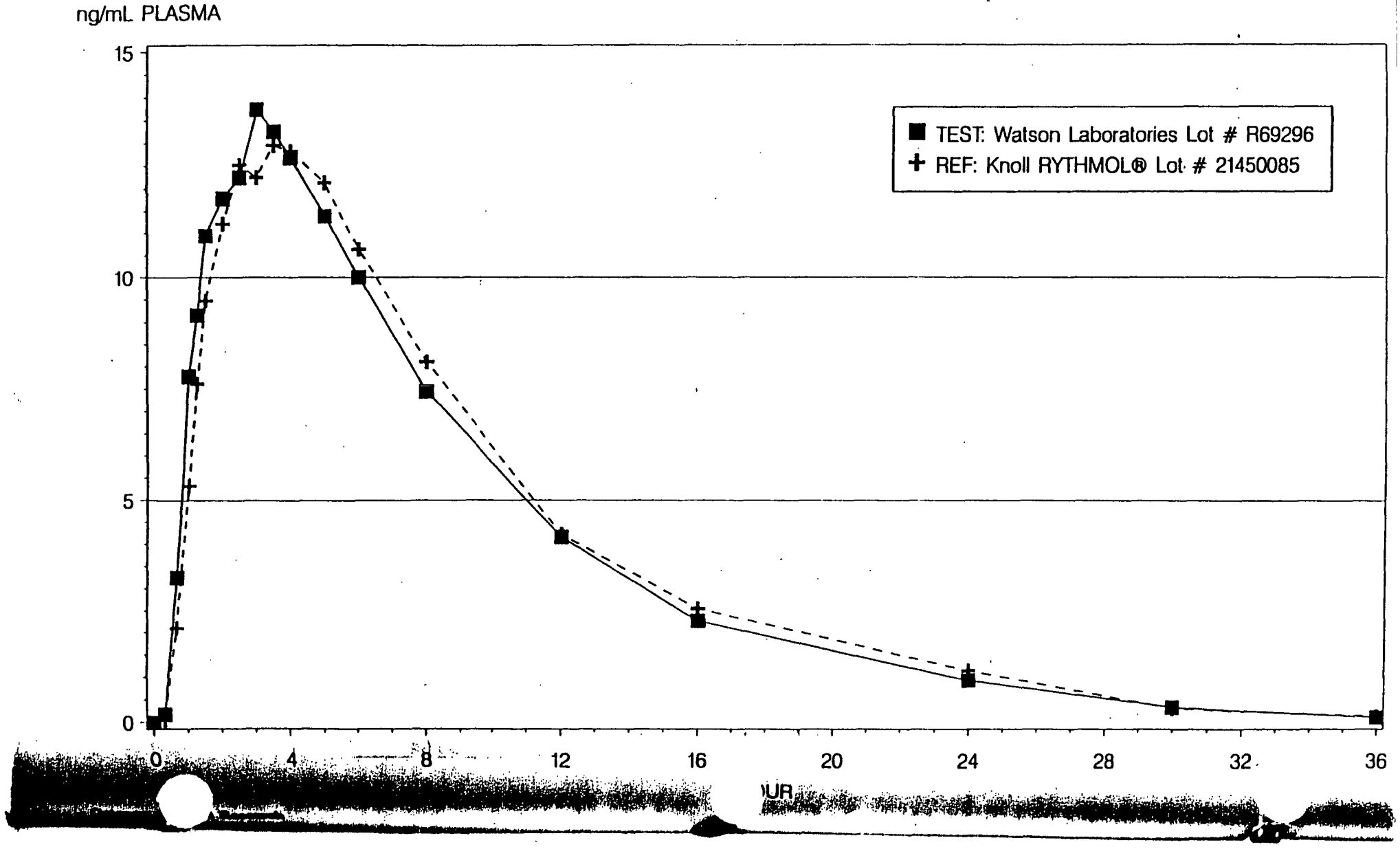
Watson Laboratories Protocol 96040, 31 Subjects



000013

Mean N–Depropylpropafenone Plasma Concentration versus Time

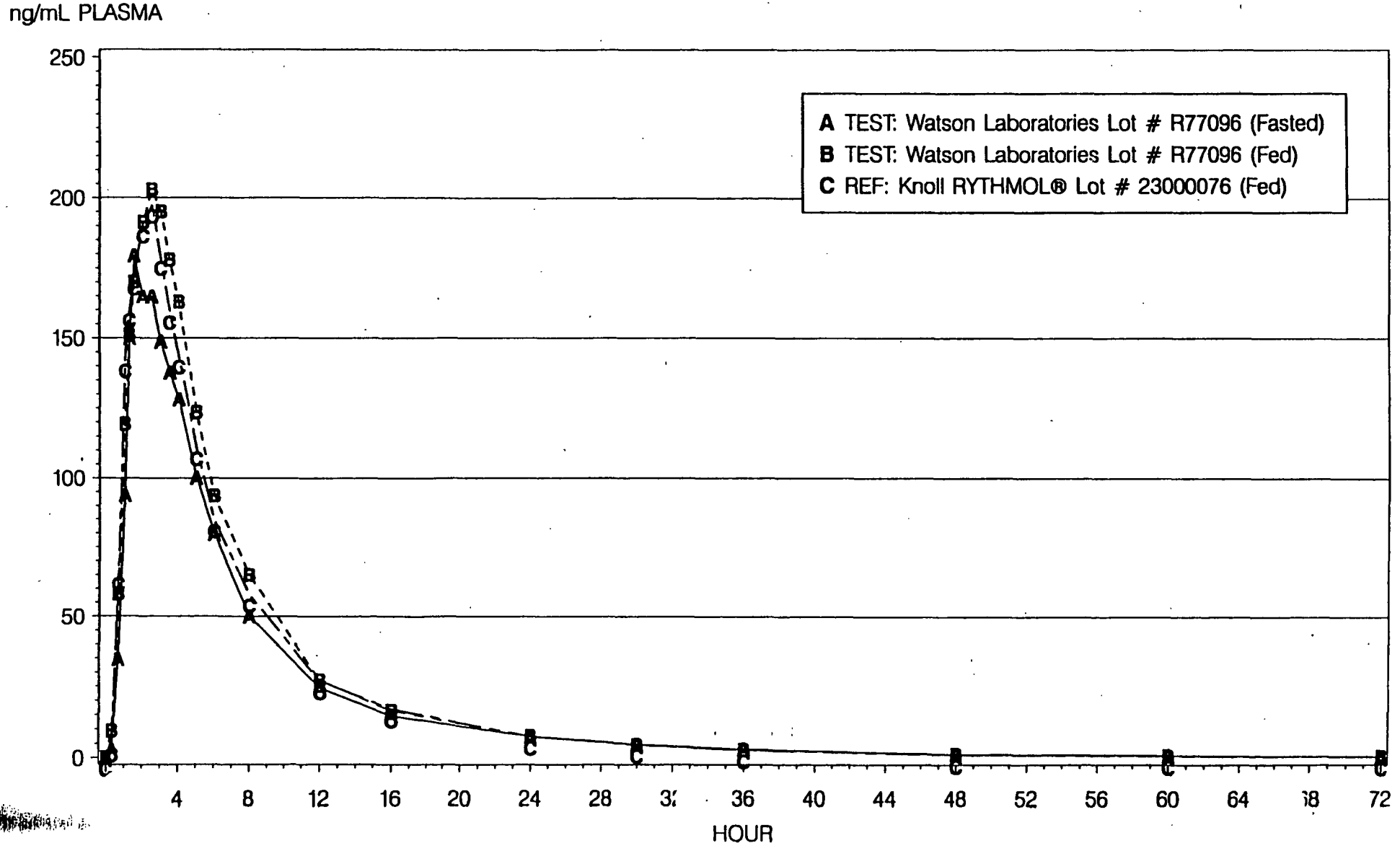
Watson Laboratories Protocol 96040, 31 Subjects



000009

Mean Propafenone Plasma Concentration versus Time

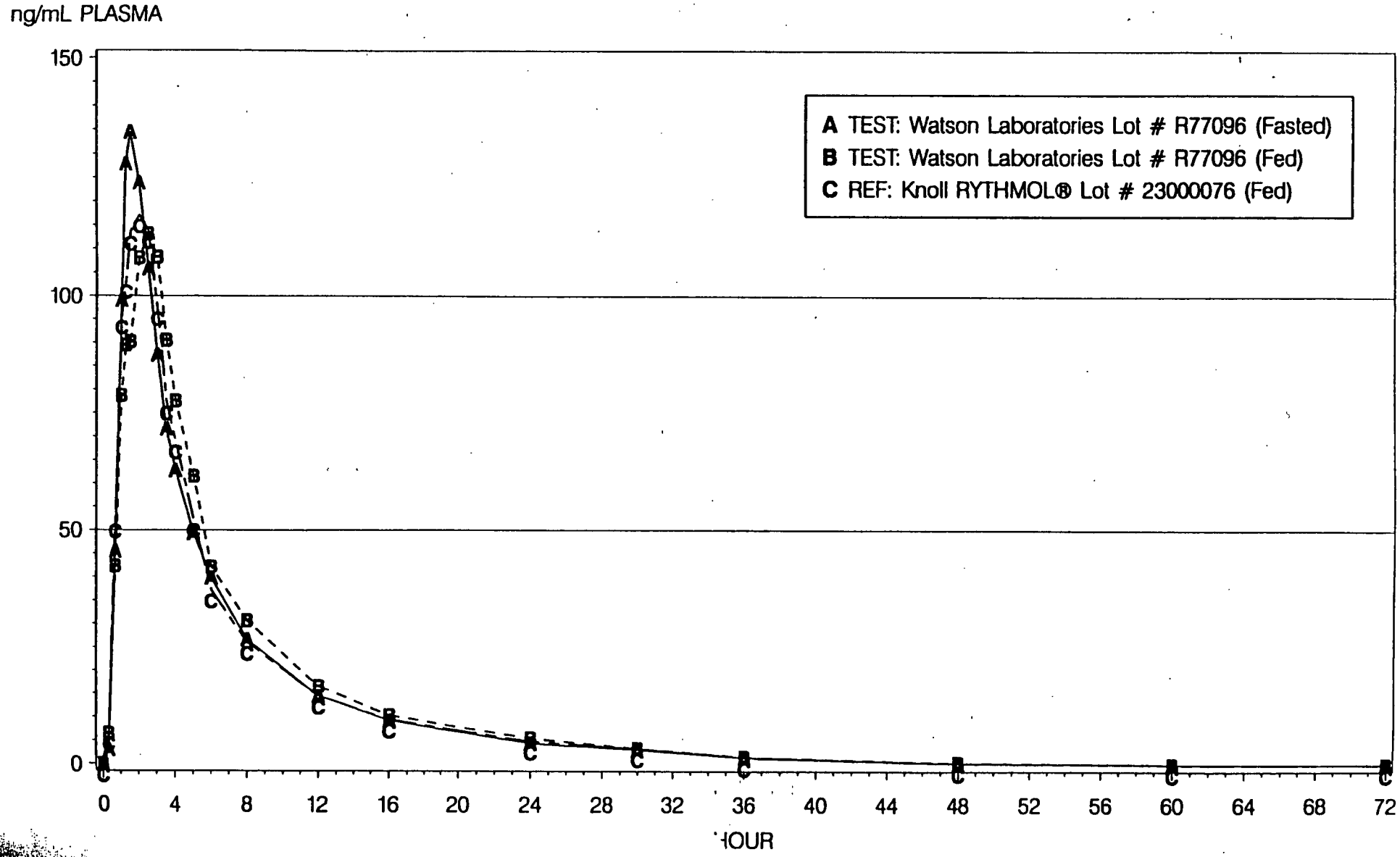
Watson Laboratories Protocol 96043, 22 Subjects



000011

Mean 5 – Hydroxypropafenone Plasma Concentration versus Time

Watson Laboratories Protocol 96043, 22 Subjects



000013

Mean N – Depropylpropafenone Plasma Concentration versus Time

Watson Laboratories Protocol 96043, 22 Subjects