# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**74-951**

# BIOEQUIVALENCE

APR 30 1997

Aspirin/Butalbital/Caffeine/Codeine Phosphate
Capsules (325/50/40/30 mg)
ANDA # 74-951
Reviewer: Hoainhon Nguyen
WP # 74951sd.896

Jerome Stevens Pharmaceuticals
Bohemia, NY
Submission Date:
August 29, 1996
April 2, 1997
April 10, 1997

Review of a Fasting Bioequivalence Study and Dissolution Data

I. Background:

The combination drug product of 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. Aspirin, the prototype of the salicylates, is a nonsteroidal anti-inflammatory agent, slightly soluble in water with pKa of 3.5. Butalbital is a short- to intermediate-acting barbiturate. Caffeine is a central nervous stimulant. Codeine phosphate is a phenanthrene-derivative opiate agonist, freely soluble in water.

The systemic availability of aspirin after an oral dose is highly dependent on the dosage form, the presence of food, the gastric emptying time, gastric pH, antacids, buffering agents, and particle size. These factors affect not necessarily the extent of absorption of total salicylates but more the stability of aspirin prior to absorption. During the absorption process and after absorption, aspirin is mainly hydrolyzed to salicylic acid and distributed to all body tissues and fluids with highest concentrations found in plasma, liver, renal cortex, heart, and lung. In plasma, about 50-80% of the salicylic acid and its metabolites are loosely bound to plasma proteins. The clearance of total salicylates is subject to saturable kinetics; however, first-order elimination kinetics are still a good approximation for doses up to 650 mg. The plasma half-life for aspirin is about 12 minutes and for salicylic acid and/or total salicylates is about 3.0 hours. The elimination of therapeutic doses is through the kidneys either as salicylic acid or other biotransformation products. The biotransformation of aspirin occurs primarily in hepatocytes. The major metabolites are salicyluric acid (75%), the phenolic and acyl glucuronides of salicylate (15%), and gentisic and gentisuric acid (1%). The bioavailability of the aspirin component of the studied combination product is

equivalent to that of a solution except for a slower rate of absorption. A peak concentration was obtained at 40 minutes after a 650 mg dose.

Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to most of the tissues in the body. They are bound to plasma and tissue proteins to a varying degree. 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. Urinary excretion products included parent drug (about 3.6% of the dose), 5-isobutyl-5-(2,3-dihydropropyl) barbituric acid (about 24%), 5-allyl-5(3-hydroxy-2-methyl-1-propyl) barbituric acid (4.8%), products with the barbituric acid ring hydrolyzed with excretion of urea (14%), as well as unidentified materials. Of the material excreted in the urine, 32% was conjugated. 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.

Like most xanthines, caffeine is rapidly absorbed and distributed in all body tissues and fluids. Caffeine is cleared rapidly through metabolism and excretion in the urine. The plasma half-life is about 3 hours. Hepatic biotransformation prior to excretion results in about equal amounts of 1-methyl-xanthine and 1-methyluric acid. Of the 70% of the dose that has been recovered in the urine, only 3% was unchanged drug. The bioavailability of the caffeine component of the studied combination drug product is equivalent to that of a solution except for a slightly longer time to peak. A peak concentration was obtained in less than an hour for an 80 mg dose.

Codeine is readily absorbed form the gastrointestinal tract. It is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by parenchymatous organs such as liver, spleen, and kidney. Codeine is not bound to plasma proteins and does not accumulate in body tissues. 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. The urinary secretion products consist of free and glucuronide-conjugated codeine (about 10%), free and conjugated morphine (10%), normorphine (4%), and hydrocodone (1%). The remainder of the dose is excreted in feces. 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. Bioequivalence Study: (Protocol No. 960366)

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Jerome-Stevens' 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.

Study Investigators and Facilities:

The study was conducted at Phoenix Clinical Research Center, Quebec, Canada, between April 11 and May 9, 1996. The principal investigator was Pierre Geoffroy, M.D.. Plasma samples were assayed by [redacted], under the supervision of [redacted] between May 20 and May 29, 1996.

Demographics:

Twenty-four and 2 alternate normal, healthy male 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. The subjects' weight and height ranged 61.5 - 88.2 kg and 162 - 187 cm, respectively.

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 alcohol and no xanthine-containing products were allowed 24 hours prior to their check-in appointment and throughout the period of sample. The subjects fasted for overnight prior to and 4 hours after each drug administration. The washout duration between the two phases was 28 days. Duration of confinement was 12 hours pre-dose to approximately 24 hours post-dose.

Treatments and Sampling:

The two treatments consisted of a single 2-capsule dose of either the test product or reference product taken orally with 240 ml of water.

**Test Product**: Jerome-Stevens' Aspirin/Butalbital/Caffeine/Codeine(325/50/40/30 mg) capsules, lot # 015395 (Batch size of . ,. . . units, potency of 101.5/99.6/100.2/100.4% (Aspirin/Butalbital/Caffeine/Codeine).

**Reference product**: Sandoz's Fiorinal® with Codeine capsules, lot # 589X9300 (Potency of 100.2/99.3/100.7/99.5% (Aspirin/Butalbital/Caffeine/Codeine).

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 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -12$^0$C until shipping to the analytical laboratory.

Assay Methodology:

The analytical method was developed by

A. Butalbital:

Assay Specificity:

The assay was specific for butalbital with no significant interferences seen at the retention time of the drug and internal standard in the of the predose subject samples and blank plasma standards. (Interferences seen at the retention time of butalbital in 12 and 7 of the predose samples and blank standards, respectively, were less than 47% in peak height of the LOQ standard of the same run.)

Linearity:

**(Based on actual study standard curves)**

The assay was linear in the range of 0.100 to 9.978 μg/ml of butalbital.

Reproducibility:

**(Based on actual study quality controls)**

Interday CV's were: 6.9% at 0.300 μg/ml, 3.7% at 3.995 μg/ml and 6.1% at 7.99 μg/ml.

Sensitivity:

**(Based on actual study back-calculated standard data)**

Sensitivity limit was 0.100 μg/ml for butalbital (CV% = 11.3). Any level below this limit was reported as zero.

The prestudy assay validation data showed CV% for the quality control of 0.100 μg/ml was 5.9 (n=10).

Accuracy:

**(Based on actual study quality controls)**

Percent recovery of control samples were: 100% at 0.300 μg/ml, 98.8% at 3.995 μg/ml and 96.6% at 7.990 μg/ml.

Stability:

Long-term stability of frozen samples was demonstrated **in a pre-study validation study** using frozen control samples which were prepared, stored at -22C, analyzed on Day 65 and compared with freshly prepared control samples. Ratio of mean responses was within 0.96-1.01. The actual plasma samples were first collected and stored frozen (-22C) on 04/11/96 and last analyzed on 05/29/96 (Total of 48 days).

Short-term stability (10.1 hours at room temperature), freeze-thaw stability (3 cycles), autosampler stability (2.9 hours at room temperature) and stock solution (in methanol at -22°C for 78 days) were evaluated and acceptable.

B. Codeine:

Assay Specificity:

The assay was specific for codeine with no significant interferences seen at the retention time of the drug and internal standard in the [illegible] he predose subject samples and blank plasma standards. (Interferences were seen at the retention time of codeine in 2 [illegible] of the blank standards; however, these standards were not included in the calibration and the quality controls of these runs were acceptable.)

Linearity:

**(Based on actual study standard curves)**

The assay was linear in the range of 10.0 to 1000.8 ng/ml of codeine.

Reproducibility:

**(Based on actual study quality controls)**

Interday CV's were: 6.9% at 30.1 ng/ml, 3.8% at 401.7 ng/ml and 3.2% at 803.4 ng/ml.

Sensitivity:

**(Based on actual study back-calculate standard data)**

Sensitivity limit was 10.0 ng/ml for codeine (CV% = 11.3). Any level below this limit was reported as zero.

Prestudy assay validation data showed that CV% for the quality control of 10.0 ng/ml was 12.3 (n=9)

Accuracy:

**(Based on actual study quality controls)**

Percent recovery of control samples were: 99.4% at 30.1 ng/ml, 99.8% at 401.7 ng/ml and 98.2% at 803.4 ng/ml.

Stability:

Long-term stability of frozen samples was demonstrated **in a pre-study validation study** using frozen control samples which were prepared, stored at -22C, analyzed on Day 65 and compared with freshly prepared control samples. Ratio of mean responses was within 0.93-1.01. The actual plasma samples were first collected and stored frozen (-22C) on 04/11/96 and last analyzed on 05/29/96 (Total of 48 days).

Short-term stability (10.1 hours at room temperature), freeze-thaw stability (3 cycles), autosampler stability (3.1 hours at room temperature) and stock solution (in methanol at -22$^{0}$C for 78 days) were evaluated and acceptable.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares

means, using the two, one-sided t-test.

Results:

Twenty-five of 26 enrolled volunteers completed the clinical portion of the study. Subject # 6 was withdrawn from the study 25.2 days after Period I dosing for personal reasons. The statistical analysis was performed using 24 (balanced) data sets per protocol.

A. Butalbital:

There was no significant difference (alpha=0.05) between treatments for AUC (0-T), AUC (0-Infinity), lnAUC(0-T), lnAUC(0-Infinity) and lnCMAX. There was a significant difference between treatments for CMAX (p=0.0479) and TMAX (p=0.0432). The results are summarized in the tables below:

Table I

Butalbital Comparative Pharmacokinetic Parameters

Dose=2 capsules*; n=24

| Parameters | Jerome-Stevens' Mean (CV%) | Fiorinal® Mean (CV%) | 90% C.I. | Ratio T/R |
|---|---|---|---|---|
| AUC (0-T) μg.hr/ml | 101.9** | 100.4** | [0.99;1.04] | 1.02 |
| AUC (0-Inf) μg.hr/ml | 112.7** | 110.5** | [0.99;1.06] | 1.02 |
| CMAX(μg/ml) | 2.170** | 2.100** | [1.00;1.06] | 1.03 |
| TMAX (hrs) | 1.264(58) | 1.854(88) | | |
| KEL (1/hrs) | 0.018(20) | 0.018(19) | | |
| T1/2 (hrs) | 40.73(22) | 38.68(19) | | |

*One capsule=Aspirin/Butalbital/Caffeine/Codeine(325/50/40/30 mg)

**Geometric LSMeans

Table II

Comparative Mean Plasma Levels of Butalbital

Dose=2 capsules*; n=24

μg/ml(CV%)

| Hour | Jerome-Stevens' | Fiorinal® |
|---|---|---|
| 0 | 0 | 0 |
| 0.25 | 0.178(171) | 0.173(173) |
| 0.5 | 1.351(46) | 1.086(52) |
| 0.75 | 1.807(24) | 1.664(29) |
| 1 | 1.998(15) | 1.826(18) |
| 1.33 | 1.937(11) | 1.964(10) |
| 1.67 | 1.944(11) | 1.958(10) |
| 2 | 1.904(11) | 1.890(12) |
| 2.5 | 1.867(12) | 1.868(10) |
| 3 | 1.838(12) | 1.841(11) |
| 4 | 1.792(14) | 1.785(14) |
| 6 | 1.702(12) | 1.699(12) |
| 9 | 1.570(12) | 1.645(12) |
| 12 | 1.540(12) | 1.540(13) |
| 16 | 1.457(14) | 1.462(12) |
| 24 | 1.323(14) | 1.312(13) |
| 48 | 0.856(19) | 0.856(18) |
| 72 | 0.562(22) | 0.543(26) |
| 96 | 0.373(32) | 0.368(36) |
| 120 | 0.246(35) | 0.225(46) |
| 144 | 0.154(61) | 0.133(73) |
| $AUC(0\text{-}T)_{\mu g.hr/ml}$ | 103.1(15) | 101.8(17) |
| $AUC(0\text{-}Inf)_{\mu g.hr/ml}$ | 114.4(17) | 112.3(18) |
| CMAX | 2.183(11) | 2.108(9) |

*One capsule=Aspirin/Butalbital/Caffeine/Codeine(325/50/40/30 mg)

(NOTE: ANOVA for Butalbital was repeated with Subject # 20 dropped from the

data set due to his CMAX being the first plasma concentration (under Test Treatment). 90% confidence intervals for log-transformed AUCT, AUCI and CMAX without this subject were within [0.80;1.25] (They were [0.99;1.04], [0.99;1.06, and [[1.01;1.07], respectively).)

B. Codeine:

There was no significant difference (alpha=0.05) between treatments for all analyzed parmameters. The results are summarized in the tables below:

Table III
Codeine Comparative Pharmacokinetic Parameters
Dose=2 capsules*; n=24

| Parameters | Jerome-Stevens' Mean (CV%) | Fiorinal® Mean (CV%) | 90% C.I. | Ratio T/R |
|---|---|---|---|---|
| AUC (0-T) ng.hr/ml | 235.2** | 234.9** | [0.92;1.08] | 1.00 |
| AUC (0-Inf) ng.hr/ml | 292.2** | 294.0** | [0.93;1.06] | 0.99 |
| CMAX(ng/ml) | 74.98** | 70.50** | [0.99;1.14] | 1.06 |
| TMAX (hrs) | 1.264(58) | 1.854(88) | | |
| KEL (1/hrs) | 0.018(20) | 0.018(19) | | |
| T1/2 (hrs) | 40.73(22) | 38.68(19) | | |

*One capsule=Aspirin/Butalbital/Caffeine/Codeine(325/50/40/30 mg)
**Geometric LSMeans

Table IV

Comparative Mean Plasma Levels of Codeine

Dose=2 capsules*; n=24

ng/ml(CV%)

| Hour | Jerome-Stevens' | Fiorinal® |
|---|---|---|
| 0 | 0 | 0 |
| 0.25 | 0 | 0 |
| 0.5 | 32.39(95) | 28.33(112) |
| 0.75 | 57.72(42) | 60.37(50) |
| 1 | 67.65(24) | 64.37(23) |
| 1.33 | 66.61(20) | 64.37(23) |
| 1.67 | 62.57(22) | 62.14(21) |
| 2 | 56.75(20) | 56.06(22) |
| 2.5 | 48.37(32) | 48.13(29) |
| 3 | 42.70(26) | 43.10(23) |
| 4 | 34.01(25) | 34.40(28) |
| 6 | 17.90(33) | 20.33(53) |
| 9 | 3.05(179) | 2.92(179) |
| 12 | 0 | 0 |
| 16 | 0 | 0 |
| 24 | 0 | 0 |
| $AUC(0\text{-}T)_{ng.hr/ml}$ | 243.7(28) | 246.3(32) |
| $AUC(0\text{-}Inf)_{ng.hr/ml}$ | 300.1(24) | 304.1(26) |
| CMAX | 76.86(22) | 73.42(31) |

*One capsule=Aspirin/Butalbital/Caffeine/Codeine(325/50/40/30 mg)

(NOTE: ANOVA for Codeine was repeated with Subjects # 1, 16, 18 and 20 dropped from the data set due to their CMAX's being the first plasma concentration (under Reference Treatment for Subjects # 1 and 20; and under Test Treatment for Subjects #16,20 and 18). 90% confidence intervals for log-transformed AUCT, AUCI and CMAX without these subjects were within [0.80;1.25] (They were [0.91;1.11], [0.92;1.06, and [[0.98;1.16], respectively).)

Adverse Effects:

No serious medical events were reported during the study. There were 21 probably or possibly drug-related mild reactions reported (8 and 12 reactions during test and reference treatments, respectively) including numbness in arms, feet, face, fingers, cheeks, hands, knees and neck, pain in upper abdomen, vomiting, dizziness, euphoria, lightheadedness and stomachache.

III. Dissolution Testing: USP method and specification.

Drug (Generic Name): Aspirin/Butalbital/Caffeine/Codeine Capsules Firm: Jerome-Stevens
Dose Strength: 325mg/50mg/40mg/30mg ANDA # 74-951
Submission Date: August 29, 1996

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP XXIII Basket __ Paddle X RPM 50 No. Units Tested: 12
Medium: Water Volume: 1000 ml
Reference Drug: (Manuf.) Fiorinal with Codeine Capsules (Sandoz)
Assay Methodology: _____
deine)

II. Results of In-Vitro Dissolution Testing:

| Sampling Times (min.) | Test Product Lot # 015395 | | | Reference Product Lot # 589X9300 | | |
|---|---|---|---|---|---|---|
| 1. Aspirin: | Strength (mg) 325 | | | Strength (mg) 325 | | |
| | Mean % Dissolved | Range | (CV) | Mean % Dissolved | Range | (CV) |
| 15 | 74.1 | | (6.9%) | 63.2 | | (8.4%) |
| 30 | 92.2 | | (3.8%) | 76.6 | | (6.4%) |
| 45 | 97.7 | | (2.2%) | 83.0 | | (5.2%) |
| 60 | 99.6 | | (1.6%) | 87.6 | | (4.7%) |

2. Butalbital:

| Sampling Times (min.) | Test Product Strength (mg) 50 Lot # 015395 Mean % Dissolved | Range | (CV) | Reference Product Strength (mg) 50 Lot # 589X9300 Mean % Dissolved | Range | (CV) |
|---|---|---|---|---|---|---|
| 15 | 74.1 | | (6.9%) | 68.5 | | (7.4%) |
| 30 | 92.2 | | (3.8%) | 78.4 | | (5.7%) |
| 45 | 97.7 | | (2.2%) | 84.1 | | (4.7%) |
| 60 | 99.6 | | (1.6%) | 88.3 | | (4.2%) |

3. Caffeine:

| | Strength (mg) 40 Mean % Dissolved | Range | (CV) | Strength (mg) 40 Mean % Dissolved | Range | (CV) |
|---|---|---|---|---|---|---|
| 15 | 84.3 | | (8.8%) | 57.1 | | (14.6%) |
| 30 | 97.5 | | (3.3%) | 73.9 | | (10.1%) |
| 45 | 99.4 | | (1.3%) | 82.7 | | (7.0%) |
| 60 | 99.6 | | (1.1%) | 88.7 | | (5.6%) |

4. Codeine:

| | Strength (mg) 30 Mean % Dissolved | Range | (CV) | Strength (mg) 30 Mean % Dissolved | Range | (CV) |
|---|---|---|---|---|---|---|
| 15 | 85.7 | | (9.7%) | 56.8 | | (15.4%) |
| 30 | 98.5 | | (3.0%) | 77.1 | | (9.5%) |
| 45 | 99.8 | | (1.1%) | 87.1 | | (5.8%) |
| 60 | 99.9 | | (0.9%) | 93.1 | | (4.1%) |

USP Current Specification:
NLT 75% (all components) dissolved in 60 minutes

IV. Comments:

1. The single-dose, fasting bioequivalence study conducted by Jerome-Stevens on the test product, Aspirin/Butalbital/Caffeine/Codeine, 325/50/40/30 mg, lot # 015395, comparing it with the reference product, Fiorinal®with Codeine Capsules, lot # 589X9300, demonstrates that the test product is equivalent to the reference product in their rate and extent of absorption as measured by lnCMAX, lnAUC(0-T) and lnAUC(0-Infinity) of butalbital and codeine.

2. The in vitro dissolution data for the test and reference products are acceptable.

V. Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Jerome-Stevens on the test product, Aspirin/Butalbital/Caffeine/Codeine Capsules, 325/50/40/30 mg, lot # 015395, comparing it with the reference product, Sandoz's Fiorinal®with Codeine Capsules, lot # 589X9300, has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product, Jerome-Stevens' 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 Jerome-Stevens 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 37C using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than 75% of the labeled amount of aspirin, butalbital, caffeine and codeine in the dosage form is dissolved in 60 minutes.

Hoainhon Nguyen
Division of Bioequivalence

Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 4/24/97

Concur: _____ Date: 4/30/97

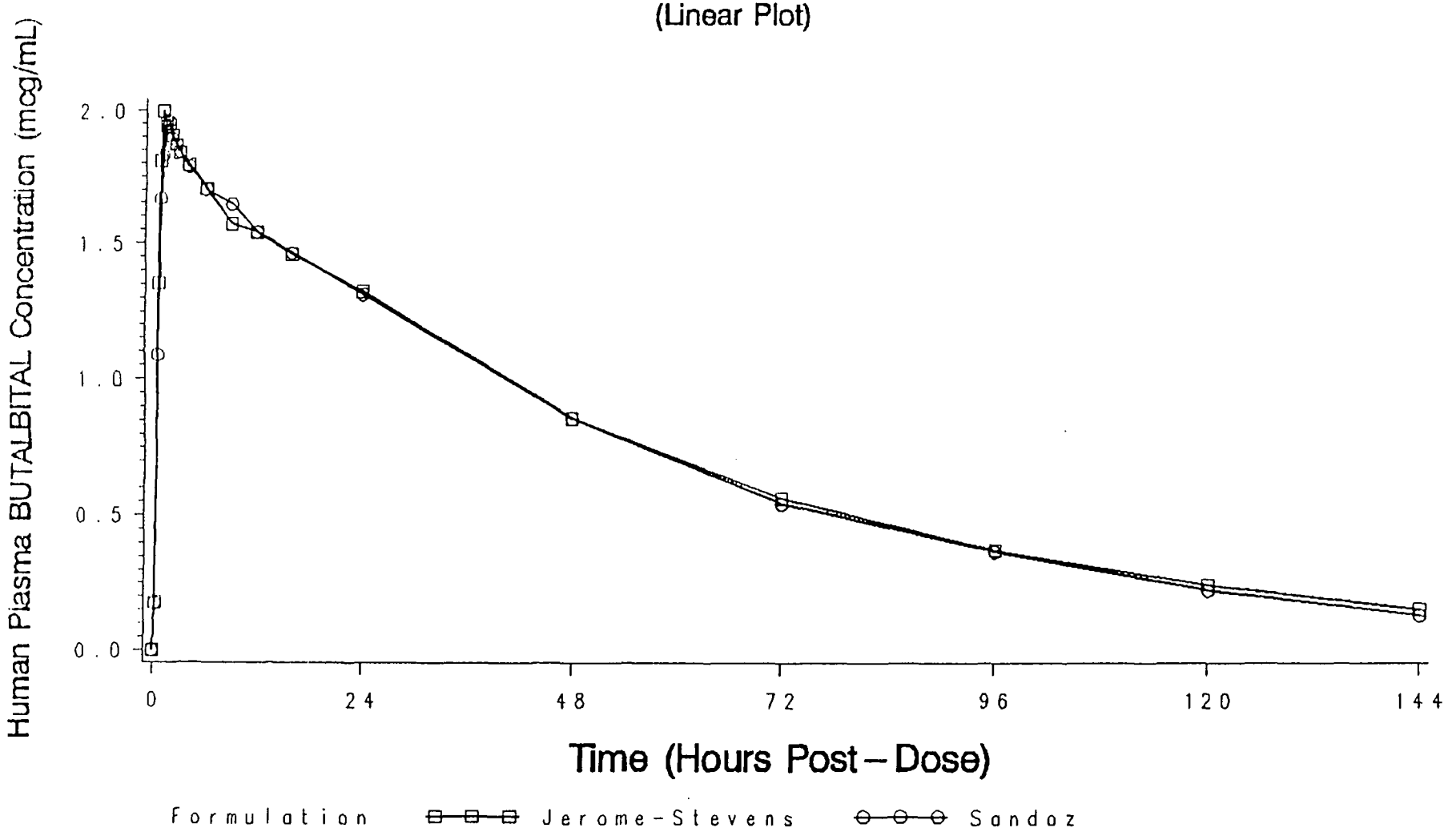
for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence

# Figure 4

Project No. 960366

Mean Human Plasma Butalbital Concentrations

(Linear Plot)

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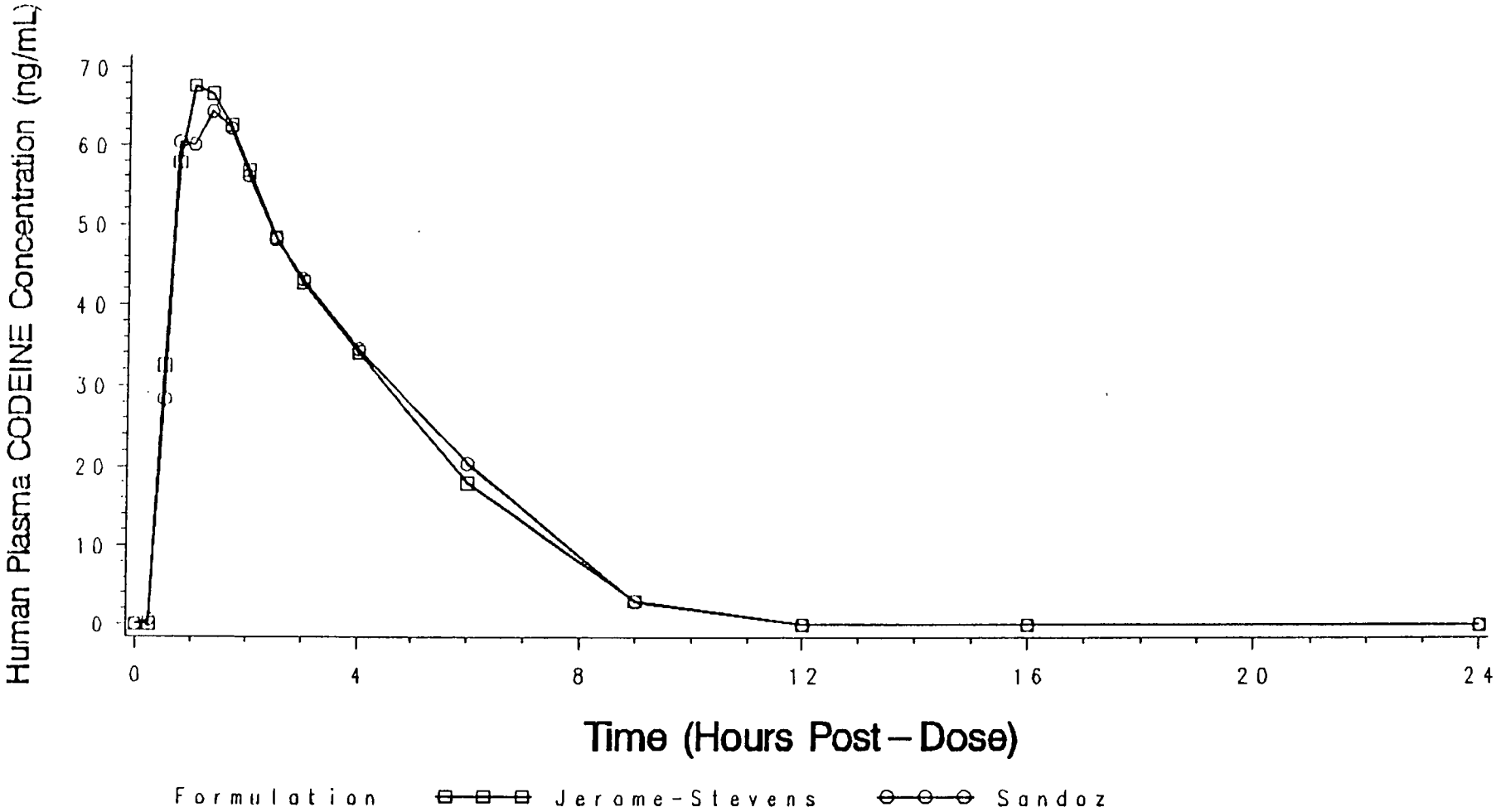
# Figure 2

## Project No. 960366

## Mean Human Plasma Codeine Concentrations

## (Linear Plot)

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**Components and Composition Statements**

| COMPONENTS | mg/Capsule |
|---|---|
| a. Aspirin | 325.0 |
| b. Butalbital | 50.0 |
| c. Caffeine | 40.0 |
| d. Codeine Phosphate | 30.0 |
| e. Starch | ) |
| f. Microcrystalline Cellulose | ) |
| g. Talc | ) |
| h. Colloidal Silicon Dioxide | 3 |
| i. Stearic Acid | 2 |
| j. | 1 )mg (approx.) |