CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74803

BIOEQUIVALENCY REVIEW(S)

JAN 8 1998

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 74-803 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, 20 mg

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

Your dissolution testing of the test product in 900 mL of 0.1N HCl, using USP 23, apparatus II (paddle), at 50 rpm is not acceptable.

Please conduct the dissolution testing in 900 mL of water, using USP 23, apparatus II (paddle), at 50 rpm with valid assay methodology.

The dissolution results should meet the following specifications: Not less than % of the labeled amount of the drug (Fluoxetine) in the dosage form is dissolved in 30 minutes.

Note: The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot numbers of the samples undergoing dissolution testing should be identical to those used in the in vivo study. The dissolution profile for the test and reference products should include dissolution time points below and above the specification time point (30 minutes).

Sincerely yours,

/S/

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #74-803 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Fluoxetine HCL Capsules, 20 mg and 10 mg.

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 ml of water, at 37°C using Apparatus #2 (Paddle) at 50 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.

Important Note: Please submit dissolution testing data (for the 20 mg and 10 mg strengths) from your first three production batches using the above mentioned dissolution method. The dissolution profile which you submit should be accompanied by dissolution data from a current batch of the reference listed drug.

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

Fluoxetine Hydrochloride
20 mg Capsules
ANDA #74-803
Reviewer: Z.Z. Wahba
File #74803fa.697

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
June 06, 1997

AMENDMENT TO A REVIEWED IN VIVO BIOEQUIVALENCE STUDY UNDER FASTING CONDITIONS

AND

REVIEW OF IN VIVO BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS AND IN VITRO DISSOLUTION TESTING DATA

I. Amendment to a Reviewed In Vivo Bioequivalence Study Under Fasting Conditions

BACKGROUND

The firm has previously submitted an in vivo bioequivalence study (single dose) under fasting conditions comparing its test drug product, Barr's Fluoxetine HCL Capsules, 20 mg and the reference product, Eli Lilly's Prozac® Capsules, 20 mg.

The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated May 15,1996, ANDA #74-803) due to deficiency comments.

In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

Comment #1

Limited Food Effect Study:
Due to the fact that the labeling of reference listed drug (RLD) indicates that the drug may be administered with or without food and also "food does not appear to affect the systemic bioavailability of the drug". Therefore, a food study is required for this product to demonstrate that the generic formulation will behave similarly to the RLD formulation under fasting and non-fasting conditions.

The single-dose post-prandial bioequivalence study using a three-way crossover study design comparing equal doses of the test and reference products. The study should be conducted in a random, three-treatment (Treatments 1&2: the test and reference products should be dosed immediately after standard breakfast, Treatment 3: the test product should be dosed under fasting conditions), three-period, cross-over design using a minimum of 18 healthy subjects. An adequate wash-out period between periods 1, 2, and 3 dosing should be applied.

Note: A standard breakfast should be as follows:
one buttered English muffin
one fried egg
one slice of American cheese
one slice of Canadian bacon
one serving of hashed brown potatoes
eight fluid ounces (240 mL) of whole milk
six fluid ounces (180 mL) of orange juice.

Response to Comment #1

The firm has submitted a non-fasting study which is included in this report. The non-fasting study was reviewed and found acceptable (see the part "review of in vivo bioequivalence study under non-fasting conditions" of this report).

The firm's response to comment #1 is acceptable.

Comment #2

The following items are missing from the submission:

a. Stability data regarding effect of room temperature during handling of the samples.

b. The batch/lot size for the test product, the assay potency and content uniformity data for both the test and reference products, in addition, the date of manufacture of the test product should be included.

Response to Comment #2.a.

The firm stated that the requested data were not included in the original submission because at the time the bioequivalence study (under fasting conditions) was conducted the firm thought that data obtained from standard and control samples

of each analytical run were enough to validate the analytical methodology.

In the present supplement, the firm provided the information needed (see the analytical methods section for the bioequivalence study under non-fasting conditions, pages #1582-1583, Vol.B2.5).

The firm's response to comment #2.a. is acceptable.

Response to Comment #2.b.

The batch/lot size of the test product was capsules.
Assay potency of the test product = 99.1%
Assay potency of the reference product = 100.6%
Content uniformity of the test product = 99.0%
Content uniformity of the reference product = 99.9%
The date of manufacture of the test product was the date of mixing 6/28/95 while the encapsulation date was 7/6/95 to 7/7/95.

The firm's response to comment #2.b. is acceptable.

Comment #3

Submit a comparative dissolution study for both the test and reference drug products, performed simultaneously. The dissolution data should include the number of capsules (not less than 12), type and volume of the medium, the method that has been used, and the date the testing was performed. The dissolution testing should be done on capsules from the same lot number that was used in the in vivo bioequivalence study. The comparative dissolution profiles (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (%C.V.), and date(s) of analysis.

Response to Comment #3

The firm has submitted comparative dissolution data for its drug product, Fluoxetine HCl Capsules, 20 mg and the reference listed drug, Eli Lilly's Prozac® Capsules, 20 mg. The firm's dissolution conditions are summarized below:

Method:	USP 23 apparatus II (Paddle) at 50 rpm
Medium:	900 mL 0.1N HCL

Temperature: 37°C ± 0.5°C
No. Units Tested: 12 Capsules
Specification: NLT % (Q) is dissolved in 30 minutes
Reference product: Eli Lilly's Prozac® Capsules, 20 mg.

Table . In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine HCl
Dose Strength: 20 mg
ANDA No.: 74-803
Firm: Barr Laboratories
Submission Date: June 06, 1997
File Name: 74803fa.697

I. Conditions for Dissolution Testing:

USP 23 Method Basket: Paddle: X RPM: 50
No. Units Tested: 12 Capsules
Medium: 0.1N HCl
Volume: 900 mL
Specifications: NLT % (Q) is dissolved in 30 minutes
Reference Drug: Eli Lilly's Prozac® Capsules, 20 mg

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #5R87719 Strength(mg) 20			Reference Product Lot #8AM94A Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	82.4		12.8	78.5		8.6
15	89.7		8.7	95.6		5.8
30	95.2		4.2	102.0		2.2
45	97.6		3.4	102.5		2.4

COMMENTS

1. The dissolution testing of the test product in 900 mL of 0.1N HCl, using USP 23, apparatus II (paddle), at 50 rpm is not acceptable.

2. The firm should conduct the dissolution testing in 900 mL of water, using USP 23, apparatus II (paddle), at 50 rpm with valid assay methodology.

3. The dissolution results should meet the following specifications: Not less than % of the labeled amount of the

drug (Fluoxetine) in the dosage form is dissolved in 30 minutes.

The firm's response to comment #2.b. is not acceptable.

Comment #4

The Physician's Desk Reference (PDR), 49 Ed. (pages 943-947) report the following statements:

* A dose of 20 mg/day , administered in the morning, is recommended as the initial dose.
* Studies comparing fluoxetine 20, 30, 40 and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory antidepressant response.
* Doses above 20 mg/day may be administered on a once a day (morning) or b.i.d. schedule (ie, morning and noon) and should not exceed a maximum dose of 80 mg/day.

In the study, the firm administered three capsules of 20 mg fluoxetine at the same time to each subject. Therefore, the firm should respond to the following item:

a. The rational of administering dosage which is three time higher than the recommended dose.

Response to Comment #4.a.

Barr Laboratories reviewed data obtained from a previous study experience with the 60 mg single dose conducted by and found no significant deleterious adverse effects. Both the Physicians Desk Reference and the AHFS indicated that variable blood concentrations could be expected to occur after dosing with fluoxetine. Since the expected LLOQ was 1 ng/mL and the metabolite could very conceivably produce data which might not exceed peak levels of 10 ng/mL, a 40 mg dose was deemed unacceptable and the dose of 60 mg was selected. Barr Laboratories, Inc. and investigators, medical personnel and IRB all agreed to proceed with the 60 mg dose.

The firm's response to comment #2.b. is acceptable.

Comment #5

Provide a brief description on the analytical methodology procedure.

Response to Comment #5

The analytical methodology used for Barr's Fluoxetine 20 mg Capsule fasting study is entitled Analysis of Fluoxetine and Norfluoxetine in Human Plasma." A brief summary of this follows. A 1.0 mL sample volume is required for analysis. The sample is kept frozen at -20°C prior to analysis. At the time of analysis fluoxetine, norfluoxetine and the internal standard protryptyline are extracted from basic, heparinized human plasma using . The compounds are then acid back-extracted into % phosphoric acid. separation is achieved by

Fluorescence detection with an excitation wavelength of 230 nm and an emission wavelength of 305 nm is used to detect fluoxetine and norfluoxetine. This method is validated with a minimum quantifiable level of 2.00 ng/mL for fluoxetine and 2.00 ng/mL for norfluoxetine. The upper level is 500 ng/mL for each analyte. A linear weighted (1/concentration squared) least squares regression analysis is used to quantitate unknown samples.

II. REVIEW OF IN VIVO BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS AND IN VITRO DISSOLUTION TESTING DATA

OBJECTIVE:
To review:

Barr's in vivo bioequivalence study (single dose) under non-fasting conditions comparing its 20 mg strength Fluoxetine HCl Capsules to the reference listed drug, Eli Lilly's Prozac® Capsules, 20 mg.

BACKGROUND:
Fluoxetine is a selective serotonin reuptake inhibitor. It is primarily indicated for the treatment of depression. The exact mechanism of action is still not completely understood.

Following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from ng/mL are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, fluoxetine may be administered with or without food. It is extensively metabolized in the liver to norfluoxetine and a number of unidentified metabolites. The only identified, active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. Fluoxetine has an elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration. Norfluoxetine has an elimination half-life of 4 to 16 days after acute and chronic administration.

Fluoxetine HCL is currently marketed as Prozac® oral Capsules, 20 mg and 10 mg; and Prozac® oral solution, 20 mg/5 mL, manufactured by Dista (Eli Lilly).

A dose of 20 mg/day, administered in the morning, is recommended as the initial dose. The maximum fluoxetine dose should not exceed 80 mg/day.

III. BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS (clinical study project #P96-150)

A. Sponsor:
Barr Laboratories, Inc.
2 Quaker Road
Pomona, NY 10970

Clinical Facility:

Principle Investigator:

Analytical Facility:

Statistical Analysis:

Clinical Study Dates:
Period I: August 10, 1996
Period II: October 12, 1996
Period II: January 04, 1997

Analysis Schedule Dates:
Analysis of samples began on March 10, 1997 and completed on April 14, 1997.

B. **STUDY DESIGN**:

Randomized, three-way crossover, single dose study, under non-fasting and fasting conditions.

C. **SUBJECTS**:

Twenty-four (24) healthy male subjects were enrolled in the study and all subjects completed the study (subjects #1-24). The subjects were 18 to 40 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Inclusion, Exclusion and Restriction Criteria:
Same as in study #P95-251 under fasting conditions

D. Treatment Plan:

Test Product:

Treatment A: **Fasting Conditions**, 3 X 20 mg Barr's Fluoxetine HCL, Lot #5R87719, Lot size capsules, assay 99.1%, content uniformity 99.0%.

Treatment B: **Non-fasting conditions**, 3 X 20 mg Barr's Fluoxetine HCL, Lot #5R87719, Lot size capsules, assay 99.1%, content uniformity 99.0%.

Reference Product:

Treatment C: **Non-fasting conditions**, 3 X 20 mg Eli Lilly's Prozac® Capsules, Lot #8AM94A, assay 100.6%, content uniformity 99.9%, expiration date: Oct./97.

Washout period: at least 9 weeks

E. DRUG, FOOD AND FLUID INTAKE:

Subjects who received treatment A, fasted overnight for 10 hours before dosing and for 4 hours after drug administration. Subjects who were fed standard recommended breakfast prior to dosing (treatments B and C) only fasted for 9.5 hours. Treatments B and C differed from treatment A in that the subjects were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug administration. Each dose was followed by 8 fluid ounces (240 mL) of room temperature tap water according to randomized dosing schedule. Water was not permitted for 1 hour before and 2 hour after dosing, but was allowed at all other times. Standard meals were provided at appropriate times thereafter (at 4.5 and 9.5 hours after dosing).

F. ASSAY METHODOLOGY:

Precision and accuracy of the method (for both fluoxetine and norfluoxetine) are shown in Tables #1-4.

Table #1
Precision and Accuracy of the Assay Method from Calibration Standards Samples (Fluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy (%Difference)
2.00	48	2.01	3.79	0.571
5.0	48	4.93	4.55	-1.36
10.0	48	9.99	4.82	-0.130
25.0	48	25.1	4.09	0.263
50.0	48	49.7	3.36	-0.607
100.0	46	99.3	3.51	-0.661
250.0	46	254	3.68	1.14
500.0	47	503	3.85	0.550

Table #2
Precision and Accuracy of the Assay Method from Calibration Concentrations Samples (norfluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy (%Difference)
2.00	48	2.01	3.02	0.285
5.0	48	4.95	3.41	-0.960
10.0	48	10.0	5.39	0.257
25.0	48	25.2	3.24	0.704

50.0	48	50.0	3.18	-0.092
100.0	46	99.6	3.28	-0.428
250.0	45	252	4.01	0.655
500.0	47	498	4.86	-0.408

Table #3

Inter-Assay Precision and Accuracy of the Assay Method from the Quality Control Samples (Fluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy %Difference
5.0	72	5.05	5.67	1.02
40.0	72	40.1	4.16	0.141
400.0	72	402	4.18	0.500

Table #4

Inter-Assay Precision and Accuracy of the Assay Method from the Quality Control Samples (Norfluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy %Difference
5.0	71	4.86	5.72	-2.72
40.0	72	39.0	4.72	-2.39
400.0	72	396	5.63	-1.10

5. Recovery: (pp 1577-1579, Vol. B2.5)
The overall percent recovery of fluoxetine and norfluoxetine were 43.5% and 38.6% with CV% range of 1.57%-13.4% and 2.52-12.7%, respectively.

6. Stability:
(The stability data are presented on pages #1554-1555, #1580-1585; Vol. B2.5).

1. Fluoxetine and norfluoxetine were stable at room temperature during 3 freeze/thaw cycles conducted over 48 hours.

2. Long term stability data showed that fluoxetine and

norfluoxetine were stable for 365 days at -20 °C.

G. **BLOOD SAMPLING**:

Blood samples were collected at 0 (pre-dose), 2, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48, 60, 72, 96, 120, 144, 192, 240, 312, 408, 504, 600 and 696 hours post-dosing. The plasma samples were separated, collected and promptly stored frozen at -20 °C until analysis.

H. **ADVERSE EVENTS**: (pp #510-518; Vol. B2.2)

One hundred forty-two adverse events were reported in twenty subjects out of twenty-four subjects. The summary of the adverse events are presented in Attachment #1. None of the adverse events was considered serious or resulted in terminating any subject from study participation.

I. **IN VIVO BE STUDY AND STATISTICAL ANALYTICAL**:

Twenty-four (24) healthy male subjects were enrolled in the study and all subjects completed the study (subjects #1-24).

Adverse Events:
The adverse reactions are reported on page #510-519, Vol. B2.2. The following are the adverse events summary for study subjects under non-fasting conditions. None of the adverse events was considered serious or resulted in terminating any subject from study participation.

Parameter	Treat A (# of Subjects)	Treat B (# of Subjects)	Treat C (# of Subjects)
Headache	19	40	21
Respiratory Disorder (such as nasal congestion, stuffy head, chest congestion)	8	6	7
Rhinitis (runny nose, sneezing)	6	15	7

Dyspepsia (heartburn)	--	3	4
Pharyngitis (sore throat)	3	5	5
Conjunctivitis (itchy eyes)	--	2	1
coughing	2	5	6
Pain (sore ribs, chest, neck, knee, eye, back)	5	6	4
Myalgia (muscles ache)	4	4	2
Right Wrist Sprain			1
Vomiting*	--	4	2
Abdominal Pain and upset stomach	2	6	6
Nausea	--	--	2
Rigors (chills)	--	1	1
Hot Flushes (head hot)	--	2	2
Tremors (shakiness)	--	-	2
Earache	--	--	2
Tooth Disorder (Toothache)	-	2	--
Tendinitis	2	--	--
Fever (Feverish)	--	1	--
Dizziness	4	3	4
Fatigue	--	--	2
Urinary Retention	2	--	--
Diarrhea	3	2	--
Sinusitis	--	3	-

Edema (swollen right wrist or arm)	2	--	--

* Vomiting occurred after 11:35 hours post-dosing.

The pharmacokinetic parameters of fluoxetine and norfluoxetine were analyzed using

The pharmacokinetic parameters for the plasma fluoxetine and norfluoxetine concentrations, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the Tables below:

Table #5
Fluoxetine Mean Plasma Concentrations (ng/mL) in 24 Subjects Following 3X20 mg Oral Dose of Fluoxetine HCL Under Non-Fasting Conditions
(Test Lot #5R87719, Reference Lot #8AM94A)

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
0	0.00	0.00	0.00	0.00	0.00	0.00	.
2	13.88	10.48	3.35	3.73	0.98	2.15	4.15
4	31.16	11.53	21.27	10.09	14.96	9.58	1.47
5	38.00	11.54	33.65	10.59	29.72	11.98	1.13
6	43.21	11.39	42.92	12.94	41.92	11.98	1.01
7	44.67	11.50	43.78	11.67	42.04	9.92	1.02
8	44.56	11.11	**44.02**	10.40	**42.88**	10.05	1.01
10	42.24	9.77	41.99	11.03	42.52	11.25	1.01
12	39.44	10.09	39.57	10.15	40.97	10.49	1.00
24	28.12	8.48	28.15	8.55	29.39	8.48	1.00
36	25.30	9.78	25.69	11.07	25.05	7.86	0.98
48	18.88	8.80	19.31	8.46	19.77	8.51	0.98
60	18.07	9.69	17.99	9.46	18.85	11.57	1.00
72	13.86	8.24	13.35	7.46	13.66	7.52	1.04
96	10.31	7.30	9.81	7.07	9.81	6.37	1.05
120	7.40	6.28	7.35	6.05	7.27	6.06	1.01
144	5.22	5.83	5.24	5.74	5.32	6.25	1.00
192	3.01	4.89	2.51	4.55	2.80	4.51	1.20
240	1.73	3.55	1.62	3.87	1.68	3.93	1.07
312	1.24	3.27	0.78	2.67	0.90	2.96	1.58
408	0.48	1.92	0.48	1.84	0.50	1.89	1.02
504	0.27	1.31	0.29	1.44	0.28	1.35	0.91
600	0.19	0.95	0.21	1.05	0.23	1.11	0.91
696	0.16	0.78	0.15	0.72	0.18	0.86	1.09

(CONTINUED)

TIME HR	RMEAN13	RMEAN23
0	.	.
2	14.17	3.42
4	2.08	1.42
5	1.28	1.13
6	1.03	1.02
7	1.06	1.04

8	1.04	1.03
10	0.99	0.99
12	0.96	0.97
24	0.96	0.96
36	1.01	1.03
48	0.95	0.98
60	0.96	0.95
72	1.01	0.98
96	1.05	1.00
120	1.02	1.01
144	0.98	0.98
192	1.07	0.90
240	1.03	0.97
312	1.38	0.87
408	0.97	0.95
504	0.97	1.06
600	0.86	0.94
696	0.91	0.84

MEAN1=Test-Fast MEAN2=Test-NonFast MEAN3=Ref.-NonFast
MEAN23=Mean T/R (under non-fasting conditions)
Unit: Plasma Level=NG/ML Time=HRS

Table #6
Summary of Pharmacokinetics Parameters (Fluoxetine) in 24 Subjects Following 3X20 mg Oral Dose of Fluoxetine HCL Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	3198.50	2402.10	3063.08	2287.28	3125.96	2349.39	1.04
AUCT	2949.25	2165.21	2835.75	2117.53	2896.83	2116.29	1.04
CMAX	47.02	12.49	46.77	11.08	46.62	11.45	1.01
KE	0.02	0.01	0.02	0.01	0.02	0.01	0.99
*LAUCI	2636.62	0.60	2560.67	0.57	2612.11	0.57	1.03
*LAUCT	2439.79	0.60	2357.74	0.58	2426.95	0.57	1.03
*LCMAX	45.55	0.26	45.58	0.23	45.30	0.25	1.00
THALF	53.02	37.60	51.34	37.43	52.62	40.43	1.03
TMAX	7.38	1.34	7.38	1.64	8.00	2.27	1.00

(CONTINUED)

	RMEAN13	RMEAN23
PARAMETER		
AUCI	1.02	0.98
AUCT	1.02	0.98
CMAX	1.01	1.00
KE	0.99	1.00
*LAUCI	1.01	0.98
*LAUCT	1.01	0.97
*LCMAX	1.01	1.01
THALF	1.01	0.98
TMAX	0.92	0.92

MEAN1=Test-Fast MEAN2=Test-NonFast MEAN3=Ref.-NonFast
RMEAN23=Mean T/R (under non-fasting conditions)
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR

* The values represent the geometric means (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma fluoxetine levels for the test and reference products reached a maximum level of concentration around 8.0 hours (Table #5 and Figures #1&2).

2. Under non-fasting conditions, the ratios of the test mean to the reference mean (RMEAN2/3) for the log-transformed AUCt, AUCi and Cmax were all within the acceptable range of 0.8 to 1.25 (Table #6).

3. The average values of T1/2, Tmax and Kel for the test product were comparable to the reference product values under the same conditions (Table #6).

NORFLUOXETINE DATA:

Table #7
Mean Plasma Concentrations (ng/mL)
of Norfluoxetine in 24 Subjects
Following 3X20 mg Oral Dose of Fluoxetine HCL
Under Non-Fasting Conditions
(Test Lot #5R87719, Reference Lot #8AM94A)

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
0	0.00	0.00	0.00	0.00	0.00	0.00	.
2	1.34	1.45	0.00	0.00	0.12	0.57	.
4	5.55	1.90	3.81	2.15	2.36	2.02	1.46
5	7.55	2.37	6.27	2.26	5.28	2.24	1.20
6	9.42	3.38	8.29	2.70	8.02	3.20	1.14
7	10.45	3.39	9.18	3.07	8.80	3.27	1.14
8	11.35	3.54	10.26	3.99	9.75	3.87	1.11
10	12.80	4.48	11.31	4.10	11.19	3.95	1.13
12	13.54	4.40	12.65	4.48	12.91	4.80	1.07
24	15.52	4.65	14.82	4.80	15.16	4.92	1.05
36	20.65	5.88	19.98	5.89	20.15	6.61	1.03
48	18.98	4.92	19.42	6.10	19.75	5.51	0.98
60	23.03	6.02	**22.32**	5.62	**23.68**	7.63	1.03
72	20.47	4.98	19.77	5.10	20.19	5.08	1.04
96	21.04	4.87	20.59	5.20	20.65	5.52	1.02
120	20.37	4.62	20.12	4.99	20.36	4.92	1.01
144	19.41	4.66	19.30	4.70	19.81	5.23	1.01
192	17.51	5.14	16.72	4.14	17.74	5.27	1.05
240	14.40	4.91	14.92	3.92	15.42	5.66	0.97
312	11.44	4.40	11.07	4.30	11.84	4.42	1.03
408	8.52	8.50	7.42	3.67	7.49	4.23	1.15
504	5.08	4.69	4.71	3.69	4.63	4.27	1.08
600	2.61	3.48	2.59	3.54	2.56	3.56	1.01
696	1.58	2.90	1.44	2.51	1.71	3.27	1.09

(CONTINUED)

	RMEAN13	RMEAN23
TIME HR		
0	.	.
2	11.48	0.00
4	2.36	1.62
5	1.43	1.19
6	1.17	1.03
7	1.19	1.04
8	1.16	1.05
10	1.14	1.01
12	1.05	0.98
24	1.02	0.98
36	1.02	0.99
48	0.96	0.98
60	0.97	0.94
72	1.01	0.98
96	1.02	1.00
120	1.00	0.99
144	0.98	0.97
192	0.99	0.94
240	0.93	0.97
312	0.97	0.93
408	1.14	0.99
504	1.10	1.02
600	1.02	1.01
696	0.92	0.85

MEAN1=Test-Fast MEAN2=Test-NonFast MEAN3=Ref.-NonFast
MEAN23=Mean T/R (under non-fasting conditions)
Unit: Plasma Level=NG/ML Time=HRS

Table #8
Summary of Pharmacokinetics Parameters (Norfluoxetine) in 24 Subjects Following 3X20 mg Oral Dose of Fluoxetine HCL Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	8271.29	3551.92	8021.29	2886.94	8374.00	3749.93	1.03
AUCT	7343.38	2860.31	7106.42	2244.38	7322.75	2627.37	1.03
CMAX	24.25	7.31	22.94	5.73	24.95	7.52	1.06
KE	0.00	0.00	0.00	0.00	0.01	0.00	1.00
*LAUCI	7687.86	0.38	7578.61	0.34	7756.74	0.39	1.01
*LAUCT	6840.01	0.40	6697.10	0.38	6819.09	0.42	1.02
*LCMAX	22.77	0.42	21.73	0.41	23.23	0.46	1.05
THALF	156.01	61.45	165.14	89.10	164.30	93.37	0.94
TMAX	90.50	76.96	87.00	56.53	87.75	50.40	1.04

(CONTINUED)

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.99	0.96
AUCT	1.00	0.97
CMAX	0.97	0.92

KE	0.96	0.96
*LAUCI	0.99	0.98
*LAUCT	1.00	0.98
*LCMAX	0.98	0.94
THALF	0.95	1.01
TMAX	1.03	0.99

MEAN1=Test-Fast MEAN2=Test-NonFast MEAN3=Ref.-NonFast
RMEAN23=Mean T/R (under non-fasting conditions)
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma norfluoxetine levels for the test and reference products reached a maximum level of concentration around 60 hours (Table #7 and Figures #3&4).

2. Under non-fasting conditions, the ratios of the test mean to the reference mean (RMEAN2/3) for the log-transformed AUCt, AUCi and Cmax were all within the acceptable range of 0.8 to 1.25 (Table #8).

3. The average values of T1/2, Tmax and Kel for the test product were comparable to the reference product values under the same conditions (Table #8).

IV. COMMENTS:

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Barr's Fluoxetine HCL Capsules, 20 mg and the reference product, Eli Lilly's Prozac® Capsules, 20 mg are bioequivalent. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax for Fluoxetine and Norfluoxetine were all within the acceptable range of 80-125%.

2. Under non-fasting conditions: The firm's in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Barr's Fluoxetine HCL Capsules, 20 mg and the reference product, Eli Lilly's Prozac® Capsules, 20 mg are bioequivalent. The ratios of the test mean to the reference mean for the AUCt, AUCi, Cmax were within the acceptable range of 0.8-1.25.

V. DEFICIENCY:

The dissolution testing of the test product in 900 mL of 0.1N HCl, using USP 23, apparatus II (paddle), at 50 rpm is not acceptable.

The firm should conduct the dissolution testing in 900 mL of water, using USP 23, apparatus II (paddle), at 50 rpm with valid assay methodology.

The dissolution results should meet the following specifications: Not less than % of the labeled amount of the drug (Fluoxetine) in the dosage form is dissolved in 30 minutes.

Note: The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot numbers of the samples undergoing dissolution testing should be identical to those used in the in vivo study. The dissolution profile for the test and reference products should include dissolution time points below and above the specification time point (30 minutes).

VI. RECOMMENDATION:

The in vivo Bioequivalence study conducted by Barr Laboratories under fasting conditions on its test product, Fluoxetine Hydrochloride Capsules, 20 mg, (Lot #5R87719) versus the listed reference product, Eli Lilly's Prozac® Capsules, 20 mg, (Lot #8AM94A) has been found to be incomplete by the Division of Bioequivalence due to the deficiency cited above.
The firm should be informed of the deficiency and recommendation.

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 74-803 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, 20 mg

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

Your dissolution testing of the test product in 900 mL of 0.1N HCl, using USP 23, apparatus II (paddle), at 50 rpm is not acceptable.

Please conduct the dissolution testing in 900 mL of water, using USP 23, apparatus II (paddle), at 50 rpm with valid assay methodology.

The dissolution results should meet the following specifications: Not less than % of the labeled amount of the drug (Fluoxetine) in the dosage form is dissolved in 30 minutes.

Note: The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot numbers of the samples undergoing dissolution testing should be identical to those used in the in vivo study. The dissolution profile for the test and reference products should include dissolution time points below and above the specification time point (30 minutes).

Sincerely yours,

/S/

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

BIOEQUIVALENCY - DEFICIENCIES

1. **FOOD STUDY** (STP) — Strength: 20 mg
   Clinical:
   Analytical
   Outcome: IC

2. **DISSOLUTION DATA** (DIS) — Strength: 20 mg
   Outcome: IC

3. **STUDY AMENDMENT** (STA) — Strength: 20 mg
   Outcome: IC

OUTCOME DECISIONS: IC - Incomplete

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence, Review Branch III

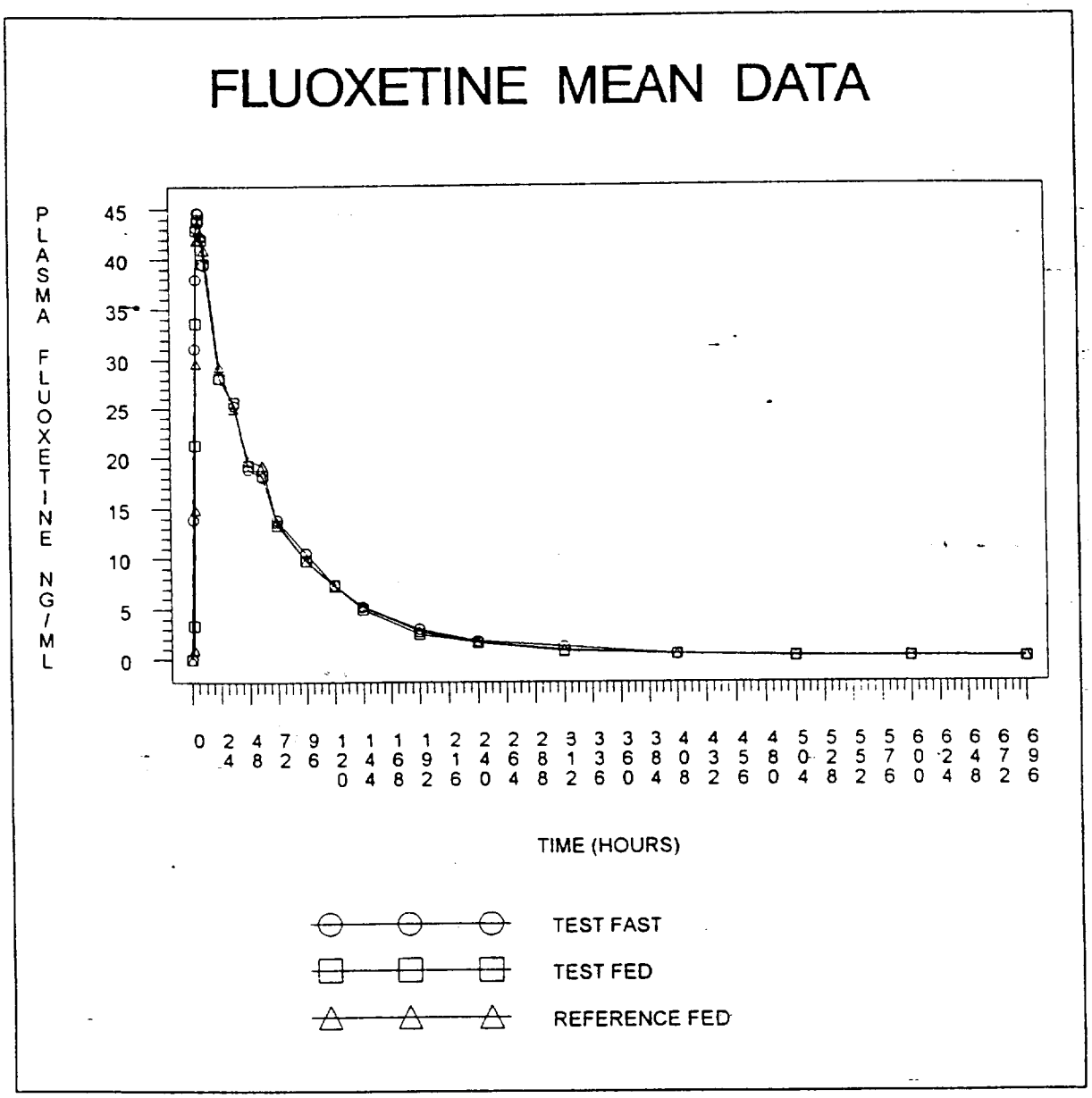
RD INITIALED RMHATRE /S/
for FT INITIALED RMHATRE _____ 12/22/97

Concur: /S/ Date: 12/24/97
Dale Conner, Pharm.D.
Acting Director
Division of Bioequivalence

FLUOXETINE HCl 20 MG CAPSULE FOOD STUDY
BARR P96-150

ANDA #74-803

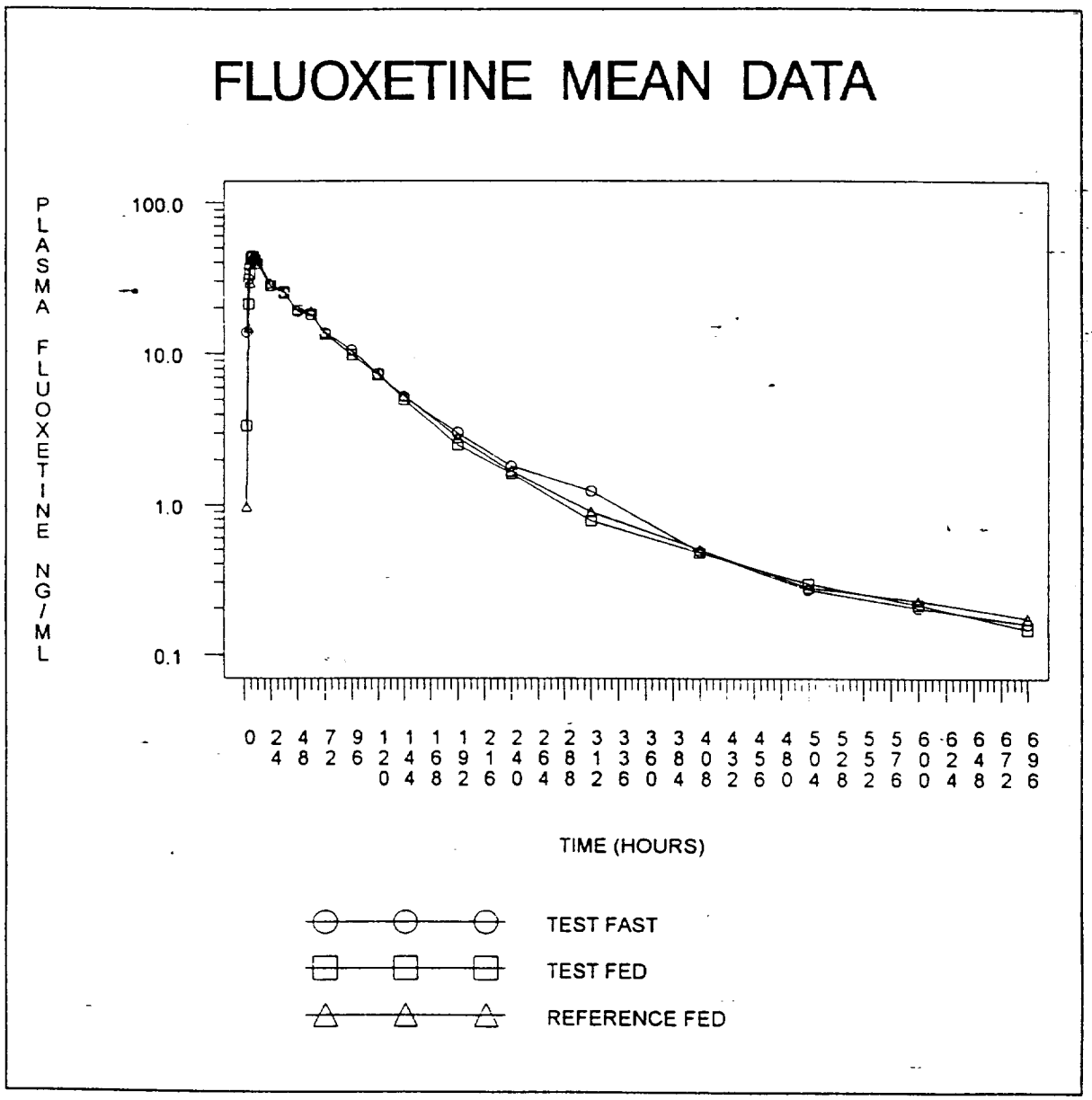
Figure #1 Linear Plot of Mean Plasma Fluoxetine Concentrations *vs* Time



FLUOXETINE HCl 20 MG CAPSULE FOOD STUDY
BARR P96-150

ANDA # 74-803

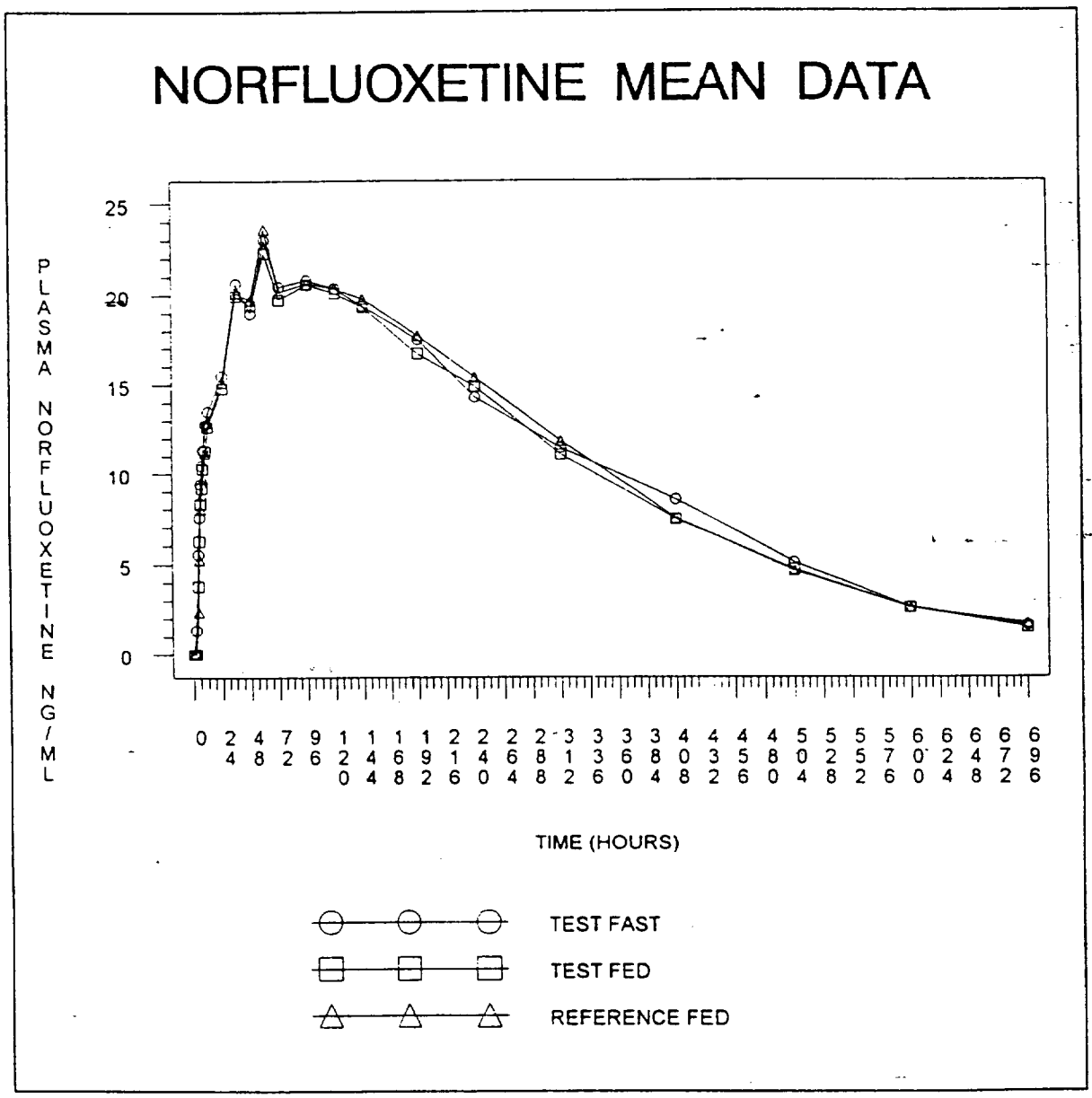
Figure #2 Semi-logarithmic Plot of Mean Plasma Fluoxetine Concentrations vs Time



FLUOXETINE HCl 20 MG CAPSULE FOOD STUDY
BARR P96-150

ANDA # 74-803

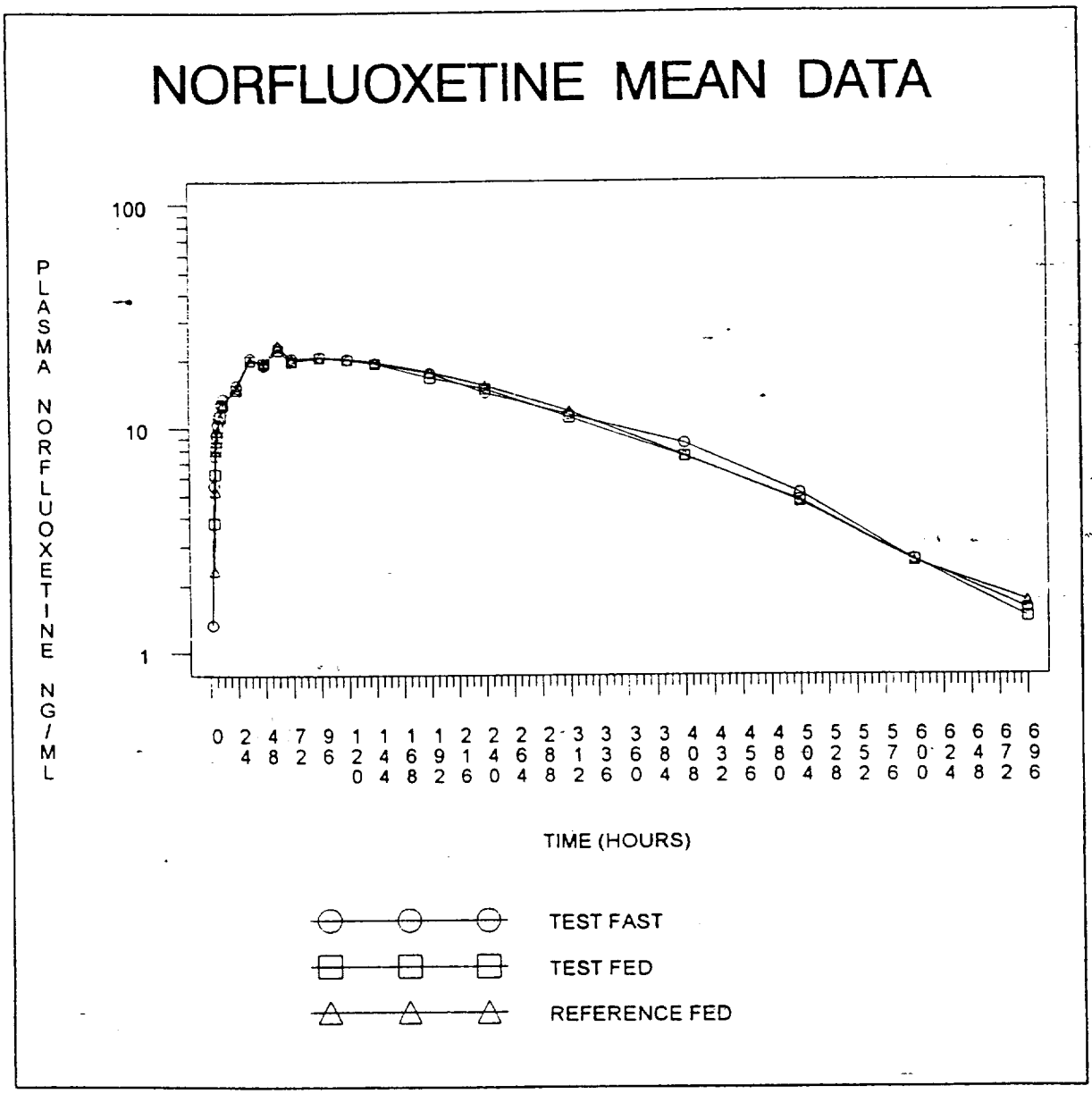
Figure #3 Linear Plot of Mean Plasma Norfluoxetine Concentrations *vs* Time



FLUOXETINE HCl 20 MG CAPSULE FOOD STUDY
BARR P96-150

ANDA #74-803

Figure #4 Semi-logarithmic Plot of Mean Plasma Norfluoxetine Concentrations vs Time



Fluoxetine Hydrochloride
20 mg Capsules
ANDA #74-803
Reviewer: Z.Z. Wahba
File #74803a1.A98

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
April 29, 1998
June 15, 1998
August 18, 1998

REVIEW OF AN AMENDMENT AND A WAIVER REQUEST

I. BACKGROUND

1. The firm has previously submitted two in vivo bioequivalence studies (single-dose fasting and single-dose post-prandial) comparing its test drug product, Barr's Fluoxetine HCL Capsules, 20 mg to the reference product, Eli Lilly's Prozac® Capsules, 20 mg.

2. The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated December 24, 1997, ANDA #74-803) due to a deficiency regarding the dissolution data.

3. The firm has requested a waiver of in vivo bioequivalence study requirements for its drug product, Barr's Fluoxetine HCL Capsules, 10 mg. The reference listed product is Eli Lilly's Prozac® Capsules, 10 mg.

II. DEFICIENCY COMMENT:

The firm was asked to submit complete dissolution testing data using USP 23 apparatus #2 (Paddle) at 50 rpm in 900 mL of water.

THE FIRM'S RESPONSE TO COMMENT:

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

Apparatus:	USP 23 apparatus 2 (Paddles) at 50 rpm
Medium:	900 mL water
Test Product:	Barr's Fluoxetine HCL Capsules, 20 mg, lot #5R87719
	Barr's Fluoxetine HCL Capsules, 10 mg, lot

#5R87618

Ref. Product: Eli Lilly's Prozac® Capsules, 20 mg, lot #8AM94A
Eli Lilly's Prozac® Capsules, 10 mg, lot #8NE08M

Number of Units: 12 Capsules

The dissolution testing results are shown in the following table

Table. In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine HCL Capsules
Dose Strength: 20 mg and 10 mg
ANDA No.: 74-803
Firm: Barr Laboratories, Inc.
Submission Date: April 29, 1998
File Name: 74803a1.a98

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL water
Reference Drug: Eli Lilly's Prozac® Capsules, 20 mg and 10 mg

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Fluoxetine Lot # 5R87719 Strength(mg) 20			Reference Product Prozac® Lot #8AM94A Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	79		12.5	60		31.6
15	86		7.8	92		6.5
30	93		3.8	96		1.8
45	93		2.6	96		1.6

Sampling Times (Minutes)	Test Product Fluoxetine Lot #5R87618 Strength(mg) 10			Reference Product Prozac® Lot #8NE08M Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV

10	84			9.7	83		17.7
15	87			7.4	97		3.2
30	92			4.3	99		2.7
45	94			3.6	99		2.6

III. COMMENTS ON THE DISSOLUTION TESTING (NOT TO BE RELEASED UNDER FOI):

1. The firm conducted the dissolution testing on expired batches, test (20 mg strength, lot #5R87719, manufacturing date June 95, dissolution testing date 2/23/98) and reference (20 mg strength, lot #8AM94A, expiration date October 95, dissolution testing date 2/23/98) products. Also, the dissolution testing on the 10 mg strength was conducted on expired batches, test (lot #5R87618, manufacturing date June 95, dissolution testing date 2/23/98) and reference (lot #8NE08M, expiration date September 96, dissolution testing date 2/23/98) products.

2. In the original submission (6/6/97), the firm conducted the dissolution in 900 mL of 0.1N HCl, using USP 23, apparatus II (paddle), at 50 rpm which was not acceptable by the Division of Bioequivalence. The Division requested the firm conduct the dissolution testing in 900 mL of water, using USP 23, apparatus II (paddle), at 50 rpm.

3. On April 29, 1998, the firm resubmitted the dissolution data applying the Agency's dissolution specification on its bio-lot which had expired.

4. The firm's justification of using the expired bio-lot was due to ongoing patent litigation with Eli Lilly (the innovator of the drug). Therefore, the firm has not manufactured any validation batches.

5. The dissolution data for 10 mg and 20 mg strengths are acceptable.

6. Important note: The firm is required to submit dissolution

data (for the 20 mg and 10 mg strengths) from its first three production batches using the above-mentioned dissolution method. The test product dissolution data should be accompanied by dissolution data from a current batch of the reference listed drug.

IV. FORMULATION

(page 6-16 and 6-17, volume A3.2, under Part II, Section VI)

Barr's formulation of its drug product, Fluoxetine HCL Capsules, 10 mg and 20 mg is presented below.

Formulation Comparison

Ingredients	10 mg Capsule	20 mg Capsule
	mg/capsule	mg/capsule
Fluoxetine Hydrochloride	11.2*	22.4*
Lactose Monohydrate, NF (Fast-Flo)		
Microcrystalline Cellulose, NF (Avicel® PH-101)		
Starch, NF (Corn Starch-Purity 21)		
Stearic Acid, NF (Hystrene)		
Total Weight		

*22.4 mg and 11.2 mg of Fluoxetine Hydrochloride are equivalent to 20 mg and 10 mg Fluoxetine, respectively.

V. RECOMMENDATIONS

1. The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions, conducted by Barr Laboratories, Inc. on its Fluoxetine HCL Capsules, 20 mg (lot #5R87719), comparing it to the reference product, Eli Lilly's Prozac® Capsules, 20 mg (lot #8AM94A), have been found acceptable. The two studies demonstrate that under fasting and non-fasting conditions, Barr's Fluoxetine HCL Capsules, 20 mg is bioequivalent to the reference listed product, Eli Lilly's Prozac® Capsules, 20 mg.

2. The dissolution testing conducted by Barr Laboratories, Inc. on its Fluoxetine HCL Capsules, 20 mg (lot #5R87719) and 10 mg (lot #5R87618) are acceptable. The waiver of the in vivo bioequivalence study requirements for the 10 mg strength of the test product is granted. The Division of Bioequivalence deems the 10 mg strength of the test product to be bioequivalent to the reference listed product, Eli Lilly's Prozac® Capsules, 10 mg.

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 Apparatus #2 (Paddle) at 50 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.

The firm should be informed of the above recommendations.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT BDA 8/21/98
FT INITIALLED BDAVIT /S/ 8/21/98

Concur: /S/ Date: 8/21/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #74-803 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Fluoxetine HCL Capsules, 20 mg and 10 mg.

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 ml of water, at 37°C using Apparatus #2 (Paddle) at 50 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.
>
> Important Note: You are required to submit dissolution testing data (for the 20 mg and 10 mg strengths) from your first three production batches using the above mentioned dissolution method. The dissolution profile which you submit should be accompanied by dissolution data from a current batch of the reference listed drug.

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

BIOEQUIVALENCY - ACCEPTABLE

1.	**STUDY AMENDMENT** dated 04-29-98	Strengths: 20 mg **Outcome: AC**
2.	**DISSOLUTION WAIVER** dated 06-15-98	Strengths: 10 mg **Outcome: AC**
3.	**STUDY AMENDMENT** dated 08-18-98	Strengths: 20 mg & 10 mg **Outcome: AC**

OUTCOME DECISIONS: **AC** - Acceptable
WINBIO COMMENTS: Acceptable Biostudy

MAY 15 1996

Fluoxetine Hydrochloride
20 mg Capsules
ANDA #74-803
Reviewer: Z.Z. Wahba
File #74803s.d95

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
December 09, 1995

REVIEW OF AN IN VIVO BIOEQUIVALENCE STUDY

I. OBJECTIVE:

To review:

Barr's in vivo bioequivalence study (single dose) under fasting conditions comparing its 20 mg strength Fluoxetine HCl Capsules to the reference listed drug, Eli Lilly's Prozac® Capsules, 20 mg.

II. BACKGROUND:

Fluoxetine is a selective serotonin reuptake inhibitor. It is primarily indicated for the treatment of depression. The exact mechanism of action is still not completely understood.

Following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, fluoxetine may be administered with or without food. It is extensively metabolized in the liver to norfluoxetine and a number of unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. Fluoxetine has an elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration. Norfluoxetine has an elimination half-life of 4 to 16 days after acute and chronic administration.

Fluoxetine HCL is currently marketed as Prozac® Pulvules® oral Capsules, 20 mg and 10 mg; and Prozac® oral solution, 20 mg/5 mL, manufactured by Dista (Eli Lilly).

A dose of 20 mg/day , administered in the morning, is recommended as the initial dose. The maximum fluoxetine dose should not exceed 80 mg/day.

III. BIOEQUIVALENCE STUDY UNDER FASTING CONDITIONS (clinical study project #P95-251)

A. SPONSOR:

Barr Laboratories, Inc.
2 Quaker Road
Pomona, NY 10970

Clinical Facility:

Principle Investigator:

Analytical Facility:

Statistical Analysis:

Clinical Study Dates:
Period I: July 22 - September 12, 1995
Period II: September 23 - October 24, 1995

Analysis Schedule Dates:
Analysis of samples began on March 20, 1995 and ended on April 18, 1995.

B. **STUDY DESIGN**:

Randomized, two-way crossover, single dose study, under fasting conditions.

C. **SUBJECTS**:

Thirty eight (38) healthy male subjects were enrolled in the study but 37 subjects completed the clinical study. Subject #36 failed to return to the facility to complete Period 2. Therefore, the data set used for statistical analyses contained data from 37 subjects (subjects #1-35, 37 and 38).

Subject Inclusion Criteria:

1. The subjects were within 18 to 40 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.
2. Only medically healthy subjects as determined by normal history, physical examination, laboratory profiles and EKG were enrolled in the study.

Subject Exclusion Criteria:

1. History of cardiovascular, respiratory, renal, gastrointestinal, immunologic, neurologic, hepatic, hematopoietic or psychiatric disease.
2. History of chronic alcohol consumption or drug addiction.
3. Tested positive for hepatitis B surface antigen screen or a reactive HIV 1 & 2 antibody screen.
4. Allergy to the class of drug being tested.
5. Use of tobacco in any form
6. Participated in a previous clinical trail or donated blood within the past 30 days.
7. Treatment with any known hepatic enzyme inducing or inhibiting agents within the past 30 days prior to dosing.

Subject Restrictions:

1. No subject took any medications, including OTC products for at least 2 weeks prior to the beginning of the study and until completion of the study.
2. No alcoholic, xanthine and caffeine containing foods and beverages were allowed during the study.

D. **TREATMENT**:

Test Product: 3 X 20 mg Barr's Fluoxetine HCL, Lot #5R87719, Lot size (not given), assay (not given), content uniformity (not given).

Reference Product: 3 X 20 mg Eli Lilly's Prozac® Capsules, Lot #8AM94A, assay (not given), content uniformity (not given), expiration date: Oct./97.

Washout period: 63 days

E. **DRUG, FOOD AND FLUID INTAKE**:

Subjects fasted for at least 10 hours (overnight) before dosing and for at least 4 hours after dosing. Each dose was followed by 240 mL of water according to randomized dosing schedule. Water intake was restricted from 1.0 hour prior to and 2.0 hours after drug administration. At 2 hours post-dose, all subjects consumed 240 mL of water. Four hours after the dose, water was allowed ad lib, if requested. Standard meals were provided at appropriate times thereafter.

F. **SUBJECT MONITORING**:

Vital signs (blood pressure and heart rates) were monitored predose (-1 hr) and at 12 and 24 hours post-dose (the values

were reported on pages #06-01577 to 06-01582, vol. #6).

G. ASSAY METHODOLOGY:

Table #1
Precision and Accuracy of the Assay Method from Calibration Concentrations Samples (Fluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy (%Difference)
2.00	70	2.01	9.57	0.316
5.0	72	4.99	5.75	-0.172
10.0	72	9.93	2.94	-0.675
25.0	72	24.7	1.84	-1.12
50.0	72	49.7	1.67	-0.57
100.0	72	99.7	2.01	-0.275
250.0	72	253	1.83	1.14
500.0	72	507	1.98	1.36

Table #2
Precision and Accuracy of the Assay Method from Calibration Concentrations Samples (norfluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy (%Difference)
2.00	70	2.04	8.39	2.08
5.0	69	4.89	4.98	-2.12
10.0	70	9.63	2.61	-3.68
25.0	70	23.7	1.82	-5.30
50.0	70	48.4	2.05	-3.15
100.0	70	98.2	2.08	-1.79
250.0	70	262	1.78	4.90
500.0	70	545	2.08	9.03

Table #3
Pre-Study Validation of Inter-Assay Precision and Accuracy of the Assay Method from the Quality Control Samples (Fluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy %Difference
5.0	107	4.82	5.41	-3.53
40.0	108	39.6	2.81	-1.4
400.0	108	407	2.70	1.66

Table #4
Pre-Study Validation of Inter-Assay Precision and Accuracy of the Assay Method from the Quality Control Samples (Norfluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy %Difference
5.0	105	5.53	5.71	10.7
40.0	105	43.1	3.33	7.76
400.0	105	435	3.05	8.83

Table #5
Within-Study Validation of Intra-Assay Precision and Accuracy of the Assay Method in Human Plasma Samples (Fluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy %Difference
2.0	6	1.96	13.1	-1.77
5.0	6	5.01	4.61	0.25
40.0	6	38.9	2.13	-2.64
400.0	6	384	0.84	-4.04

Table #6
Within-Study Validation of Inter-Assay Precision and Accuracy of the Assay Method in Human Plasma Samples (Fluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy %Difference
2.0	12	2.11	13.2	5.48
5.0	12	4.92	4.49	-1.50
40.0	12	39.0	4.69	-2.51
400.0	12	393	3.00	-1.71

Table #7
Within-Study Validation of Intra-Assay Precision and Accuracy of the Assay Method in Human Plasma Samples (Norfluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy %Difference
2.0	6	2.08	10.2	4.00
5.0	6	4.54	4.29	-9.17
40.0	6	37.9	1.73	-5.24
400.0	6	361	0.76	-9.73

Table #8
Within-Study Validation of Inter-Assay Precision and Accuracy of the Assay Method in Human Plasma Samples (Norfluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy %Difference
2.0	12	2.09	10.3	4.49
5.0	12	4.73	5.30	-5.42
40.0	12	36.8	5.03	-7.91
400.0	12	373	2.99	-6.87

5. Stability: The freeze/thaw cycles and long-term stability data are summarized in Tables #9&10. The stability data of control samples at room temperature has not been reported.

Table #9
Freeze/Thaw Cycles Stability Data

Storage Conditions	Stability as %Original 5.0 ng/mL	40 ng/mL	400 ng/mL
Freeze/thaw, 3-cycles			
For Fluoxetine:			
1st freeze/thaw cycle (n=2)	5.06(+1.2%)	39(-2.5%)	384(-4.0%)
2nd freeze/thaw cycle (n=2)	5.08(+1.6%)	38.9(-2.7%)	378(-5.5%)
3rd freeze/thaw cycle (n=2)	5.05(+1.0%)	38.6(-3.5%)	394(-1.5%)
For Norfluoxetine:			
1st freeze/thaw cycle (n=2)	4.99(-0.2%)	36.8(-8.0%)	369(-7.7%)
2nd freeze/thaw cycle (n=2)	4.72(-5.6%)	37.4(-6.5%)	365(-8.7%)
3rd freeze/thaw cycle (n=2)	5.04(+0.8%)	37.7(-5.7%)	384(-4.0%)

Table #10
Long-Term Stability Samples

Storage Conditions	Stability as %Original 50.0 ng/mL	100 ng/mL	250.0 ng/mL
Long term freezing for approximately 12 months (n=6)			
For Fluoxetine:	52.4(+4.87%)	107(+6.93%)	267(+6.14%)
For Norfluoxetine:	50.4(+0.83%)	104(+3.89%)	262(+4.70%)

I. **BLOOD SAMPLING**:

Blood samples were collected at 0 (pre-dose), 2, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 144, 240, 312, 408, 576 and 744 hours post-dosing. The plasma samples were separated, collected and promptly stored frozen at -20 °C until analysis.

J. **ADVERSE EVENTS**:

Adverse reactions have been reported (vol. #6, pages 06-01539 to 06-01542 and 06-01632 to 06-01637). Several subjects experienced adverse events during the study with some possibilities of linkage to the test or reference drug product. None of the adverse events was considered serious or resulted in terminating any subject from study participation.

K. **Protocol Deviations**:

The deviations are reported on page #06-01535, vol. #6). There were three deviations from the protocol instructions of no nonprescription medications of within 7 days of period I. Subjects #28, 37 and 38 consumed multivitamin (2 tablets), advil (400 mg) and multivitamin (1 tablet), respectively. These deviations were viewed as not clinically significant by the investigators.

L. **Statistical analyses**:

The statistical analyses were performed on the plasma fluoxetine (n=37) and norfluoxetine (n=37) data to compare the test and reference treatments. The pharmacokinetic parameters for fluoxetine and its metabolite norfluoxetine are summarized in the tables below:

Table #11
Mean Plasma Concentrations (ng/mL) of Fluoxetine in 37 Subjects Following 20 mg Oral Dose of Fluoxetine HCL Under Fasting Conditions

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	0.00	0.00	0.00	0.00	.
2	10.95	5.76	8.03	4.37	1.36
4	27.61	7.68	25.35	8.24	1.09
5	33.59	7.82	32.12	7.87	1.05
6	37.24	8.06	36.36	8.08	1.02
7	**37.74**	8.56	**37.07**	8.46	**1.02**
8	36.37	7.48	36.84	8.20	0.99
10	34.04	6.91	33.84	7.86	1.01
12	32.07	7.19	31.85	7.87	1.01
16	26.98	6.85	26.62	7.16	1.01
24	22.16	6.55	22.38	6.34	0.99
36	18.95	6.75	18.94	6.99	1.00
48	14.34	5.96	14.19	6.17	1.01
72	9.24	5.03	9.15	5.32	1.01
96	5.87	4.64	5.87	4.88	1.00
144	2.60	3.44	2.29	3.65	1.14
240	0.49	1.77	0.59	1.90	0.83
312	0.17	1.02	0.19	1.15	0.89
408	0.09	0.56	0.09	0.57	0.99
576	0.00	0.00	0.00	0.00	.
744	0.00	0.00	0.00	0.00	.

MEAN1=Test MEAN2=Reference MEAN12=Mean T/R

Table #12
Summary of Pharmacokinetics Parameters (Fluoxetine) in 37 Subjects Following 20 mg Oral Dose of Fluoxetine HCL Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	1829.62	1054.74	1809.68	1118.27	1.01
AUCI	2007.41	1142.10	1991.59	1199.16	1.01
CMAX	39.12	8.02	38.36	8.58	1.02
KE	0.02	0.01	0.02	0.01	0.98
THALF	37.82	16.74	37.80	18.37	1.00
TMAX	6.49	1.02	7.14	0.79	0.91
*LAUCT	1632.34	0.47	1588.37	0.50	1.03
*LAUCI	1795.77	0.46	1758.61	0.49	1.02
*LCMAX	38.31	0.21	37.40	0.23	1.02

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR

* The values represent the geometric means (antilog of the means of the logs).

Table #13
LSMeans and 90% Confidence Intervals
(Fluoxetine)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCT	1835.98	1814.40	97.63	104.74
AUCI	2014.14	1996.64	97.54	104.21
CMAX	39.14	38.39	99.38	104.51
*LAUCT	1636.49	1590.99	**99.35**	**106.49**
*LAUCI	1800.26	1761.45	**98.89**	**105.63**
*LCMAX	38.32	37.41	**99.94**	**104.99**

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML
* The values represent the geometric means (antilog of the means of the logs).

Table #14
Test/Reference Products Ratios for Pharmacokinetic Parameters for Individual Subjects (Fluoxetine)

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12

1=Test product 2=Reference product

Table #15
Summary of Mean and SD of Individual T/R Ratios
(Fluoxetine)

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	37	1.04	0.14		
RAUCI12	37	1.03	0.13		
RCMAX12	37	1.03	0.09		
RTMAX12	37	0.92	0.18		
RKE12	37	1.00	0.12		
RTHALF12	37	1.02	0.13		

1. The mean plasma fluoxetine levels reached a maximum level of concentration around 7.0 hours (Table #11 and the attached Figures #1&2). Mean blood levels-time profiles were comparable between the test and reference products under the same conditions.

2. The arithmetic test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 1.01, 1.01 and 1.02, respectively. The geometric test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 1.03, 1.02 and 1.02, respectively (Table #12). The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptable range of % (Table #13).

   There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUC and C_{max}.

3. The average values of $T_{1/2}$, T_{max} and K_{el} for the test product were comparable to the reference product values (Table #12).

NORFLUOXETINE DATA:

Table #16
Mean Plasma Concentrations (ng/mL)
of Norfluoxetine in 37 Subjects
Following 20 mg Oral Dose of Fluoxetine HCL
Under Fasting Conditions

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	0.00	0.00	0.00	0.00	.
2	2.54	1.76	1.73	1.67	1.47
4	7.91	3.09	7.10	2.50	1.11
5	10.41	3.44	9.88	3.21	1.05
6	12.72	4.78	11.98	4.11	1.06
7	14.00	4.96	13.51	4.38	1.04
8	14.47	5.16	14.55	4.91	0.99
10	15.96	5.64	15.75	5.22	1.01
12	17.52	6.02	17.44	5.86	1.00
16	18.42	6.10	18.26	5.84	1.01
24	19.17	6.16	19.88	6.20	0.96
36	**25.36**	7.69	**25.61**	7.33	**0.99**
48	24.56	7.17	24.72	7.07	0.99
72	25.11	7.00	24.95	6.47	1.01
96	24.13	6.12	24.38	6.34	0.99
144	21.33	5.19	21.69	5.06	0.98
240	15.83	5.42	15.91	3.91	1.00
312	12.01	4.03	12.00	3.42	1.00
408	8.03	3.22	7.99	2.97	1.00
576	3.19	2.70	3.05	2.56	1.05
744	0.98	1.79	0.95	1.72	1.03

MEAN1=Test MEAN2=Reference MEAN12=Mean T/R

Table #17
Summary of Pharmacokinetics Parameters (Norfluoxetine)
in 37 Subjects Following 20 mg Oral Dose of
Fluoxetine HCL Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	8006.11	2446.93	7998.19	2248.36	1.00
AUCI	8879.86	2525.93	8909.65	2338.41	1.00
CMAX	27.13	7.25	26.88	6.80	1.01
KE	0.005	0.001	0.005	0.001	1.01
THALF	159.35	41.13	160.14	40.04	1.00
TMAX	64.22	41.97	69.08	33.87	0.93
*LAUCT	7596.51	0.35	7637.87	0.33	0.99
*LAUCI	8505.10	0.31	8566.02	0.30	0.99
*LCMAX	25.96	0.32	25.83	0.31	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR

* The values represent the geometric means (antilog of the means of the logs).

Table #18
LSMeans and 90% Confidence Intervals
(Norfluoxetine)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCT	8011.62	7999.22	97.89	102.42
AUCI	8886.73	8912.65	97.72	101.69
CMAX	27.12	26.88	98.60	103.20
*LAUCT	7596.30	7633.20	**97.02**	**102.08**
*LAUCI	8507.05	8564.17	**97.34**	**101.37**
*LCMAX	25.95	25.81	**98.19**	**102.91**

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
UNIT: AUC=NG HR/ML CMAX=NG/ML
* The values represent the geometric means (antilog of the means of the logs).

Table #19
Test/Reference Products Ratios for Pharmacokinetic Parameters for Individual Subjects (Norfluoxetine)

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12

1=Test product 2=Reference product

Table #20
Summary of Mean and SD of Individual T/R Ratios (Norfluoxetine)

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	37	1.00	0.09		
RAUCI12	37	1.00	0.07		
RCMAX12	37	1.01	0.08		
RTMAX12	37	1.00	0.48		
RKE12	37	1.01	0.11		
RTHALF12	37	1.00	0.12		

1. The mean plasma norfluoxetine levels reached a maximum level of concentration around 36.0 hours (Table #16 and the attached Figures #3&4). Mean blood levels-time profiles were comparable between the test and reference products under the same conditions.

2. The arithmetic test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 1.00, 1.00 and 1.01, respectively. The geometric test/reference mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 0.99, 0.99 and 1.01, respectively (Table #17). The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptable range of (Table #18).

   There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUC and C_{max}.

3. The average values of $T_{1/2}$, T_{max} and K_{el} for the test product were comparable to the reference product values (Table #17).

IV. FORMULATION

Barr's formulation of its drug product, Fluoxetine HCL Capsules, 20 mg is presented in Table #21

Table #21
Formulation Comparison

Ingredients	mg/capsule
Fluoxetine Hydrochloride	22.4*
Lactose Monohydrate, NF (Fast-Flo)	
Microcrystalline Cellulose, NF (Avicel® PH-101)	
Starch, NF (Corn Starch-Purity 21)	
Stearic Acid, NF (Hystrene)	
Total Weight	mg/dose

*22.4 mg of Fluoxetine Hydrochloride is equivalent to 20 mg Fluoxetine

For the capsule shell components list (see page 07-00005, vol. C1.8).

V. COMMENT:

Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Barr's Fluoxetine HCL Capsules, 20 mg and the reference product, Eli Lilly's Prozac® Capsules, 20 mg are bioequivalent. The 90% confidence intervals for the log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for Fluoxetine and Norfluoxetine were all within the acceptable range of %. However, the submission has been found incomplete by the Division of Bioequivalence for the deficiencies cited below.

VI. DEFICIENCIES:

1. Limited Food Effect Study:
Due to the fact that the labeling of reference listed drug (RLD) indicates that the drug may be administered with or without food and also "food does not appear to affect the systemic bioavailability of the drug". Therefore, a food study is required for this product to demonstrate that the generic formulation will behave similarly to the RLD formulation under fasting and non-fasting conditions.

   The single-dose post-prandial bioequivalence study using a three-way crossover study design comparing equal doses of the test and reference products. The study should be conducted in a random, three-treatment (Treatments 1&2: the test and reference products should be dosed immediately after standard breakfast, Treatment 3: the test product should be dosed under fasting conditions), three-period, cross-over design using a minimum of 18 healthy subjects. An adequate wash-out period between periods 1, 2, and 3 dosing should be applied.

   Note: A standard breakfast should be as follows:
   - one buttered English muffin
   - one fried egg
   - one slice of American cheese
   - one slice of Canadian bacon
   - one serving of hashed brown potatoes
   - eight fluid ounces (240 mL) of whole milk
   - six fluid ounces (180 mL) of orange juice.

2. The following items are missing from the submission:
   a. Provide the Stability data regarding effect of room temperature during handling of the samples.

   b. The batch/lot size for the test product, the assay potency and content uniformity data for both the test and reference products, in addition to the date of manufacturing the test product should be included.

3. Submit a comparative dissolution study for both the test and reference drug products, performed simultaneously. The dissolution data should include the number of capsules (not less than 12), type and volume of the medium, the method that has been used, and the date the testing was performed. The dissolution testing should be done on capsules from the same lot number that was used in the in vivo bioequivalence study. The comparative dissolution profiles (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (%C.V.), and date(s) of analysis.

4. The Physician's Desk Reference (PDR), 49 Ed. (pages 943-947) report the following statements:
   * A dose of 20 mg/day , administered in the morning, is recommended as the initial dose.
   * Studies comparing fluoxetine 20, 30, 40 and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory antidepressant response.
   * Doses above 20 mg/day may be administered on a once a day (morning) or b.i.d. schedule (ie, morning and noon) and should not exceed a maximum dose of 80 mg/day.

   In the study, the firm administered three capsules of 20 mg fluoxetine at the same time to each subject. Therefore, the firm should respond to the following item:

   a. The rational of administering dosage which is three time higher than the recommended dose.

5. Provide a brief description on the analytical methodology procedure.

II. RECOMMENDATION:

The *in vivo* Bioequivalence study conducted by Barr Laboratories under fasting conditions on its test product, Fluoxetine Hydrochloride Capsules, 20 mg, (Lot #5R87719) versus the listed reference product, Prozac^{R} Pulvules, 20 mg (Lot #8AM94A), manufactured by Eli Lilly has been found to be incomplete by the Division of Bioequivalence for the deficiencies cited above (#1-5).

The firm should be informed of the deficiencies and recommendations.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

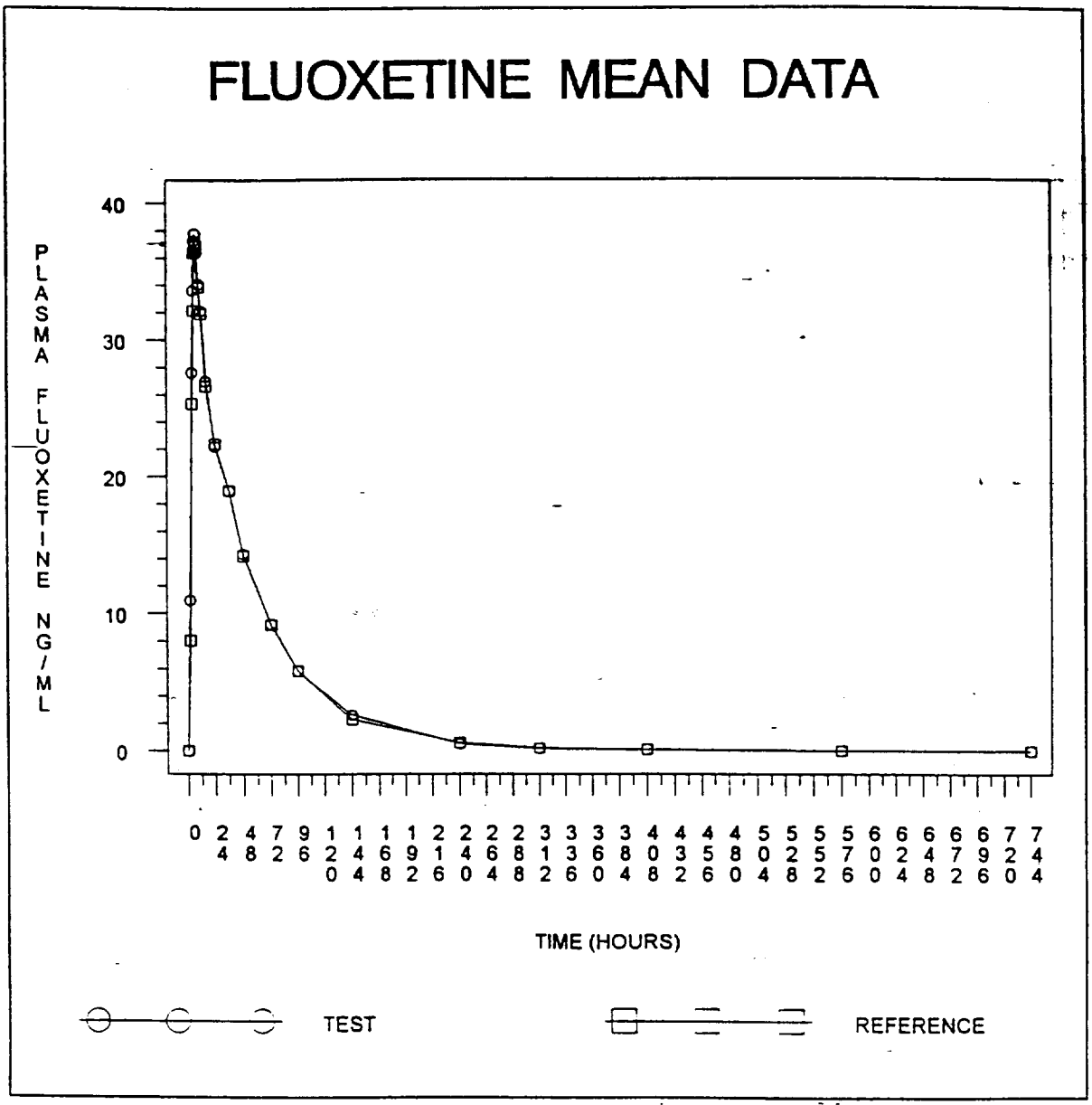
RD INITIALED RMHATRE /S/
FT INITIALED RMHATRE 5/15/96

Concur: /S/ Date: 5/15/96
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74-803 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File
ZWahba/041596/051496/file #74803s.d95

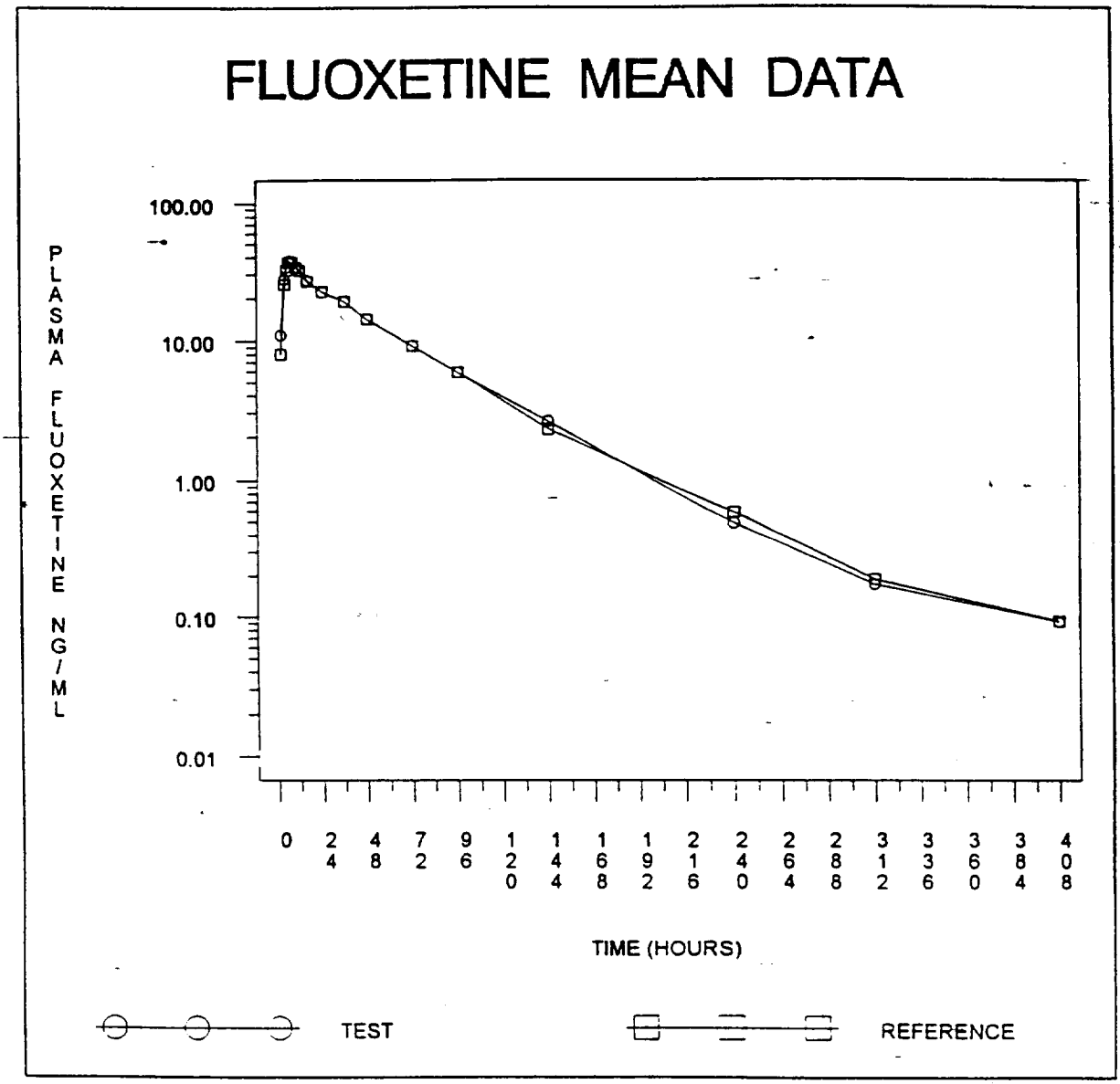
ANDA # 74-803

Figure #1 Linear Plot of Mean Plasma Fluoxetine Concentrations *vs* Time



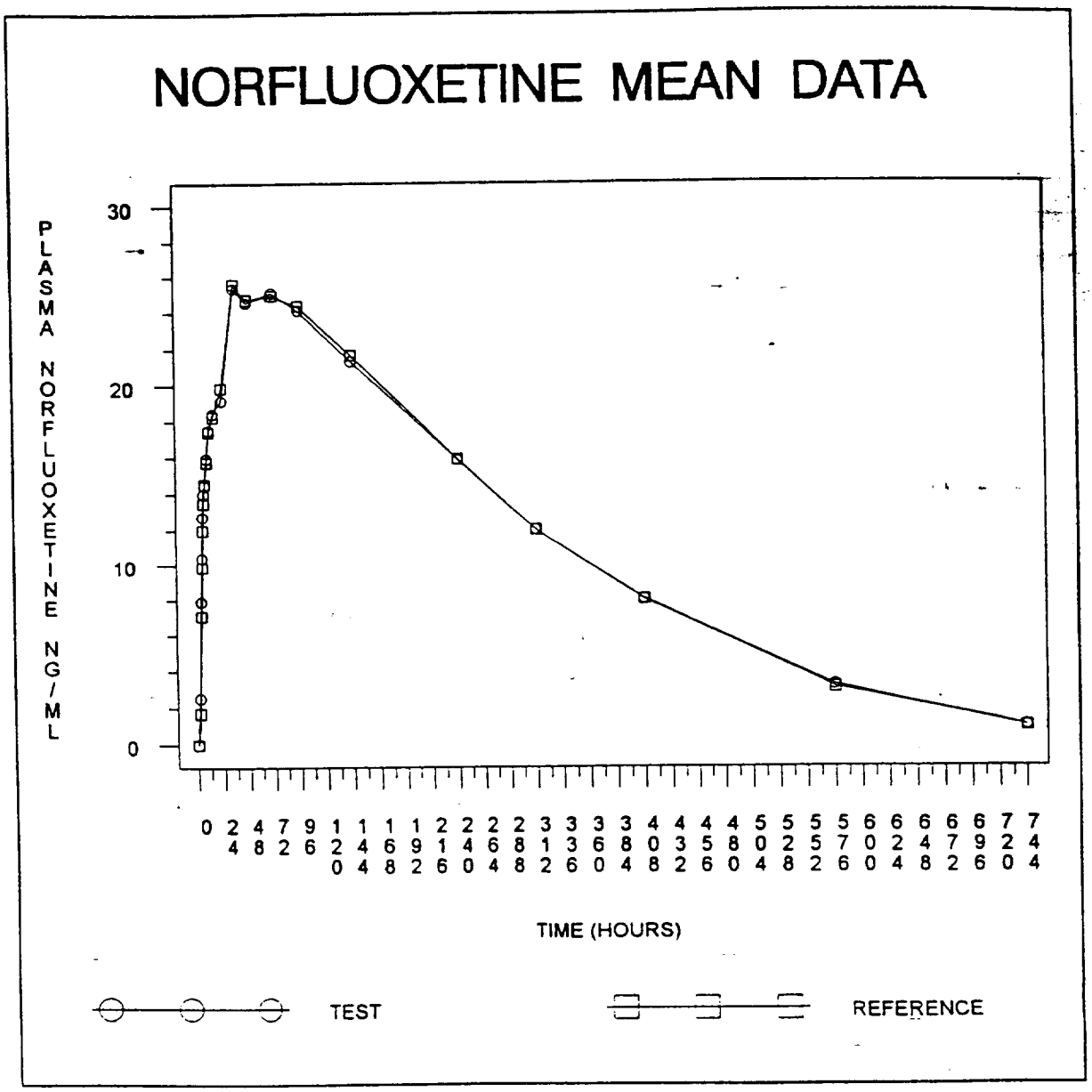
ANDA #74-803

Figure #2 Semi-logarithmic Plot of Mean Plasma Fluoxetine Concentrations *vs* Time



ANDA # 74-803

Figure #3 Linear Plot of Mean Plasma Norfluoxetine Concentrations *vs* Time



ANDA #74-803

Figure #4 Semi-logarithmic Plot of Mean Plasma Norfluoxetine Concentrations *vs* Time