CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-351

BIOEQUIVALENCE REVIEW(S)

File

OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 75-351 **SPONSOR:** Endo Pharmaceuticals

DRUG & DOSAGE FORM: Butalbital/Aspirin/Caffeine/Codeine PhosphateCapsules, USP (50/325/40/30 mg)

STRENGTH(s): (50/325/40/30 mg)

TYPE OF STUDIES: Fasting ~~and~~ SD bioequivalence studi~~es~~ and *in vitro* dissolution testing

STUDY SITES: Clinical:

Analytical:

STUDY SUMMARY: Acceptable

DISSOLUTION: Acceptable

PRIMARY REVIEWER: James E. Chaney, Ph.D. **BRANCH:** I

INITIAL: _____ **DATE:** 8/12/98

BRANCH CHIEF: Yih Chain Huang, Ph.D. **BRANCH:** I

INITIAL: _____ **DATE:** 8/12/98

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: _____ **DATE:** 8/12/98

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: _____ **DATE:** _____

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-351 APPLICANT: Endo Pharmaceuticals

DRUG PRODUCT: Butalbital/Aspirin/Caffeine/Codeine Phosphate Capsules, USP (50/325/40/30 mg)

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

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

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,

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

Butalbital/Aspirin/
Caffeine/Codeine Phosphate
Capsules, USP (50/325/40/30 mg)
ANDA # 75-351
Reviewer: James Chaney
WP #75351SD.398

Endo Pharmaceuticals
Garden City, NY
Submission Date:
March 31, 1998

Review of a Fasting Bioequivalence Study and Dissolution Data

I. BACKGROUND

The combination drug product Aspirin/Butalbital/Caffeine/ Codeine Phosphate Capsules (325/50/40/30 mg) is used for the relief of the symptom complex of tension (or muscle contraction) headache.

Butalbital is well absorbed from the gastrointestinal tract. Elimination of butalbital is primarily via the kidney (59%-88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. The bioavailability of the butalbital component of the studied combination drug product is equivalent to that of a solution except for a decrease in the rate of absorption. A peak concentration is obtained at about 1.5 hours after a 100 mg dose.

Codeine is readily absorbed from the gastrointestinal tract. The plasma half-life is about 2.9 hours. The elimination of codeine is mainly via the kidneys, and about 90% of an oral dose is excreted by the kidneys within 24 hours of dosing. At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours. The bioavailability of the codeine component of the studied combination drug product is equivalent to that of a solution. Peak concentrations were obtained at 1 hour after a 60 mg dose.

The most commonly reported adverse events associated with the use of this combination drug product are nausea and/or abdominal pain, drowsiness, and dizziness.

Recommended dosage is one or 2 capsules every 4 hours with total daily dosage not exceeding 6 capsules.

The reference listed drug product is Fiorinal® with Codeine Capsules USP, manufactured by Sandoz.

The Division of Bioequivalence requires measurement of only two components of the product, Butalbital and Codeine, for satisfying the bioequivalence approval criteria.

The firm has submitted the results of a single-dose, two-way crossover, fasting bioequivalence study comparing its test

product with the RLD product. Comparative dissolution data were also submitted.

II. STUDY OBJECTIVE

The purpose of this study was to evaluate the bioequivalency of Endo Pharmaceuticals' Aspirin/Butalbital/Caffeine/Codeine (325/50/40/30 mg) capsules and Sandoz's Fiorinal® with Codeine Capsules, in a fasting single dose, two-treatment, two-period crossover study design.

III. STUDY INVESTIGATORS AND FACILITIES

The biostudy was conducted by The principal investigator was Plasma samples were assayed by under the supervision of

IV. STUDY DATES

The biostudy was conducted between August 16, 1997 and September 21, 1997. Sample analysis was conducted between October 10, 1997 and November 19, 1997.

V. CLINICAL

Demographics: Twenty-eight (15 male and 13 female) normal, healthy volunteers between 18-45 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests.

Inclusion/exclusion criteria: Subjects did not have any history of: hypersensitivity to aspirin or any other nonsteroidal anti-inflammatory drugs, caffeine or other xanthines, codeine or other narcotics, butalbital or other barbiturates; alcoholism or drug abuse; cardiovascular, pulmonary, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric.

Restrictions: They were free of all medications at least 7 days prior to each study period and allowed no concomitant medications during the study sessions. No caffeine-containing products were allowed 48 hours prior to their check-in appointment and throughout the period of sample.

Monitoring: Vital signs (blood pressure, pulse rate, respiration

rate and temperature) were recorded at screening, at check-in of each period and at the end of the study. In addition, blood pressure and pulse rate were recorded pre-dose and at 1, 2, 4 and 6 hours postdose. vital signs were measured at other times when deemed necessary.

Confinement: Subjects were housed from the evening before dosing until after the 24-hour blood draw. They returned for subsequent blood draws at 24-hour intervals until 192 hours post-dose.

Fasting/Meals: Subjects were required to fast for at least 10 hours before dosing and for 4 hours thereafter. Water was not permitted for 1 hour before and 2 hours after the dosing, but was allowed at all other times. Standard meals were provided at approximately 4 and approximately 10 hours after drug administration and at appropriate times thereafter. During housing, post-dose meal plans were identical for both periods.

Washout time between doses: 28 days

Treatments: The two treatments consisted of a single -capsule dose of either the test product or reference product taken orally with of water. Butalbital levels were measured in all samples; codeine levels were measured in the predose to the 12-hour post-dose samples.

Test Product: Endo Pharmaceuticals' Aspirin/Butalbital/Caffeine/Codeine(325/50/40/30 mg) capsules, lot # LB104A (Batch size of iits, potency of 100.8/99.0/99.7/103.1% (Aspirin/Butalbital/Caffeine/Codeine).

Reference product: Sandoz's Fiorinal® with Codeine capsules, lot # 653Z2277. Potency of 100.2/99.3/100.7/99.5% (Aspirin/ Butalbital/Caffeine/Codeine). Expiry January 2000.

Sampling: Blood samples were collected at predose, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 9, 12, 16, 24, 48, 72, 96, 120 and 144, 168 and 192 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at for analysis.

VI. STATISTICAL ANALYSIS

Analysis of variance was performed on the untransformed pharmacokinetic parameters with the exception of the AUCT/AUCI ratio. Also, log-transformed data was used for analysis of AUC0-t, AUCI and CMAX. The ANOVA model included sequence, subjects nested within sequence, period, and treatments as factors. The significance of the sequence effect was tested

using the subjects nested within sequence as the error term. A 5% level of significance was used for within subject comparisons and a 10% level of significance was used for within subject comparisons. Each analysis of variance included calculation of LSmeans, adjusted differences between formulation means and the standard error associated with these differences. The analyses were done with SAS GLM procedures.

VII. ANALYTICAL

VIII. PHARMACOKINETIC RESULTS

A total of 28 healthy adult volunteers enrolled in the study and completed the crossover. Subjects 10 and 13 vomited within 5.5 hours after dosing. As per protocol and as outlined in the Protocol Deviation Authorization, samples from these subjects were not analyzed and samples from two alternate subjects (26 and 27) following the same sequence were analyzed. Also, in accordance with the protocol if more than 24 subjects finished the study, samples from the highest numbered subjects would be eliminated to leave 24 subjects; subjects 25 and 28 were excluded. Thus, the data set used for statistical and pharmacokinetic analyses contains data from 24 subjects.

BUTALBITAL

The mean concentrations of butalbital at each time point for each product are summarized in Table 1. A linear plot of the mean plasma concentration for butalbital as a function of time is shown in Figure 1. The two curves are very similar.

Table 1. Mean Plasma Concentrations (μg/mL) of Butalbital Following Administration of Test or Reference as 2 Capsule Doses (100 Mg) under Fasting Conditions (N=24)							
	Endo Pharmaceuticals			Fiorinal®			
TIME	N	Mean	%CV	N	Mean	%CV	T/R
0	24	0.0000	-	24	0.0000	-	-
0.25	24	0.1862	168.7	24	0.1638	203.3	1.14
0.5	24	1.1233	63.9	24	1.2282	63.2	0.91
0.75	24	1.8030	36.6	24	1.7860	43.0	1.01
1	24	1.9998	26.1	24	1.9949	28.6	1.00
1.33	24	2.1079	21.6	24	2.0995	19.4	1.00
1.67	24	2.0635	17.4	24	2.0408	15.4	1.01
2	24	2.0059	15.9	24	2.0420	16.5	0.98
2.5	24	1.9795	17.5	24	1.9476	16.9	1.02
3	24	1.9229	15.2	24	1.8898	15.4	1.02
4	24	1.8777	15.8	24	1.8660	16.8	1.01
6	24	1.7313	16.4	24	1.7525	17.1	0.99
9	24	1.6521	15.7	24	1.6391	17.9	1.01
12	24	1.5795	14.8	24	1.6133	17.1	0.98
16	24	1.4737	16.3	24	1.5014	18.3	0.98
24	24	1.3096	17.5	24	1.3478	15.1	0.97
48	24	0.8645	15.5	24	0.8661	17.6	1.00
72	24	0.5701	22.4	24	0.5661	20.9	1.01
96	24	0.3801	28.4	24	0.3754	28.9	1.01
120	24	0.2505	29.9	24	0.2497	30.5	1.00
144	23	0.1489	62.7	24	0.1531	50.2	0.97
168	24	0.0965	85.6	24	0.0959	77.0	1.01
192	24	0.0409	145.6	24	0.0498	138.1	0.82

The comparison of arithmetic means, LSmeans and geometric LSmeans with 90% confidence intervals for the pharmacokinetic parameters of butalbital are shown in Table 2.

Table 2. Comparison of Mean (%CV) Pharmacokinetic Results for Butalbital Between The Test and Reference Products Administered as 2 Capsule Doses (100 Mg) under Fasting Conditions (N=24)

Parameter	Test	Reference	T/R	90% C.I.
Arithmetic Means				
AUCT	108.3 (17.6)	109.2 (16.7)	0.99	--
AUCI	116.4 (16.8)	117.4 (16.4)	0.99	--
CMAX	2.30 (16.5)	2.29 (19.3)	1.00	--
THALF	41.6 (18.7)	41.6 (16.6)	1.00	--
TMAX	1.53 (60.0)	1.52 (43.8)	1.00	--
AUCT/AUCI	0.93 (2.4)	0.93 (2.1)	1.00	--
Geometric LSMeans				
AUCT	106.8	107.8	0.99	96.2-101.9
AUCI	114.9	116.0	0.99	96.2-102.0
CMAX	2.28	2.25	1.02	98.0-105.3

Arithmetic mean test/reference ratios of the pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for butalbital are shown in Table 3. Arithmetic mean $AUC_{0-t}/AUC_{0-\infty}$ ratios for butalbital are shown in Table 4.

Table 3. Arithmetic Mean Butalbital Test/Reference Ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} Following Administration of a Single-Dose of Test or Reference as 2 Capsule Doses (100 Mg) under Fasting Conditions (N=24)

	AUCT	AUCI	CMAX
Mean	0.99	0.99	1.02
%CV	8.39	8.23	10.36
Min	0.83	0.83	0.83
Max	1.16	1.14	1.31

Table 4. Arithmetic Mean Butalbital AUC_{0-t} to AUC_{0-inf} Ratios Following Administration of Test or Reference as 2 Capsule Doses (100 Mg) under Fasting Conditions (N=24)		
	TEST	REFERENCE
Mean	0.93	0.93
%CV	2.43	2.09
Min	0.86	0.89
Max	0.96	0.96

CODEINE

The mean concentrations of Codeine at each time point for each product are summarized in Table 5. A linear plot of the mean plasma concentration for Codeine as a function of time is shown in Figure 2. The two curves are very similar.

Table 5. Mean Plasma Concentrations (μg/mL) of Codeine Following Administration of Test or Reference as 2 Capsule Doses (60 Mg) under Fasting Conditions (N=24)							
	Endo Pharmaceuticals			Fiorinal®			
Time	N	Mean	%CV	N	Mean	%CV	T/R
0	24	0.00	-	24	0.00	-	-
0.25	24	4.62	206.7	24	3.18	339.9	1.45
0.5	24	56.23	101.1	24	59.18	96.0	0.95
0.75	24	114.46	55.4	24	122.39	60.2	0.94
1	24	146.63	43.1	24	138.51	45.1	1.06
1.33	24	154.98	34.0	24	154.08	35.1	1.01
1.67	24	152.81	28.4	24	145.82	30.8	1.05
2	24	140.55	24.1	24	139.57	30.7	1.01
2.5	24	119.86	25.2	24	120.31	29.1	1.00
3	24	104.03	25.3	24	103.07	27.0	1.01
4	24	82.60	26.3	24	77.58	28.8	1.06
6	24	44.29	26.7	24	41.65	35.7	1.06
9	24	21.83	39.7	24	19.15	43.3	1.14
12	24	4.32	166.0	24	5.12	138.7	0.84

The comparison of arithmetic means, LSmeans and geometric LSmeans with 90% confidence intervals for the pharmacokinetic parameters of Codeine are shown in Table 6.

Table 6. Comparison of Mean (%CV) Pharmacokinetic Results for Codeine Between The Test and Reference Products Administered as 2 Capsule Doses (60 Mg) under Fasting Conditions (N=24)

Parameter	Test		Reference		T/R	90% C.I.
Arithmetic Means						
AUCT	670.3	(27.4)	649.6	(30.2)	1.03	
AUCI	745.2	(25.5)	714.1	(28.1)	1.04	
CMAX	173.4	(27.9)	171.5	(31.5)	1.01	
THALF	2.69	(14.8)	2.53	(15.1)	1.06	
TMAX	1.45	(29.7)	1.40	(34.1)	1.04	
AUCT/AUCI	89.6	(5.0)	90.6	(4.4)	0.99	
Geometric LSMeans						
AUCT	664.7		620.6		1.04	97.8-110.3
AUCI	720.6		686.5		1.05	99.2-111.2
CMAX	166.6		162.4		1.03	95.4-110.3

Arithmetic mean test/reference ratios of the pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for codeine are shown in Table 7. Arithmetic mean $AUC_{0-t}/AUC_{0-\infty}$ ratios for codeine are shown in Table 8.

Table 7. Arithmetic Mean Codeine Test/Reference Ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} Following Administration of a Single-Dose of Test or Reference as 2 Capsule Doses (60 Mg) under Fasting Conditions (N=24)

	AUCT	AUCI	CMAX
Mean	1.05	1.06	0.99
%CV	16.3	15.2	4.6
Min	0.75	0.79	0.91
Max	1.37	1.36	1.09

Table 8. Arithmetic Mean Codeine AUC_{0-t} to AUC_{0-inf} Ratios Following Administration of a Single-Dose of Test or Reference as 2 Capsule Doses (100 Mg) under Fasting Conditions (N=24)		
	TEST	REFERENCE
Mean	0.93	0.93
%CV	2.43	2.09
MIN	0.86	0.89
MAX	0.96	0.96

Adverse Effects: No serious medical events were reported during the study and no medication was required for any event.

IX. FORMULATION

Butalbital/Aspirin/Caffeine and Codeine Phosphate Capsules, USP 50/325/40/30 mg

Ingredients	mg/Capsule
Aspirin, USP	325.00
Butalbital, USP	50.00
Caffeine, USP (Anhydrous)	40.00
Codeine Phosphate, USP	30.00
Microcrystalline Celluose, (02)	
Sodium Lauryl Sulfate,	
Pregelatinized Starch,	
Talc,	
Colloidal Silicon Dioxide,	
Stearic Acid,	
Total:	**605.00**

X. DISSOLUTION TESTING

The firm conducted the dissolution study following the USP dissolution method and tolerance specifications for its product. The dissolution methods and data obtained using the above method are shown in Table 9.

XI. COMMENTS

1. The study is acceptable.
2. The dissolution testing conducted by the firm is acceptable.
3. The analytical data is acceptable.

4. The assayed potency and the content uniformity of the test and reference products are satisfactory.
5. The pharmacokinetic parameters and statistics were calculated by the reviewer and were in satisfactory agreement with what the firm reported.
6. The *in vitro* dissolution data for the test and reference products are acceptable.

RECOMMENDATIONS:

1. The single-dose, fasting bioequivalence study conducted by Endo Pharmaceuticals on its test product, Aspirin/ Butalbital/Caffeine/Codeine Capsules, 325/50/40/30 mg, comparing it with the reference product, Sandoz's Fiorinal® with Codeine Capsules, has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product, Endo Pharmaceuticals' Aspirin/Butalbital/ Caffeine/Codeine Capsules, 325/50/40/30 mg, is bioequivalent to the reference product, Sandoz's Fiorinal® with Codeine Capsules, under fasting conditions.

2. The *in-vitro* dissolution testing conducted by Endo Pharmaceuticals on its Aspirin/Butalbital/Caffeine/Codeine Capsules (325/50/40/30 mg), has been found acceptable.

   The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of water at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of aspirin, butalbital, caffeine and codeine in the dosage form is dissolved in minutes.

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

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FT INITIALED YCHuang

Date 8/12/98

Concur:

Date 8/12/98

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

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Table 9. In Vitro Dissolution Testing

Drug (Generic Name): Aspirin/Butalbital/Caffeine/Codeine Capsules
Dose Strength: 325 mg/50mg/40mg/30mg
ANDA No.: ANDA # 75-351
Firm: Endo Pharmaceuticals
Submission Date: 3/31/98

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: Water Volume: 1000 mL
Specifications:
Reference Drug: Fiorinal with Codeine Capsules (Sandoz)
Assay Methodology:

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II. Results of In Vitro Dissolution Testing:

Sample Times (Min)	Test Product			Reference Product		
	Mean %	Range	%CV	Mean %	Range	%CV
Butalbital						
	Lot # LB104 Strength(mg) 50			Lot # 653Z2277 Strength(mg) 50		
10	94.1	86.4-98.3	4.3	66.3	60.0-73.1	6.1
20	97.2	89.0-101.5	3.6	74.0	70.3-80.5	4.7
30	98.7	90.2-102.9	3.5	79.0	74.7-85.1	4.2
45	99.2	91.3-103.1	3.0	84.5	80.8-89.9	3.5
60	99.9	92.2-102.2	2.8	88.6	85.6-92.5	2.8

(Continuation of Table 9)

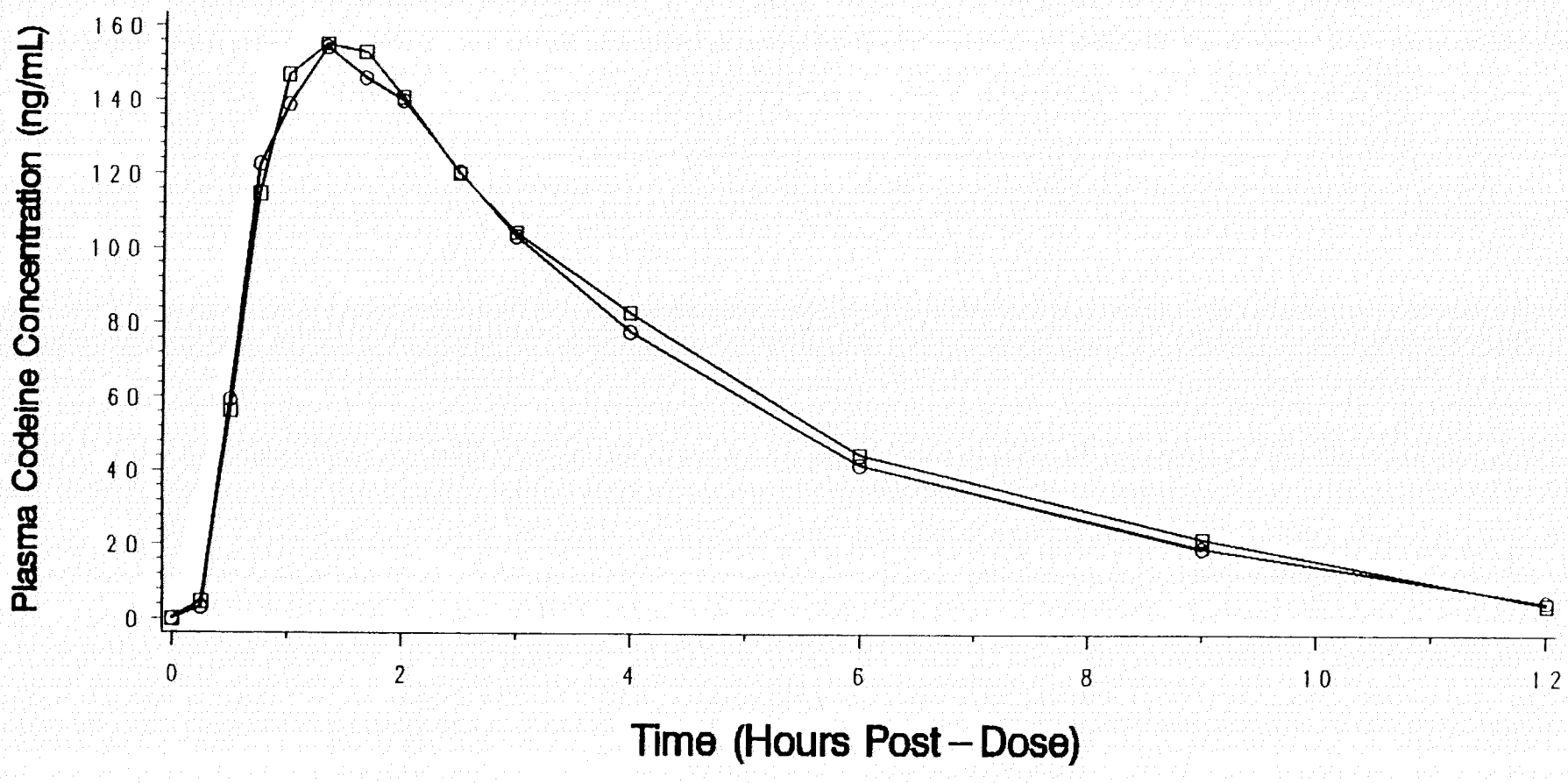
Aspirin						
	Strength(mg) 325			Strength(mg) 325		
10	92.3	77.1-98.0	7.1	62.4	54.4-66.9	6.8
20	97.5	87.4-104.2	5.4	72.3	67.4-78.1	5.4
30	99.2	89.3-104.6	4.7	78.7	71.4-84.4	4.8
45	101.4	91.3-106.7	4.4	85.0	80.3-89.7	3.7
60	102.7	93.1-106.7	3.9	89.5	85.9-91.9	3.0
Caffeine						
	Strength(mg) 40			Strength(mg) 40		
10	100.4	93.5-103.9	2.6	49.8	42.1-56.3	8.6
20	101.6	94.3-105.7	2.8	63.2	56.0-69.8	6.5
30	102.3	94.6-105.9	3.0	72.4	65.0-80.2	5.8
45	101.9	94.8-105.8	2.7	82.1	75.9-90.4	4.6
60	102.2	95.3-104.8	2.6	88.7	83.3-95.7	3.6
Codeine						
	Strength(mg) 30			Strength(mg) 30		
10	102.6	95.4-106.3	3.0	45.8	40.8-53.9	10.9
20	104.0	96.7-108.2	3.0	61.8	55.3-72.4	8.2
30	104.1	97.0-108.5	2.7	72.9	66.1-83.3	6.8
45	104.5	97.4-108.8	2.8	83.8	78.2-91.2	4.9
60	104.7	97.7-107.5	2.7	90.7	87.2-95.6	3.2

Figure /

Project No. 960411

Mean Plasma Codeine Concentrations

(Linear Plot)



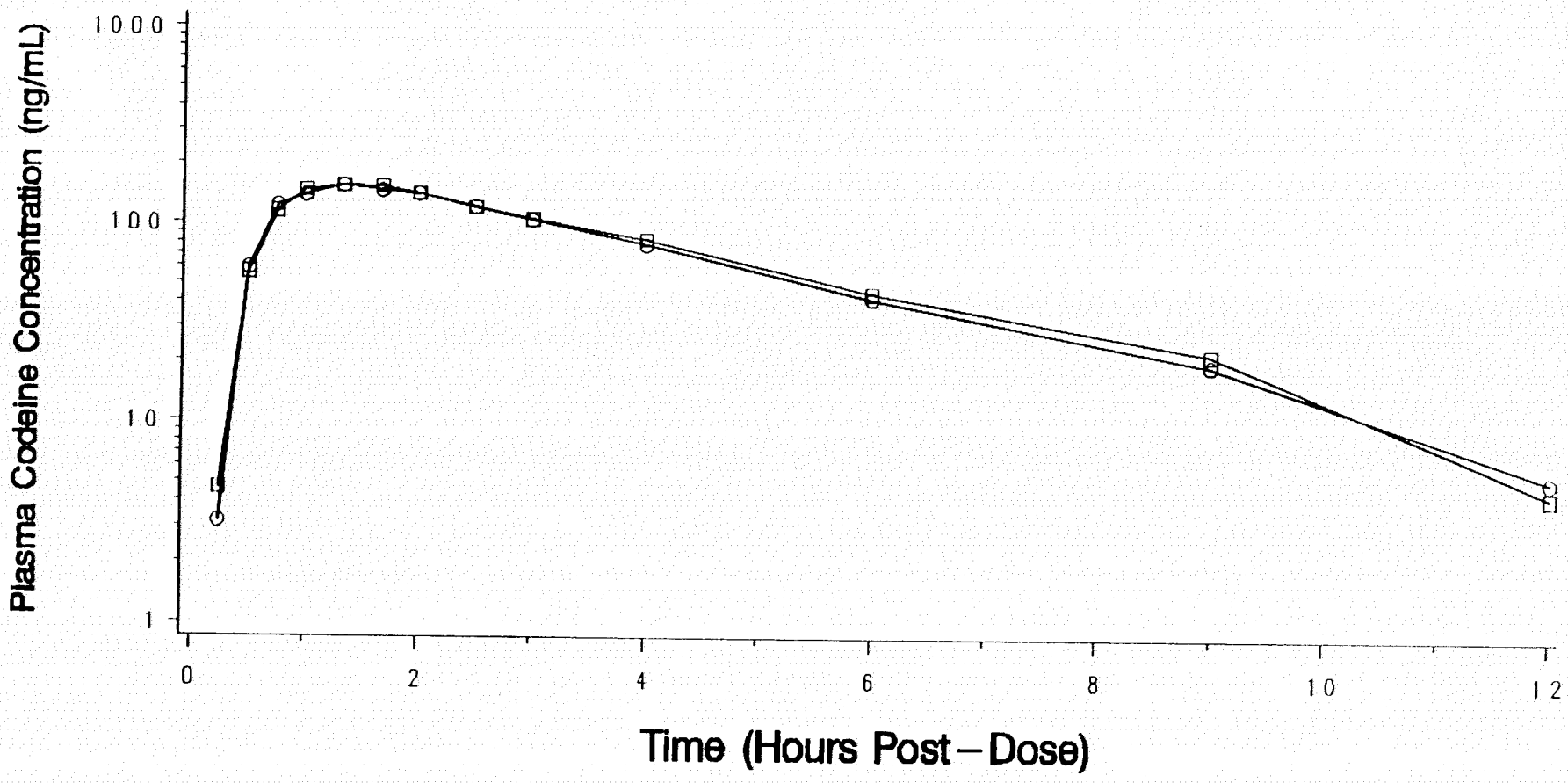
DEFAULT (27NOV97)

Figure 2

Project No. 960411

Mean Plasma Codeine Concentrations

(Semi – Log Plot)



DEFAULT (27NOV97)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-351 APPLICANT: Endo Pharmaceuticals

DRUG PRODUCT: Butalbital/Aspirin/Caffeine/Codeine Phosphate Capsules, USP (50/325/40/30 mg)

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

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

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,

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