

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER **74865** _____

BIOEQUIVALENCE REVIEW(S)

ANDA 74-865

Danbury Pharmacal, Inc.
Attention: William R. McIntyre, Ph.D.
131 West Street
Danbury CT 08610
|||||

5 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Mexiletine Hydrochloride Capsules USP, 150 mg, 200 mg, and 250 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.
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 water at 37°C using USP 23 Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

Not less than 75% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

~~Keith K. Chan, Ph.D.~~
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 28 1996

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Mexiletine Hydrochloride
Capsules

Danbury Pharmacal

150 mg, 200 mg and 250 mg
Capsules

Danbury, CT

ANDA #74865

Submission Date:

Reviewer: Moo Park

February 29, 1996

Filename: 74865SDW.296

**Review of Two *In Vivo* Bioequivalence Studies, Dissolution
Data and Waiver Request**

I. Objectives

Review of:

- Danbury's two *in vivo* bioequivalence studies under fasting and non-fasting conditions comparing its 250 mg strength Mexiletine Capsules to the reference drug product, Boehringer Ingelheim's Mexitil^R Capsules 250 mg.
- Dissolution data for 150 mg, 200 mg and 250 mg strengths test and reference drug products.
- Waiver requests for the 150 mg and 200 mg strength capsules.

II. Background

Mexiletine HCl is an orally active antiarrhythmic agent that is structurally similar to lidocaine. The drug has been proven to be effective in the suppression of symptomatic ventricular arrhythmias (ventricular tachycardia, couplets and PVCs) in controlled clinical trials and in long term use. Serious adverse events have occasionally been reported. The most common adverse reactions to Mexiletine are reversible upper GI and CNS effects, which can often be avoided by administration with food and careful dosage titration.

Mexiletine is well absorbed (approximately 99%) from the GI tract. Unlike lidocaine, its first-pass metabolism is low. Peak blood levels are reached in 2-3 hours. In normal subjects, the plasma elimination half-life of the drug is approximately 10-12 hours. It is 50-60% bound to plasma protein, with a volume of distribution of 5-7 liters/kg. Mexiletine is metabolized in the liver.

Approximately 10% is excreted unchanged by the kidney. While urinary pH does not normally have much influence on elimination, marked changes in urinary pH influence the rate of excretion: acidification accelerates excretion, while alkalinization retards it.

Mexiletine is available commercially as Mexitil oral, 150 mg, 200 mg and 250 mg capsules, manufactured by Boehringer Ingelheim. The usual oral dosage is 200 to 300 mg (up to a maximum of 400 mg) given every 8 hours with food or antacids. For rapid response, an initial dose of 400 mg may be given. Reduced dosage may be required in patients with hepatic impairment.

III. Study Details

A. BE Study under Fasting Conditions

1. Objective: To compare the single-dose bioavailability of Danbury and Boehringer Ingelheim (Mexitil[®]) 250 mg Mexiletine HCl capsules under fasting conditions.
2. Protocol #920999
3. Study design: Open-label, randomized, 2-way crossover, single-dose, fasting study.
4. Study sites:
 - Clinical study:

 - Analytical:
5. Investigators:
 - Principal investigator:
International

 - Analytical investigator:
6. Clinical study dates: 2/10/93-2/19/93
Assay dates: 5/7/93-5/26/93
7. Number of subjects: All 26 non-smokers enrolled completed the crossover. Samples from the first 12 subjects on each sequence to complete the crossover were assayed. Thus, statistical analyses were performed on data from 24 subjects (Subject Nos. 1-24).

Screening: Subjects were non-smoking male volunteers, 18-45 years of age, weighing at least 60 kg, who are within 15% of their ideal weights (Table of Desirable Weights of Adults, Metropolitan Life Insurance Company, 1983). Medical histories and demographic data, including name, sex, age, race, body weight (kg), height (cm), body build and smoking habits were recorded. Each subject received a complete physical examination, 12-lead EKG and the laboratory tests of hematologic, hepatic and renal functions. Only medically healthy subjects with clinically normal laboratory profiles and EKG were enrolled in the study.

8. Product information:

Test Product: Danbury 250 mg Mexiletine HCl capsules (Control No: 09520C; Catalog No. 5872, expiry date: not given).

Reference Product: Boehringer Ingelheim (Mexitil) 250 mg Mexiletine HCl capsules {Lot No. 682001A, expiry date: 7/95}.

9. Dosing: Single oral 250 mg dose, administered with 240 mL of ambient temperature water.

10. Blood sampling: Blood samples were collected in Vacutainers containing EDTA before dosing and at the following times after dosing: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 16, 24, 36 and 48 hours.

11. Safety monitoring: Blood pressure and heart rate measurements were performed pre-dose and approximately 10 minutes before the blood draws at 2 and 4 hours after dosing. Vital sign measurements were performed at other times when deemed necessary. No safety problems were encountered.

12. Food and water intake: Subjects fasted overnight before dosing and for 4 hours thereafter. Water was not permitted for 2 hours before and 4 hours after dosing, but was allowed at all other times. Standard meals were provided at 4 and approximately 9 hours after dosing and at appropriate times thereafter. Meal plans were identical for both periods.

13. Housing: From 12 hours before dosing until after the 36-hour blood draw. Subjects returned for the 48-hour blood draw.

14. Washout period: 7 days between doses.

15. IRB and informed consent: Yes

16. Assay of plasma samples:

17. Pharmacokinetic and statistical analysis: SAS-GLM procedure was used on AUCT, AUCI, CMAX, TMAX, KE, THALF and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for AUCT, AUCI and CMAX.

B. BE Study under Non-fasting Conditions

1. Objective: To compare the single-dose bioavailability of Danbury and Boehringer Ingelheim (Mexitil^R) 250 mg Mexiletine HCl capsules under nonfasting conditions, and to compare the bioavailability of the Danbury product under nonfasting and fasting conditions, for labeling purposes.

2. Protocol #921001

3. Study design: Open-label, randomized, three-way crossover study to compare the single-dose bioavailability of Danbury and Boehringer Ingelheim (Mexitil) 250 mg Mexiletine HCl capsules under nonfasting conditions, and to compare the bioavailability of the Danbury product under nonfasting and fasting conditions.

4. Study sites:
Clinical study:

Analytical:

5. Investigators:
Principal investigator:

Analytical investigator:

6. Clinical study dates: 5/27/93-6/12/93

Assay dates: 6/17/93-8/2/93

7. Number of subjects: Of the eighteen subjects enrolled in the study, one did not complete the crossover. Subject No. 18 withdrew from the study after Period 1 for personal reasons. Thus, statistical analyses were performed on data from 17 subjects (Subjects No. 1-17).

8. Product information:

Test Product: Danbury 250 mg Mexiletine HCl capsules
(Control No: 09520C; Catalog No. 5872,
expiry date: not given).

Reference Product: Boehringer Ingelheim (Mexitil) 250 mg

Mexiletine HCl capsules {Lot No. 682001A, expiry date: 7/95}.

9. Dosing regimen:

Regimen #1: Single oral 250 mg dose, administered with 240 mL of water at ambient temperature.

Regimens #2 and 3: Single oral 250 mg dose, administered with 240 mL of water at ambient temperature 20 minutes after a standard breakfast.

Test Regimen #1: Danbury 250 mg Mexiletine HCl capsules USP Control No. 09520C (catalog No. 5872), expiry date: not given, administered under fasting conditions.

Test Regimen #2: Danbury 250 mg Mexiletine HCl capsules USP Control No. 09520C (Catalog No. 5872), expiry date: not given, administered under nonfasting conditions.

Ref. Regimen #3: Boehringer Ingelheim (Mexitil) 250 mg Mexiletine HCl capsules - Lot No. 682001A, expiry date: 7/95, administered under nonfasting conditions.

10. Blood sampling: Blood samples were collected in Vacutainers containing EDTA before dosing and at the following times after dosing: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 16, 24, 36 and 48 hours.

11. Safety monitoring: Blood pressure and heart rate measurements were performed pre-dose and approximately 10 minutes before the blood draws at 2 and 4 hours after dosing. Vital sign measurements were performed at other times when deemed necessary. No safety problems were encountered.

12. Food and water intake:

Regimen #1: Subjects fasted overnight before dosing and for 4 hours thereafter.

Regimens #2 and 3: Subjects were required to fast overnight until 20 minutes prior to their scheduled dosing times when they were given a standard breakfast. Subjects fasted for 4 hours after dosing.

All Regimens: Water intake was restricted for 2 hours before and 4 hours after drug administration, but allowed at all other times. Standard meals were provided at 4 and approximately 9 hours after drug administration and at

appropriate times thereafter. During housing, meal plans (at 4 and 9 hours post-dose) were identical for all three periods.

13. Housing: From 12 hours before dosing until after the 36-hour blood draw. Subjects returned for the 48-hour blood draw.
 14. Washout period: 7 days between doses.
 15. IRB and informed consent: Yes
 16. Assay of plasma samples:
 17. Pharmacokinetic and statistical analysis: SAS-GLM procedure was used on AUCT, AUCI, CMAX, TMAX, KE, THALF and blood levels at each sampling points. Test product/reference product ratios were calculated for AUCT, AUCI and CMAX.
- IV. Validation of Assay Method for Plasma Samples

V. In Vivo Results with Statistical Analysis

Danbury conducted two in vivo bioequivalence studies as summarized below: BE study under fasting conditions and BE study under non-fasting conditions.

A. BE Study under Fasting Conditions

A total of 26 healthy non-smoking male volunteers enrolled in and completed the 2-period crossover study. Statistical analyses were performed on data from the first 12 subjects on each sequence (subjects #1-24).

Protocol deviations: Subject No. 1 reported that he consumed 20 mL of Pepsi-Crystals 15.0 hours prior to Period 2 dosing. Six insignificant blood collection time deviations were reported. The deviations listed above were judged unlikely to affect the bioavailability comparison.

Medical events: Three insignificant medical events were reported (test product: 2/ 1 subject; reference product: 1/ 1 subject). No medication was required for any medical event.

1. Mean plasma levels

Mean mexiletine plasma levels are comparable for the test and reference products throughout the sampling period as shown in Table 1 and Figure P-1. Peak Mean plasma levels were 465 ng/mL at 3 hours for the test product and 444 ng/mL at 2.5 hours for the reference product.

Table 5. MEAN PLASMA MEXILETINE LEVELS FOR TEST AND REFERENCE PRODUCTS
 MEAN1=TEST PRODUCT; MEAN2=REFERENCE PRODUCT
 Danbury's test product 250 mg, Lot #09520C
 Boehringer Ingelheim's reference product 250 mg, Lot #682001A

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	8.60	16.92	48.25	43.66	0.18
1	240.97	143.93	280.73	119.75	0.86
1.5	359.50	131.60	383.08	122.61	0.94
2	428.48	125.34	437.58	103.61	0.98
2.5	464.30	111.53	444.10	106.28	1.05
3	465.15	117.03	437.74	105.28	1.06
4	464.33	113.90	431.50	109.74	1.08
6	250.94	120.51	222.33	93.68	1.13
9	248.47	84.90	228.60	64.71	1.09
12	164.80	72.01	172.73	61.56	0.95
16	121.87	63.03	114.72	44.55	1.06
24	96.57	64.22	91.66	48.20	1.05
36	32.24	35.95	32.04	24.74	1.01
48	12.29	20.95	12.99	19.57	0.95

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

1. Pharmacokinetic parameters

The test/reference ratios for non-transformed PK parameters (AUCT, AUCI and CMAX) and log-transformed PK parameters (LAUCT, LAUCI and LCMAX) are within the range of 1.0-1.05 as shown in Table 6. The 90% confidence intervals for the non-transformed PK parameters (AUCT, AUCI and CMAX) and log-transformed PK parameters (LAUCT, LAUCI and LCMAX) are within 80-125% range as shown in Table 7.

No period, treatment and sequence effects were detected for the log-transformed and non-transformed PK parameters.

Table 6. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	6381.95	2834.57	6099.17	2230.97	1.05
AUCT	5774.63	2602.23	5603.46	2004.72	1.03
CMAX	498.50	119.37	475.27	100.56	1.05
KE	0.07	0.01	0.07	0.01	1.03
LAUCI*	5874.12	0.41	5741.45	0.35	1.02
LAUCT*	5278.70	0.43	5270.99	0.36	1.00
LCMAX*	485.54	0.23	464.80	0.22	1.04
THALF	9.61	1.86	9.92	2.05	0.97
TMAX	3.00	0.75	2.77	0.77	1.08

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

Table 7. LSMEANS AND 90% CONFIDENCE INTERVALS

PARAMETER	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCI	6347.91	6071.94	97.54	111.55
AUCT	5774.63	5603.46	94.86	111.25
CMAX	498.50	475.27	98.14	111.63
LAUCI	5855.04	5732.72	95.56	109.16
LAUCT	5278.70	5270.99	91.71	109.36
LCMAX	485.54	464.80	97.91	111.45

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

B. BE Study under Non-fasting Conditions

Of the 18 subjects enrolled in the study, 17 subjects completed the 3-period crossover study. Subject #18 withdrew from the study after Period 1 for personal reasons. Thus, data from 17 subjects were used in the statistical analyses.

Protocol deviations: Eight insignificant blood collection time deviations were reported. The deviations were judged unlikely to affect the bioavailability comparison.

Medical Events: Three insignificant medical events were reported (test product: 1/ 1 subject; reference product: 2/ 2 subject). No medication was required for any medical event.

1. Mean plasma levels

The absorption of test mexiletine appears to be slightly faster under fasting conditions as compared to the absorption under non-fasting conditions as shown in Table 8 and Figure P-2.

The test and reference products under non-fasting conditions also showed difference in absorption up to 3 hours post-dose as shown by the test/reference ratio (RMEAN23) in Table 8. Absorption from the test product appears to be slower as compared to the reference product.

Table 8. MEAN PLASMA MEXILETINE LEVELS FOR TEST AND REFERENCE PRODUCTS
 MEAN1=TEST (FASTING); MEAN2=TEST (FED); MEAN3=REFERENCE (FED)
 Danbury's test product 250 mg, Lot #09520C
 Boehringer Ingelheim's reference product 250 mg, Lot #682001A

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	14.42	25.99	1.59	4.84	15.91	42.66
1	320.67	157.17	15.66	23.55	89.68	161.18
1.5	439.48	121.95	71.61	63.24	209.77	154.91
2	496.08	95.17	162.54	104.21	302.02	147.32
2.5	505.79	115.99	288.38	131.46	394.44	121.85
3	504.43	105.03	385.96	118.71	453.39	103.19
4	495.26	93.75	481.01	78.77	457.07	70.70
6	307.76	87.82	402.35	73.73	357.07	77.07
	306.91	73.39	320.24	64.42	303.59	64.70
	231.54	73.64	230.94	70.82	229.77	63.54
16	177.14	63.18	188.31	55.21	166.09	51.75
24	107.12	49.10	118.97	46.20	106.32	37.16
36	47.45	32.98	49.92	29.28	46.56	26.19
48	20.42	21.27	17.18	18.26	19.56	18.37

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.5	9.06	0.91	0.10
1	20.48	3.58	0.17
1.5	6.14	2.10	0.34
2	3.05	1.64	0.54
2.5	1.75	1.28	0.73
3	1.31	1.11	0.85
4	1.03	1.08	1.05
6	0.76	0.86	1.13
9	0.96	1.01	1.05
12	1.00	1.01	1.01
16	0.94	1.07	1.13
24	0.90	1.01	1.12
36	0.95	1.02	1.07
48	1.19	1.04	0.88

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

2. Pharmacokinetic parameters

The test/reference ratios under non-fasting conditions for the non-transformed and log-transformed pharmacokinetic parameters are within 0.98-1.03 and satisfy FDA requirements as shown in Table 9. LSMEANS are shown in Table 10. The data in Tables 9-10 show that there is a marginal food effect.

Table 9. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	7736.29	2540.87	7425.00	2132.79	7262.35	2078.33
AUCT	7287.24	2232.75	7013.88	1933.74	6840.18	1781.81
C _{MAX}	552.96	97.36	485.16	75.80	491.83	72.41
KE	0.07	0.02	0.07	0.01	0.07	0.02
LAUCI	7389.68	0.31	7147.99	0.28	6994.62	0.28
LAUCT	6987.12	0.30	6767.99	0.28	6625.05	0.26
LC _{MAX}	544.57	0.18	479.53	0.16	486.87	0.15
THALF	10.00	2.29	9.73	1.89	10.21	2.78
T _{MAX}	2.65	0.84	4.00	0.61	3.29	1.03

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.04	1.07	1.02
AUCT	1.04	1.07	1.03
C _{MAX}	1.14	1.12	0.99
KE	0.99	1.01	1.02
LAUCI	1.03	1.06	1.02
LAUCT	1.03	1.05	1.02
LC _{MAX}	1.14	1.12	0.98
THALF	1.03	0.98	0.95
T _{MAX}	0.66	0.80	1.21

UNIT: AUC=NG HR/ML C_{MAX}=NG/ML T_{MAX}=HR

Table 10. LSMEANS

	LSMEAN1	LSMEAN2	LSMEAN3
PARAMETER			
AUCI	7732.32	7441.02	7254.25
AUCT	7291.21	7034.69	6837.49
CMAX	553.19	486.49	492.78
LAUCI	7383.69	7159.23	6986.53
LAUCT	6987.18	6782.76	6620.37
LCMAX	545.17	480.75	487.81

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

VI. Product Information

1. Formulation

Test capsule formulations for the three strengths are directly proportional to each other as shown in Table 11. Reference products contain the following inactive ingredients: colloidal silicon dioxide, cornstarch, and magnesium stearate.

Table 11. Test Formulations
Unit: mg/capsule

Ingredient	150 mg Capsules	200 mg Capsules	250 mg Capsules
Mexiletine HCl, USP	150	200	250
Pregelatinized Starch, NF			
Colloidal Silicon Dioxide, NF			
Magnesium Stearate, NF			
Total Weight	240	320	400

2. Assay and content uniformity

Assay, content uniformity, batch size and expiration date for the test and reference products summarized in Table 12 are acceptable.

Table 12. Assay and Content Uniformity

Product	Assay, %	Content Uniformity, % (%CV)
Danbury's test product 250 mg, Lot #09520C Batch size: apsules	102.1	102.2 (1.1)
Boehringer Ingelheim's reference product 250 mg, Lot #682001A Exp. date: 7/95	100.4	101.3 (1.3)

VII. Dissolution

Danbury used USP dissolution method for Mexiletine HCl Capsules. All three strengths of the test product met the USP specifications as shown in Table 13. The USP dissolution method is as follows:

Medium: 900 mL of water
Apparatus: 2 (paddle) at 50 rpm
Tolerances: NLT (Q) in 30 min

VIII. Waiver Request

Danbury requested for waivers for 150 mg and 200 mg capsules of the test product. The waivers are granted based on the acceptable BE studies on 250 mg capsules, formulation proportionality and dissolution data.

IX. Comments

1. Study under fasting conditions: A total of 26 healthy non-smoking male volunteers enrolled in and completed the 2-period crossover study. Statistical analyses were performed on data from the first 12 subjects on each sequence (subjects #1-24).

Mean mexiletine plasma levels are comparable for the test and reference products throughout the sampling period. The test/reference ratios for non-transformed PK parameters (AUCT, AUCI and CMAX) and log-transformed PK parameters (LAUCT, LAUCI and LCMAX) are within the range of 1.0-1.05. The 90% confidence intervals for the non-transformed PK parameters (AUCT, AUCI and CMAX) and log-transformed PK parameters (LAUCT, LAUCI and LCMAX) are within 80-125% range and met the FDA requirements.

2. Study under non-fasting conditions: Of the 18 subjects

enrolled in the study, 17 subjects completed the 3-period crossover study. Subject #18 withdrew from the study after Period 1 for personal reasons. Thus, data from 17 subjects were used in the statistical analyses.

The test/reference ratios under non-fasting conditions for the non-transformed and log-transformed pharmacokinetic parameters are within 0.98-1.03 and satisfy FDA requirements.

3. Assay method validation: Pre-study and within-study validation data are acceptable.
4. Assay of plasma samples: It appears that the firm experienced assay problems especially under fasting conditions. There was a sign of improvement during the assay for non-fasting study. Handling of bad results were appropriate.
 - a. Study under fasting conditions: A total of 720 plasma samples were assayed. Thirty-nine (39) samples were declared as not reportable. Eight pre-dose samples were included in the not reportable list.
 - b. Study under non-fasting conditions: A total of 765 plasma samples were assayed. Three samples were declared as not reportable. Two pre-dose samples were included in the not reportable list.
5. No significant adverse reactions were reported.
6. The test formulations for the 150 mg, 200 mg and 250 mg strengths capsules are proportional in their active and inactive ingredients.
7. Assay and content uniformity data are acceptable.
8. The size of bio-batch was capsules.
9. Dissolution testing data are acceptable.

X. Deficiency

None.

XI. Recommendations

1. The two *in vivo* bioequivalence studies conducted under fasting and non-fasting conditions by Danbury Pharmacal on its Mexiletine Hydrochloride Capsules, 250 mg strength, lot #09520C, comparing it to Boehringer Ingelheim's Mexitil[®] Capsules, 250 mg strength, lot #682001A, have been found acceptable. The studies demonstrate that Danbury's Mexiletine Hydrochloride Capsules, 250 mg strength, is bioequivalent to

the reference product, Mexitil^R Capsules, 250 mg strength.

2. The USP dissolution testing conducted by Danbury on its Mexiletine Hydrochloride Capsules, 250 mg strength, lot #09520C, 200 mg strength, lot #09998C and 150 mg strength, lot #09999C, is acceptable. The formulations for the 150 mg and 200 mg strength capsules are proportionally similar to the 250 mg strength capsules of the test product which underwent two acceptable bioequivalence studies (submission date: 2/29/96). The waivers of *in vivo* bioequivalence study requirements for the 150 mg and 200 mg strengths of the test product are granted. The 150 mg and 200 mg strength capsules of the test product are therefore deemed bioequivalent to the 150 mg and 200 mg strength capsules of Mexitil^R Capsules, respectively.
3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

Not less than _____ of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.
4. From the bioequivalence point of view the firm has met the *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

The firm should be informed of the recommendations.

MOG Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

Concur: _____
Keith Chan, Ph.D.
Director
Division of Bioequivalence

Date: _____

6/27/96
6/28/96

cc: ANDA # 74-865, HFD-630(OGD), HFD-604(Hare), HFD-658 (Mhatre, Park), HFD-22 (Hooton), HFC-130/JAllen, Drug File

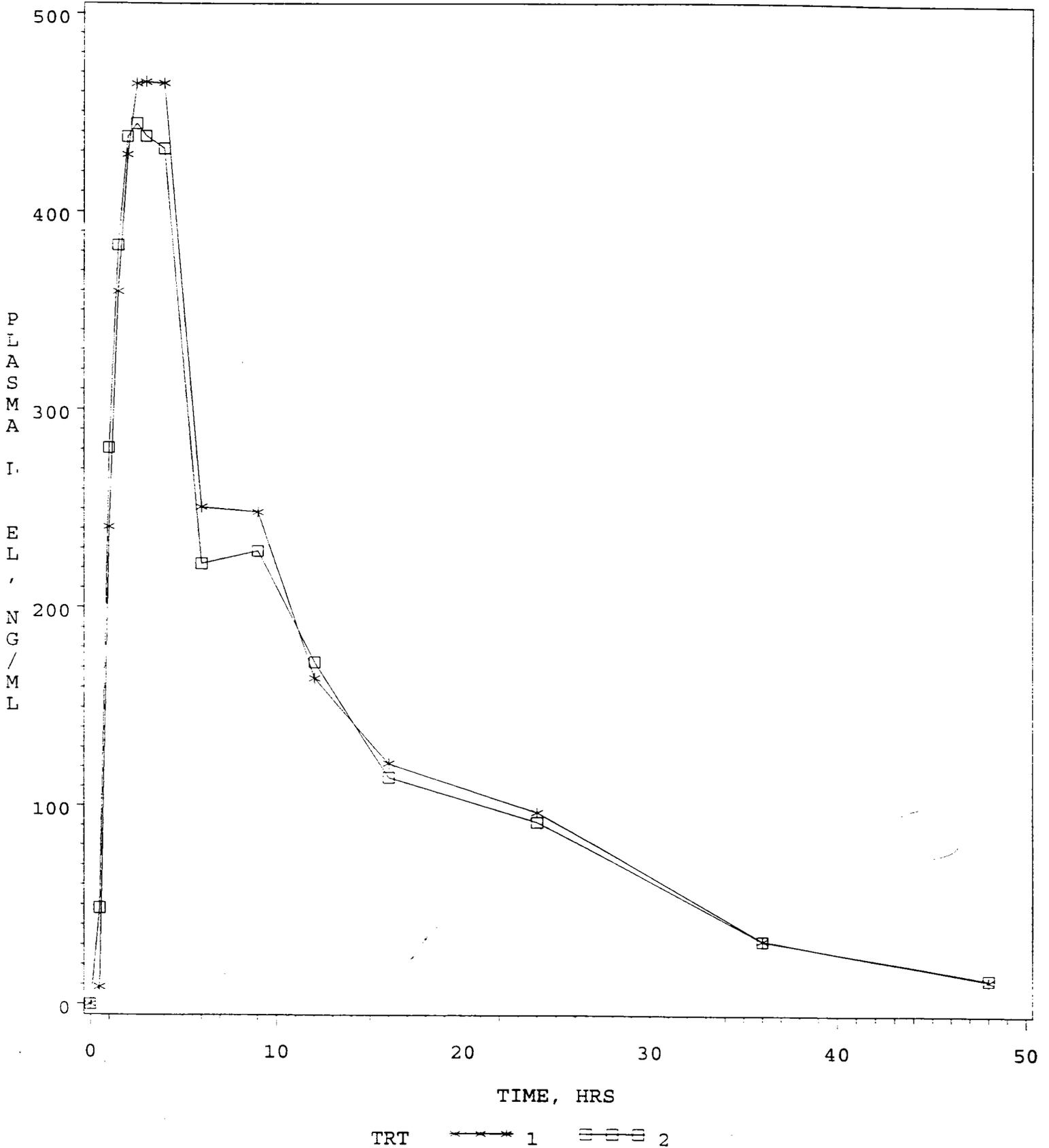
File history: Draft (6/4/96); Final (6/27/96)

Time	Test Product			Reference Product		
	Lot No:09998C	Strength:200 mg	No of Units:12	Lot No:672012A	Strength:200 mg	No of Units:24
Min	Mean	Range	%CV	Mean	Range	%CV
5	28.7		27.9	44.8		19.1
10	81.6		10	77.6		11.2
15	98.0		3.2	86.9		7.8
30	100.7		1.6	93.6		3.9

Time	Test Product			Reference Product		
	Lot No:09999C	Strength:250 mg	No of Units:12	Lot No:662012A	Strength:250 mg	No of Units:24
Min	Mean	Range	%CV	Mean	Range	%CV
5	40.8		18.7	57.3		21.4
10	84		13.2	77.5		10.9
15	90.5		9.6	88.2		8.5
30	94.8		4.7	95.4		3.8

FIG P-1. PLASMA MEXILETINE LEVELS

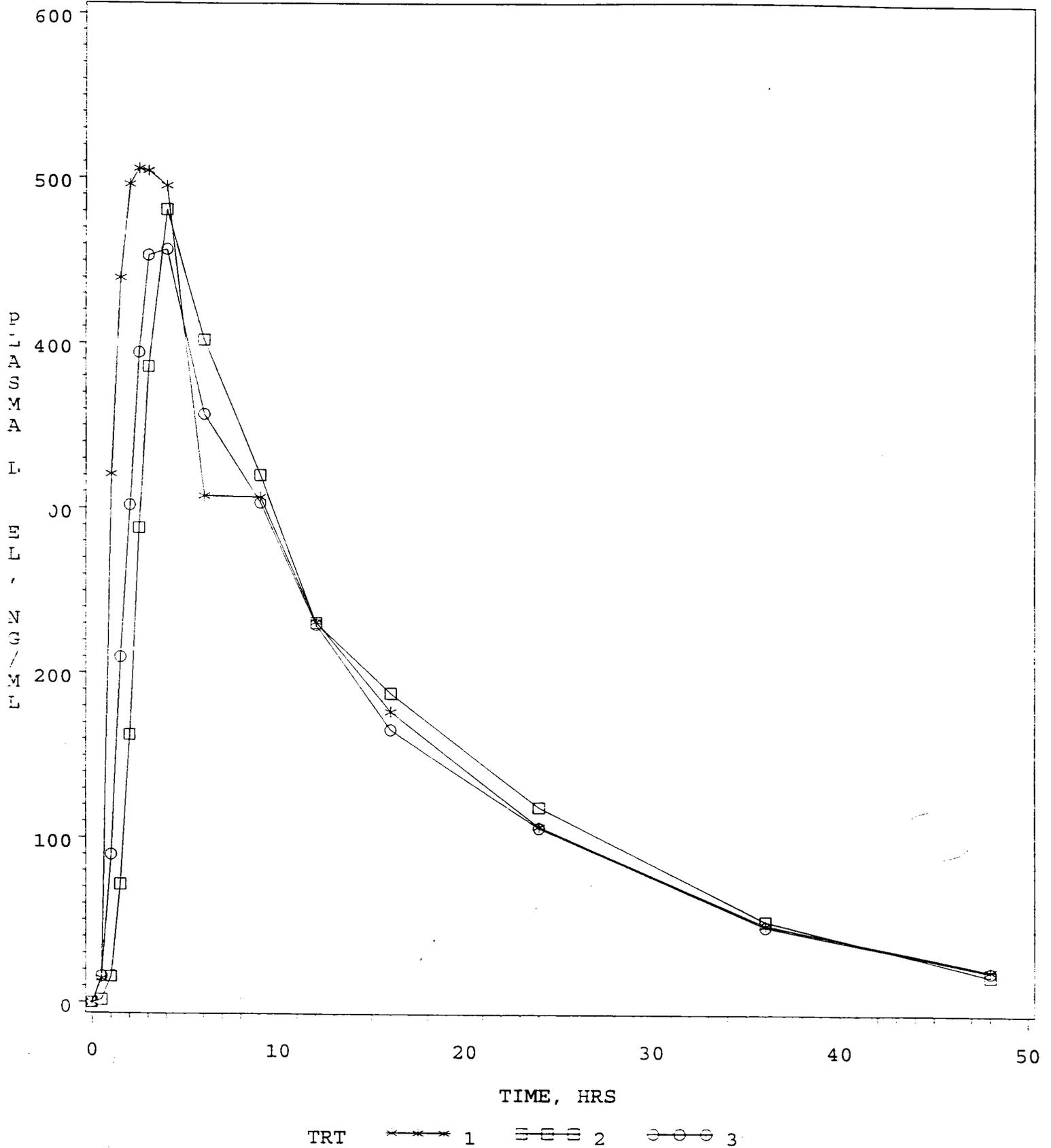
MEXILETINE HCl CAPSULES, 250 MG, ANDA #74-865
UNDER FASTING CONDITIONS
DOSE=1 X 250 MG



1=TEST PRODUCT (DANBURY) 2=REFERENCE PRODUCT (BOEHRINGER INGELHEIM)

FIG P-2. PLASMA MEXILETINE LEVELS

MEXILETINE HCl CAPSULES, 250 MG, ANDA #74-865
UNDER NON-FASTING CONDITIONS
DOSE=250 MG



1=TEST-FASTING(DANBURY) 2=TEST-FED(DANBURY) 3=REFERENCE-FED(SOHRINGER-INGELHEIM)