# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**40326**

# BIOEQUIVALENCY REVIEW(S)

# OFFICE OF GENERIC DRUGS
# DIVISION OF BIOEQUIVALENCE

**ANDA #** 40-326 **SPONSOR:** Mylan Pharmaceuticals
**DRUG & DOSAGE FORM:** Estradiol Tablets, USP
**STRENGTH:** 0.5 mg, 1.0 mg & 2.0 mg
**TYPE OF STUDY:** Fasting Bioequivalence Study, Dissolution Data and Waiver Requests
**STUDY SITES:** **CLINICAL:** Mylan
**ANALYTICAL:** Mylan Pharmaceuticals Inc. (estradiol and estrone anlysis), Morgantown, West Virginia, and

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**STUDY SUMMARY:**
Acceptable (See Review)

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**DISSOLUTION :**
Acceptable (See Review)

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**PRIMARY REVIEWER:** James E. Chaney, Ph.D. **BRANCH:** I
**INITIAL:** JEC **DATE:** 12/16/98

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**BRANCH CHIEF:** Yih Chain Huang, Ph.D. **BRANCH:** I
**INITIAL:** YCH **DATE:** 12/16/98

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**DIRECTOR, DIVISION OF BIOEQUIVALENCE:** Dale P. Conner, Pharm.D.
**INITIAL:** DPC **DATE:** 12/30/98

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

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Estradiol Tablets, USP
0.5 mg, 1.0 mg & 2.0 mg
ANDA# 40-326
Reviewer: James Chaney
WP #40326SDW.898

Mylan Pharmaceuticals
Morgantown, WV
Submission Date:
August 13, 1998

# Review of a Fasting Bioequivalence Study, Dissolution Data and Two Waiver Requests

The sponsor has submitted a fasting study and dissolution data on its estradiol 2 mg tablets. Additionally, it has submitted comparative formulation and dissolution data in support of its request for waiver of in vivo bioequivalence study requirements for estradiol 1 mg and 0.5 mg tablets.

## I. BACKGROUND

Reference Drug Product:

Estrace® 2 mg, 1 mg and 0.5 mg tablets manufactured by Bristol-Meyers Squibb.

Indication:

Treatment of a variety of symptoms associated with menopause.

Bioavailability:

Limited oral bioavailability, due to extensive first pass metabolism.

Metabolites:

Estrone sulfate as the principal circulating moiety along with other unconjugated estrogenic species like estrone. Estradiol and estrone are inter-convertible.

Half Life:

Approximately 18 hours for estradiol and estrone, and 16 hours for estrone sulfate.

$T_{max}$: Approximately 6-7 hours for estradiol and estrone, and 5 hours for estrone sulfate.

Protein Binding:

50-80% binding to serum proteins

Food Effect:

Not known. DBE has not yet required a food study on estradiol tablets.

DBE Guidance:

Not available. For determination of bioequivalence, DBE relies on baseline corrected data for three species, including estradiol, estrone and estrone sulfate.

II. OBJECTIVE

The objective of this study was to investigate the bioequivalence of Mylan estradiol tablets to Estrace® tablets under fasting conditions following a single oral 2 mg (1 x 2 mg tablet) dose.

III. STUDY FACILITIES

Clinical

Analytical

Mylan Pharmaceuticals Inc. (estradiol and estrone anlysis), Morgantown, West Virginia, and

IV. STUDY DESIGN

Open-label, randomized, single-dose 2-way crossover bioavailability study.

V. STUDY DATES

Group 1 (Subjects 1-22)
- Period 1: July 17, 1997 - July 21, 1997
- Period 2: August 7, 1997 - August 11, 1997

Group 2 (Subjects 23-34)
- Period 1: August 14, 1997 - August 18, 1997
- Period 2: September 4, 1997 - September 8, 1997

Group 3 (Subjects 35-39)
- Period 1: September 11, 1997 - September 15, 1997
- Period 2: October 2, 1997 - October 6, 1997

Mylan Analytical Phase: September 29 - December 9, 1997
(Less than % of the samples were reassayed for estradiol or free estrone on June 4, 1998.)

Quest Analytical Phase: April 9 - 30, 1998

VI. SUBJECT SELECTION

Thirty-nine, non-smoking, adult post-menopausal females ages 18-65 were accepted into the clinical phase of the study. A complete list of exclusion and inclusion criteria can be found in the protocol in Attachment 5, Section 1, pages 8 through 10.

VII. TREATMENTS

Treatment A:

Estrace® (Bristol-Myers Squibb) Tablets (2 mg) 1 x 2 mg, Lot # F6JO51A, Exp. 6/99; Content uniformity, 98.4% (1.1%CV, 96.1-99.6%); Assay, 101.0% (100.1-101.9%)

Treatment B:

Mylan Estradiol Tablets (2 mg) 1 x 2 mg, Lot # 25DO04E, Exp. TBE Lot Size - [ ] tablets Manufacturing Date - 6/04/97; Content uniformity, 100.2% (1.2%CV, 98.7-102.2); Assay, 100.2% (98.9-101.4%)

VIII. STUDY CONDUCT

The protocol and bioequivalence study were approved by an Institutional Review Board. Participating subjects signed informed consent forms.

Subjects were dosed in three groups. Group 1 was numbered 1 through 22, Group 2 was numbered 23 through 34 and Group 3 was numbered 35 through 39. Subjects were housed on the evening prior to dosing until after the 24 hour blood draw. After a supervised overnight fast of at least 10 hours, subjects received a single, oral 2 mg (1 x 2 mg) dose of Mylan estradiol tablets or Bristol-Myers Squibb Estrace® tablets with 240 mL of water at ambient temperature. Subjects received a standard meal 5 hours post-dose followed by an evening meal 10 hours after dosing and snacks at appropriate times thereafter. Subjects were required to come to the clinic for the -48 and -24 hour blood draws. Subjects were released after the 24 hour blood draw but were required to return to the clinic for the 30, 36, 48 and 60 hour blood draws. Each period was separated by a three week washout.

Serial blood samples (2 x 7 mL) were collected at -48 hour, -24 hour, predose and at 0.75, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10, 12, 15, 18, 24, 30, 36, 48 and 60 hours post-dose. Plasma was stored in labeled tubes at -70 degrees C ± 15 degrees C, pending assay, except during the analysis of estrone sulfate when samples were stored at -15 degrees C or lower.

IX. ANALYTICAL

Methods

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commercial

information

X. PHARMACOKINETICS NOTES

The three pre-application concentrations (at -48, -24 and 0 hours) were averaged to obtain baseline values for each treatment period of each subject. Plasma concentrations and pharmacokinetic parameters were then calculated with baseline subtraction for estradiol, estrone and estrone sulfate.

XI. STATISTICAL ANALYSIS

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software.

Group*treatment interaction and group*period interaction

were tested before combining all the groups. The following ANOVA model was performed to examine such interactions for LNAUCL, LNAUCI and LNCPEAK for the baseline adjusted estradiol, estrone and estrone sulfate:

Full Model = GROUP SEQ GROUP*SEQ SUB(Group*SEQ) PER GROUP*PER TREAT GROUP*TREAT

The SUB(GROUP*SEQ) term was the error term for testing the between-subject factors of GROUP, SEQ and GROUP*SEQ. The effects of PER, GROUP*PER, TREAT and GROUP*TREAT were tested by the within-subject error (model error).

If there was a group*treatment interaction of LNAUCL, LNAUCI, or LNCPEAK, each group was then analyzed separately for that analyte using a standard crossover model.

If there was no group*treatment interaction, the following reduced model was used to further test group*period interaction:

Reduced Model = GROUP SEQ GROUP*SEQ SUB(GROUP*SEQ) PER GROUP*PER TREAT

If there was a group*period interaction of LNAUCL, LNAUCI, or LNCPEAK, the reduced model was used to analyze the analyte.

If there was no group*treatment nor group*period interaction for an analyte, all groups were combined and the analyte was analyzed using the following standard crossover model:

Standard Crossover Model = SEQ SUB(SEQ) PER TREAT

XII. CLINICAL NOTES

Thirty-nine subjects were dosed in this study. Subject #7, #32, and #33 were discontinued from the study prior to dosing Period 1 due to failing to meet the entrance criteria. Subject #11 and #30 were discontinued due to an adverse experience (vomiting) after Period 1 and during Period 2, respectively. Subject #4 withdrew from the study after Period 1 due to personal reasons that were not study related. Therefore, thirty-three subjects completed this study.

Adverse Events

Attachment 5, Section 1 contains the adverse experience report for this study (pages 73 through 74). Attachment 5, Section 2 contains the complete case report forms for this study. There were nine adverse events (5 subjects) reported for this study. Of those, eight were reported as probably drug related. Subject #11 was discontinued after Period 1 due to an adverse experience (vomiting) and Subject #30 was discontinued during Period 2 due to an adverse experience (vomiting). There were no serious or life threatening adverse events reported for this

study.

XIII. PHARMACOKINETIC AND STATISTICAL RESULTS

Estradiol

Data were obtained for thirty-three subjects. Because of a group*treatment interaction of estradiol, it was not possible to combine the 3 groups for estradiol. Thus, the mean estradiol concentration versus time profiles presented in Table 1 and Figure 1 are for Group 1 only. Mean plasma profiles for estradiol are similar between Mylan estradiol tablets and Bristol-Myers Squibb Estrace® tablets.

Table 1. Arithmetic Mean Baseline Adjusted Plasma Concentrations (pg/mL) Versus Time (hr) and T/R Ratios for Estradiol in a Fasting Single Dose Study

| | REFERENCE (A) | | | TEST (B) | | | T/R |
|---|---|---|---|---|---|---|---|
| Time | N | Mean | %CV | N | Mean | %CV | |
| 0 | 19 | 0.74 | 212 | 19 | 0.58 | 194 | 0.78 |
| 0.75 | 19 | 14.86 | 73 | 19 | 12.92 | 71 | 0.87 |
| 1.5 | 19 | 17.97 | 61 | 19 | 14.29 | 73 | 0.79 |
| 2 | 19 | 19.42 | 47 | 19 | 15.44 | 54 | 0.79 |
| 3 | 19 | 24.02 | 38 | 19 | 20.36 | 39 | 0.85 |
| 4 | 19 | 28.59 | 37 | 19 | 23.51 | 43 | 0.82 |
| 5 | 19 | 29.71 | 38 | 19 | 28.39 | 44 | 0.95 |
| 6 | 19 | 33.85 | 47 | 19 | 36.59 | 53 | 1.08 |
| 7 | 19 | 33.16 | 44 | 19 | 32.24 | 42 | 0.97 |
| 8 | 19 | 33.03 | 32 | 19 | 34.48 | 41 | 1.04 |
| 10 | 19 | 32.57 | 37 | 19 | 32.88 | 36 | 1.01 |
| 12 | 19 | 33.78 | 39 | 19 | 35.23 | 36 | 1.04 |
| 15 | 19 | 31.81 | 37 | 19 | 31.81 | 34 | 1.00 |
| 18 | 19 | 28.41 | 36 | 19 | 29.71 | 40 | 1.04 |
| 24 | 19 | 25.35 | 38 | 19 | 25.89 | 37 | 1.02 |
| 30 | 19 | 23.55 | 42 | 19 | 25.02 | 48 | 1.06 |
| 36 | 19 | 20.13 | 49 | 19 | 22.85 | 46 | 1.14 |
| 48 | 19 | 10.87 | 58 | 19 | 11.44 | 60 | 1.05 |
| 60 | 19 | 10.04 | 58 | 19 | 12.04 | 69 | 1.20 |

A summary of the pharmacokinetic parameters is shown in Table 2 for estradiol. Estradiol demonstrated similar mean pharmacokinetic parameters and variability for both formulations.

Although no statistically significant group*treatment interactions for LNCPEAK and LNAUCI were observed for estradiol, the LNAUCL term showed a significant group*treatment interaction (P=0.0191). Therefore, each group was analyzed separately using

a standard crossover model. However, only the data from Group 1 (19 subjects) were utilized because the other two groups had insufficient numbers of subjects (N=9 for group 2 and N=5 for group 3) to obtain a meaningful statistical conclusion.

TABLE 2. MEAN (%CV) BASELINE ADJUSTED ESTRADIOL PHARMACOKINETIC PARAMETERS IN 19 HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 2 MG (1 X 2 MG) DOSE OF ESTRADIOL TABLETS UNDER FASTING CONDITIONS

| PARAMETER | REFERENCE (A) | | TEST (B) | | LSMEANS RATIO (B/A)* | C.I.** |
|---|---|---|---|---|---|---|
| | N | ARITHMETIC MEAN | N | ARITHMETIC MEAN | | |
| AUCL(pg*hr/mL) | 19 | 1269 (36.2) | 19 | 1320 (36.4) | 1.04 | 96%-112% |
| AUCI(pg*hr/mL) | 13 | 1757 (41.4) | 11 | 1742 (41.9) | 0.90 | 85%-96% |
| CPEAK(pg/mL) | 19 | 41.5 (35.2) | 19 | 45.2 (40.1) | 1.08 | 98%-119% |
| HALF(hr) | 13 | 24.8 (35.0) | 11 | 19.4 (35.3) | --- | --- |
| TPEAK(hr) | 19 | 10.7 (76.7) | 19 | 12.3 (66.2) | --- | --- |

*Ratio (B/A) = $e^{[LSMEAN\ of\ LnB\ -\ LSMEAN\ of\ LnA]}$

**Used Natural Log Transformed Parameter

A summary of individual test/reference ratios of the pharmacokinetic parameters AUCL, AUCI, and Cmax, and individual AUCL/AUCI ratios for estradiol are shown in Table 3.

Table 3. Statistics of Individual Estradiol AUCL, AUCI, and CPEAK Test/Reference Ratios and Individual AUCL to AUCI Ratios

| | Test/Reference | | | AUCL/AUCI | |
|---|---|---|---|---|---|
| PARAMETER | AUCL | AUCI | CPEAK | Test | Reference |
| Mean | 1.06 | 0.91 | 1.11 | 0.82 | 0.77 |
| %CV | 20 | 16 | 26 | 11 | 10 |
| Min | | | | | |
| Max | | | | | |
| N | 19 | 8 | 19 | 11 | 13 |

Estrone

The mean concentration versus time data for estrone shown in Table 4 is illustrated graphically in Figure 2. Mean plasma profiles for estrone are similar between Mylan estradiol tablets and Bristol-Myers Squibb Estrace® tablets.

Table 4. Arithmetic Mean Baseline Adjusted Plasma Concentrations (pg/mL) Versus Time (hr) and T/R Ratios for Estrone in Fasting Single Dose Study

| | REFERENCE (A) | | | TEST (B) | | | |
|---|---|---|---|---|---|---|---|
| Time | N | Mean | %CV | N | Mean | %CV | T/R |
| 0 | 33 | 2.9 | 117 | 33 | 2.2 | 96 | 0.78 |
| 0.75 | 33 | 40.5 | 87 | 33 | 30.6 | 95 | 0.76 |
| 1.5 | 33 | 102.9 | 64 | 33 | 74.0 | 63 | 0.72 |
| 2 | 33 | 140.3 | 55 | 33 | 100.3 | 44 | 0.72 |
| 3 | 33 | 202.2 | 42 | 33 | 156.1 | 37 | 0.77 |
| 4 | 33 | 250.0 | 42 | 33 | 193.9 | 38 | 0.78 |
| 5 | 33 | 250.4 | 40 | 33 | 226.1 | 33 | 0.90 |
| 6 | 33 | 313.1 | 43 | 33 | 293.5 | 38 | 0.93 |
| 7 | 33 | 282.3 | 44 | 33 | 275.3 | 40 | 0.97 |
| 8 | 33 | 270.8 | 38 | 33 | 267.2 | 37 | 0.98 |
| 10 | 33 | 243.4 | 41 | 33 | 242.3 | 34 | 1.00 |
| 12 | 33 | 222.7 | 43 | 33 | 230.6 | 38 | 1.04 |
| 15 | 33 | 173.1 | 45 | 33 | 178.8 | 41 | 1.03 |
| 18 | 33 | 140.5 | 46 | 33 | 147.1 | 48 | 1.05 |
| 24 | 33 | 113.1 | 52 | 33 | 120.2 | 50 | 1.08 |
| 30 | 33 | 99.3 | 54 | 33 | 100.6 | 52 | 1.02 |
| 36 | 33 | 82.4 | 54 | 33 | 90.3 | 52 | 1.10 |
| 48 | 33 | 48.7 | 69 | 33 | 46.2 | 67 | 0.94 |
| 60 | 33 | 30.9 | 84 | 33 | 44.1 | 138 | 1.39 |

No statistically significant group*treatment interaction nor group*period interaction was observed for estrone. A summary of the pharmacokinetic parameters is shown in Table 5 for estrone. Estrone demonstrated similar mean pharmacokinetic parameters and variability for both formulations.

TABLE 5. Mean (%CV) Baseline Adjusted Estrone Pharmacokinetic Parameters in 33 Healthy Subjects Following a Single Oral 2 Mg (1 X 2 Mg) Dose of Estradiol Tablets under Fasting Conditions

| PARAMETER | REFERENCE (A) | | TEST (B) | | LSMEANS RATIO (B/A)* | C.I.** |
|---|---|---|---|---|---|---|
| | N | ARITHMETIC MEAN | N | ARITHMETIC MEAN | | |
| AUCL(pg*hr/mL) | 33 | 6896 (42.3) | 33 | 6922 (39.7) | 1.01 | 94%-108% |
| AUCI(pg*hr/mL) | 31 | 7636 (46.6) | 28 | 7835 (45.9) | 0.97 | 91%-104% |
| CPEAK(pg/mL) | 33 | 331 (39) | 33 | 322 (34.7) | 0.97 | 92%-103% |
| HALF(hr) | 31 | 15.6 (37.5) | 28 | 16.3 (37.3) | --- | --- |
| TPEAK(hr) | 33 | 6.94 (26.2) | 33 | 7.15 (32.6) | --- | --- |

*Ratio (B/A) = $e^{[\text{LSMEAN of LnB} - \text{LSMEAN of LnA}]}$

**Used Natural Log Transformed Parameter

A summary of individual test/reference ratios of the pharmacokinetic parameters AUCL, AUCI, and Cmax, and individual AUCL/AUCI ratios for estrone is shown in Table 6.

Table 6. Statistics of Individual Estrone AUCL, AUCI, and CPEAK Test/Reference Ratios and Individual AUCL to AUCI Ratios

| | Test/Reference | | | AUCL/AUCI | |
|---|---|---|---|---|---|
| PARAMETER | AUCL | AUCI | CPEAK | Test | Reference |
| Mean | 0.99 | 0.97 | 1.03 | 0.90 | 0.91 |
| %CV | 25 | 25 | 21 | 7 | 7 |
| Min | | | | | |
| Max | | | | | |
| N | 33 | 26 | 33 | 28 | 31 |

Estrone Sulfate

The mean concentration versus time data for estrone shown in Table 7 is illustrated graphically in Figure 3. Mean plasma profiles for estrone sulfate are similar between Mylan estradiol tablets and Bristol-Myers Squibb Estrace® tablets.

Table 7. Arithmetic Mean Mean Baseline Plasma Concentrations (pg/mL) Versus Time (hr) and T/R Ratios for Estrone Sulfate in Fasting Single Dose Study

| | REFERENCE (A) | | TEST (B) | | |
|---|---|---|---|---|---|
| Time (h) | Mean | %CV | Mean | %CV | T/R |
| 0 | 21 | 195 | 22 | 212 | 1.04 |
| 0.75 | 3166 | 77 | 2205 | 75 | 0.69 |
| 1.5 | 7104 | 70 | 5153 | 75 | 0.72 |
| 2 | 9220 | 60 | 6758 | 71 | 0.74 |
| 3 | 11804 | 55 | 9614 | 58 | 0.81 |
| 4 | 11568 | 52 | 11194 | 54 | 0.97 |
| 5 | 11828 | 51 | 11866 | 48 | 1.00 |
| 6 | 11771 | 54 | 11554 | 49 | 0.98 |
| 7 | 10453 | 57 | 9720 | 46 | 0.93 |
| 8 | 9058 | 57 | 9042 | 49 | 1.00 |
| 10 | 7863 | 60 | 7942 | 52 | 1.01 |
| 12 | 7039 | 61 | 7024 | 53 | 1.00 |
| 15 | 4796 | 76 | 4862 | 70 | 1.01 |
| 18 | 3619 | 76 | 3792 | 84 | 1.05 |
| 24 | 2883 | 90 | 3088 | 100 | 1.08 |
| 30 | 2752 | 88 | 2899 | 81 | 1.05 |
| 36 | 2314 | 86 | 2367 | 87 | 1.02 |
| 48 | 1290 | 99 | 1202 | 84 | 0.93 |
| 60 | 859 | 90 | 973 | 108 | 1.14 |

There was no statistically significant group*treatment interaction for estrone sulfate but a significant group*period interaction of LNCPEAK (P=0.0376) was observed. A summary of the pharmacolkinetic parameters is shown in Table 8 for estrone sulfate. Estrone sulfate demonstrated similar mean pharmacokinetic parameters and variability for both formulations.

Table 8. Mean (%CV) Baseline Adjusted Estrone Sulfate Pharmacokinetic Parameters in 33 Healthy Subjects Following a Single Oral 2 Mg (1 X 2 Mg) Dose of Estradiol Tablets Under Fasting Conditions

| PARAMETER | REFERENCE (A) | | TEST (B) | | LSMEANS RATIO (B/A)* | C.I.** |
|---|---|---|---|---|---|---|
| | N | ARITHMETIC MEAN | N | ARITHMETIC MEAN | | |
| AUCL(pgxhr/mL) | 33 | 224004 (63.8) | 33 | 220052 (61.5) | 0.99 | 93%-106% |
| AUCI(pgxhr/mL) | 30 | 240272 (70.6) | 30 | 259228 (67.3) | 1.04 | 96%-112% |
| CPEAK(pg/mL) | 33 | 13740 (48.1) | 33 | 13089 (46.1) | 0.94 | 87%-101% |
| HALF(hr) | 30 | 15.7 (39.1) | 30 | 16.7 (32.3) | --- | --- |
| TPEAK(hr) | 33 | 4.55 (36.9) | 33 | 5.36 (23.2) | --- | --- |

*Ratio (B/A) = $e^{[\text{LSMEAN of LnB - LSMEAN of LnA}]}$

**Used Natural Log Transformed Parameter

A summary of individual test/reference ratios of the pharmacokinetic parameters AUCL, AUCI, and Cmax, and individual AUCL/AUCI ratios for estrone sulfate is shown in Table 9.

Table 9. Statistics of Individual Estrone Sulfate AUCL, AUCI, and CPEAK Test/Reference Ratios and Individual AUCL to AUCI Ratios

| | Test/Reference | | | AUCL/AUCI | |
|---|---|---|---|---|---|
| PARAMETER | AUCL | AUCI | CPEAK | Test | Reference |
| Mean | 0.99 | 1.04 | 1.01 | 0.91 | 0.93 |
| %CV | 26 | 27 | 34 | 6 | 6 |
| Min | | | | | |
| Max | | | | | |
| N | 33 | 25 | 33 | 27 | 30 |

For all three analytes tested, the 90% confidence intervals fall within 80-125% for the test to reference ratio for the natural log transformed parameters: LNAUCL, LNAUCI and LNCPEAK.

XIX. FORMULATION

The compositions of the 2 mg, 1.0 mg and 0.5 mg tablets of the test product are proportionally similar.

| Table 10. Comparative Quantitative Compositions of Estradiol Tablets, USP 0.5 mg, 1 mg And 2 mg | | | | | | |
|---|---|---|---|---|---|---|
| | 0.5 mg | | 1 mg | | 2 mg | |
| ACTIVE COMPONENTS | mg | % | mg | % | mg | % |
| Estradiol, USP | | | | | | |
| INACTIVE COMPONENTS | | | | | | |
| Anhydrous Lactose, NF** (Anhydrous DT) | | | | | | |
| Microcrystalline Cellulose, NF | | | | | | |
| Crospovidone, NF | | | | | | |
| Colloidal Silicon Dioxide, NF | | | | | | |
| Magnesium Stearate/Sodium Lauryl Sulfate | | | | | | |
| FD&C Blue #1 Lake | | | | | | |
| D&C Red #40 Lake | | | | | | |
| TOTAL TABLET WEIGHT | 85 | 100% | 85 | 100% | 85 | 100% |

**The quantity of anhydrous lactose, NF

XV. 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 14. Dissolution testing meets USP specifications.

Table 11. In Vitro Dissolution Testing

Drug (Generic Name): Estradiol Tablets
Dose Strength: 0.5, 1, and 2 mg
ANDA No.: 40-326
Firm: Mylan Pharmaceuticals, Inc.
Submission Date: 8/13/98
File Name: 40326SD.898

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle:X RPM: 100
No. Units Tested: 12
Medium: % SLS in water Volume: mL
Specifications: NLT % in 60 min
Reference Drug: Estrace® (Bristol-Myers Squibb)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

| Sampling Times (Min) | Test Product Lot 25D002E Strength(mg) 0.5 | | | Reference Product Lot MLJ14 Strength(mg) 0.5 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 20 | 92.4 | | 1.5 | 91.8 | | 3.9 |
| 40 | 97.4 | | 1.0 | 96.4 | | 2.0 |
| 60 | 99.2 | | 1.0 | 96.7 | | 1.8 |
| | Lot 25D005E Strength(mg) 1.0 | | | Lot C6K05A Strength(mg) 1.0 | | |
| 20 | 89.3 | | 1.9 | 78.9 | | 5.5 |
| 40 | 96.5 | | 1.2 | 92.0 | | 1.8 |
| 60 | 98.4 | | 1.1 | 94.6 | | 1.7 |
| | Lot 25D004E Strength(mg) 2.0 | | | Lot F6J051A Strength(mg) 2.0 | | |
| 20 | 80.5 | | 2.0 | 86.8 | | 1.8 |
| 40 | 89.7 | | 1.5 | 94.1 | | 1.4 |
| 60 | 92.8 | | 1.1 | 96.6 | | 1.4 |

XVI. COMMENTS

1a. Because LNAUCL for estradiol showed a significant group*treatment interaction (P=0.0191) each group was analyzed separately using a standard crossover model (Group 1, N=19; Group 2, N=9; Group 3, N=5). Only the data from Group 1 (19 subjects) were utilized because the other two groups had insufficient numbers of subjects (N=9 for group 2 and N=5 for group 3) to obtain a meaningful statistical conclusion.

The results reported by the firm for each of the four ways that the estradiol data were analyzed are shown in Table 12.

Table 12. Test/Reference Ratios* of the LSMeans and 90% Confidence Intervals for Estradiol

| | PARAMETER | T/R RATIO | 90 % C.I. |
|---|---|---|---|
| Group 1 N = 19 | LNAUCL | 1.04 | 96-112 |
| | LNAUCI | 0.90 | 85-96 |
| | LNCPEAK | 1.08 | 98-119 |
| Group 2 N = 9 | LNAUCL | 1.15 | 99-135 |
| | LNAUCI | 1.17 | 94-145 |
| | LNCPEAK | 1.26 | 106-150 |
| Group 3 N = 5 | LNAUCL | 0.81 | 65-100 |
| | LNAUCI | NR** | NR** |
| | LNCPEAK | 0.92 | 75-111 |
| All 33 Subjects | LNAUCL | 1.03 | 96-111 |
| | LNAUCI | 0.997 | 91-109 |
| | LNCPEAK | 1.099 | 101-119 |

*The Test/Reference LNAUCL ratios for the LSMeans
**NR = Not reported

1b. Dr. Rabi Patnaik has reanalyzed Mylan's data incorporating group and its associated parameters in the statistical

model. He analyzed the data using the following models:

A: group(1)sequence(2)group*sequence(3)
subject(group*sequence)(4)period(group)(5)treatment(6)
group*treatment(7)
[#4 was used as the error term for #s 1, 2, and 3.]
B: Same as Model A except #7 was deleted
C: sequence subject(sequence) period treatment

There are no appreciable changes in parameters, variables and confidence intervals obtained from the models used. The summary of the results is showed in Dr. Patnaik's 12/7/98 memo to Dr. Dale Conner (Attachment 2).

2. Although the firm reassayed a few of the samples for estradiol and estrone beyond 179 days following collection, more than % were assayed within the 179 day period for which long term frozen stability was validated. Therefore, the long term stability data on estradiol and estrone in frozen plasma is acceptable.

3. The firm reported the long term frozen stability for estrone sulfate was established at -15 degrees for 24 months. (See Volume 1.5, page 2222 for an amendment from the analytical laboratory to the sponsor on the long term stability prestudy validation data, and attached copy of said page as Review Attachment 1). No data was submitted to support this statement.

However, the Division of Bioequivalence has data which supports long term frozen stability for estrone sulfate under the conditions stored in plasma for the time stored.

4. The analytical data is acceptable.

5. The firm should be asked to submit complete stability data in future applications.

6. The firm did not report individual parameter test/reference ratios and individual AUCL/AUCI ratios. These ratios were calculated by the reviewer. The firm should be asked to submit this information in future applications.

7. The AUCLs and AUCIs were calculated by the reviewer and were in agreement with what the firm reported.

8. None of the Cmax values were the first nonzero concentrations.

9. The assayed potency and the content uniformity of the test and reference products are satisfactory.

10. The products used for the biostudies and the dissolution studies were from the same batch.

11. The in vitro dissolution testing conducted by Mylan comparing its estradiol 0.5 mg, 1.0 mg and 2.0 mg tablets, lots 25004E, 25005E and 25002E respectively, with the corresponding reference products is acceptable.

12. The formulations for estradiol 0.5 mg and 1 mg tablets are proportionally similar to the 2 mg tablet of the test product which underwent bioequivalence testing.

XVII. RECOMMENDATIONS

1. The in-vivo bioequivalence study conducted under fasting condition by Mylan on its estradiol 2 mg tablet, lot #25D004E, comparing it to the reference product Estrace® 2 mg tablet, lot #F6J051A, manufactured by Bristol-Meyers Squibb, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Mylan's estradiol 2 mg tablets are bioequivalent to Estrace® 2 mg tablets, manufactured by Bristol-Meyers Squibb.

2. The in vitro dissolution testing conducted by Mylan on its estradiol 2 mg, 1 mg and 0.5 mg tablets, lots 25004E, 25005E and 25002E respectively, is acceptable. The firm has conducted an acceptable single dose in vivo bioequivalence study under fasting conditions comparing the 2 mg tablet of the test product with the 2 mg tablet of the reference product, Estrace®, manufactured by Bristol-Myers Squibb. The formulations for estradiol 0.5 mg and 1 mg tablets are proportionally similar to the 2 mg tablet of the test

product which underwent bioequivalence testing. The waivers of in vivo bioequivalence study requirements for 0.5 mg and 1 mg tablets of the test product are granted. The 0.5 mg and 1 mg tablets of the test product are therefore deemed bioequivalent to the 0.5 mg and 1 mg tablets of the reference product, Estrace®, manufactured by Bristol-Myers Squibb.

3. The dissolution testing should be incorporated into firm's manufacturing and stability programs. The dissolution should be conducted in ⌋mL of ⌈ ⌋% sodium lauryl sulfate at 37°C using USP XXIII apparatus II (paddle) at 100 rpm. The dissolution testing should meet the following specifications.

   Not less than ⌈ ⌋% of the labeled amount of estradiol is dissolved from the dosage form in 60 minutes.

4. From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence and in vitro dissolution testing.

/S/

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

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 12/16/98

Concur: /S/ Date 12/30/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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HFD-651/ Bio Secretary - Bio Drug File
HFD-652/ J. Chaney
HFD-652/ Y. Huang

HFD-652/ J. Chaney JEC 12/16/98
HFD-652/ Y. Huang YH 12/16/98
HFD-617/ E. Hu
HFD-650/ D. Conner 12/30/98

BIOEQUIVALENCY - ACCEPTABLE Submission date: August 13, 1998
FASTING STUDY (STF) Strengths: 2.0 mg
Outcome: AC

Clinical:

Analytical: Mylan Pharmaceuticals Inc. (Estradiol and estrone anlysis), Morgantown,WV, and

WAIVERS (WAI) Strengths: 0.5 mg, 1.0 mg
Outcome: AC

NOTE:
AC - Acceptable UN - Unacceptable
NC - No Action IC - Incomplete

Outcome Decision: Acceptable

WINBIO COMMENTS:
The biostudy was found acceptable.

# ESTRADIOL (ESTR–9744)

## Total Dose: 2 mg (1x2mg Tablet), Study Type: Fasting
## Mean Baseline Adjusted Estradiol Plasma Concentrations
## N= 19

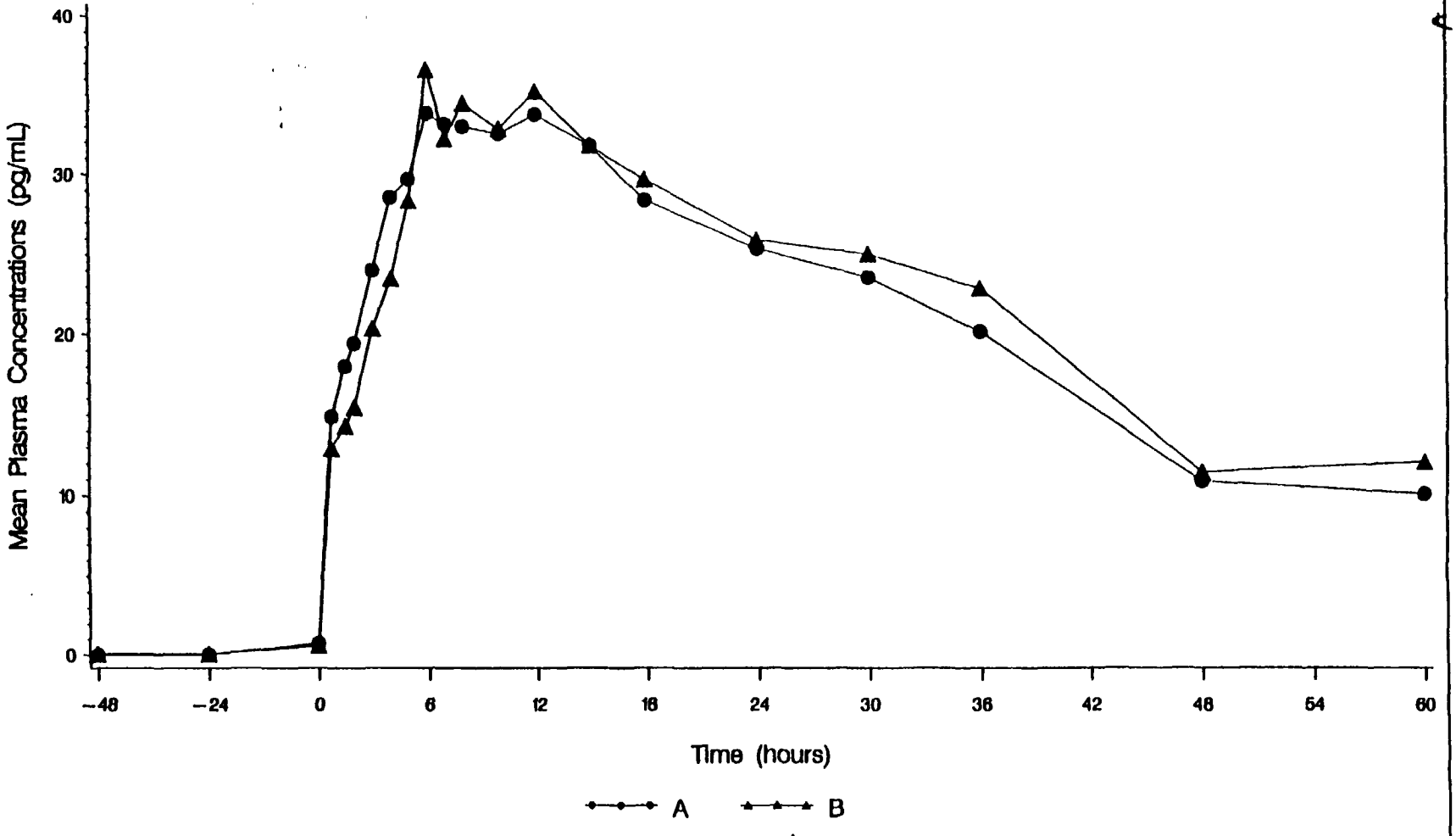


FIG. 1

Treatment A is A (Estrace #F6J051A)
Treatment B is B (Estradiol #25D004E)

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# ESTRADIOL (ESTR–9744)

Total Dose: 2 mg (1x2mg Tablet), Study Type: Fasting

Mean Baseline Adjusted Estrone Plasma Concentrations

N=33

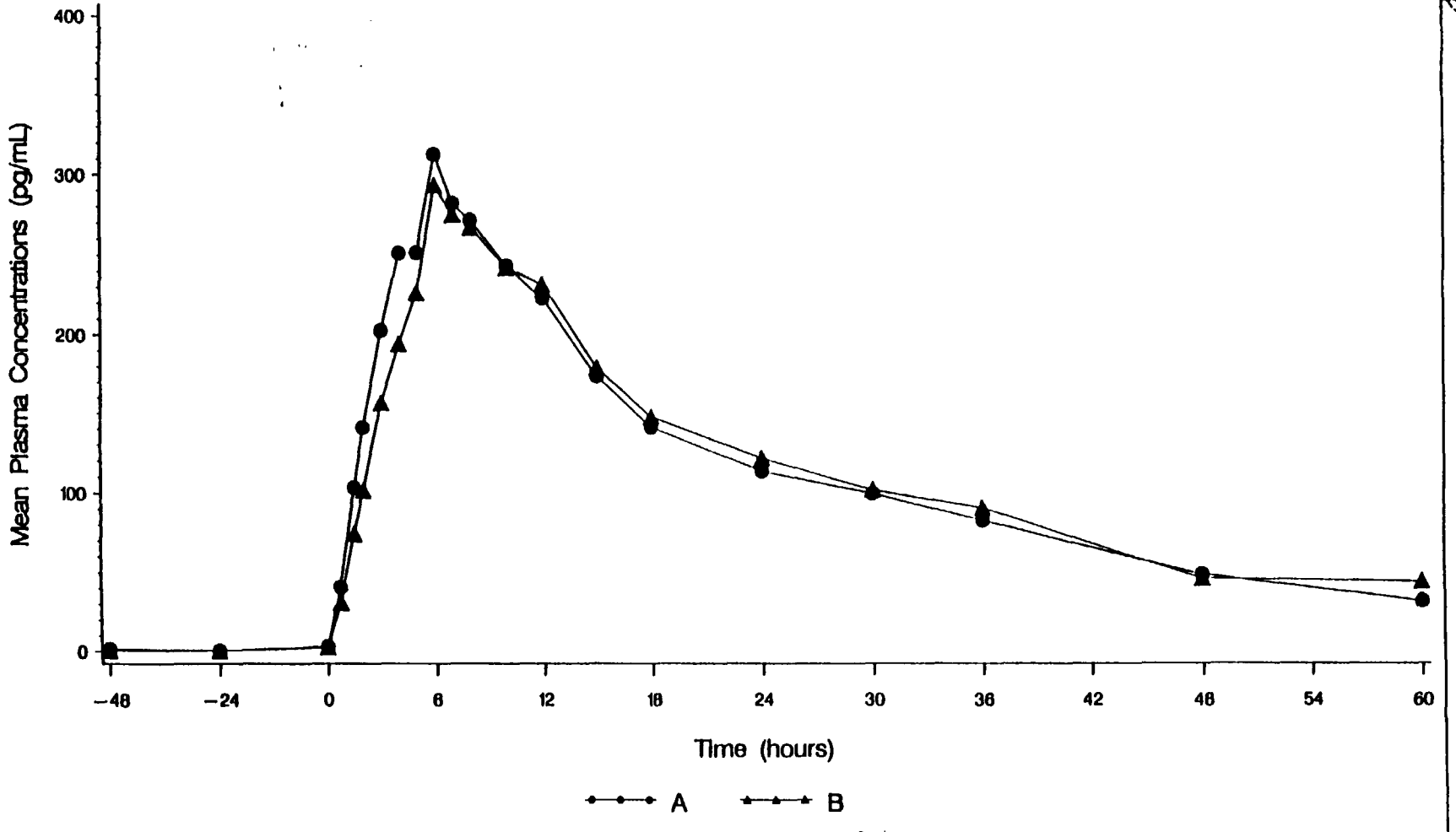


FIG. 2

Treatment A is A (Estrace #F6J051A)
Treatment B is B (Estradiol #25D004E)

# ESTRADIOL (ESTR–9744)

Total Dose: 2 mg (1x2mg Tablet), Study Type: Fasting

Mean Baseline Adjusted Estrone Sulfate Plasma Concentrations

N=33

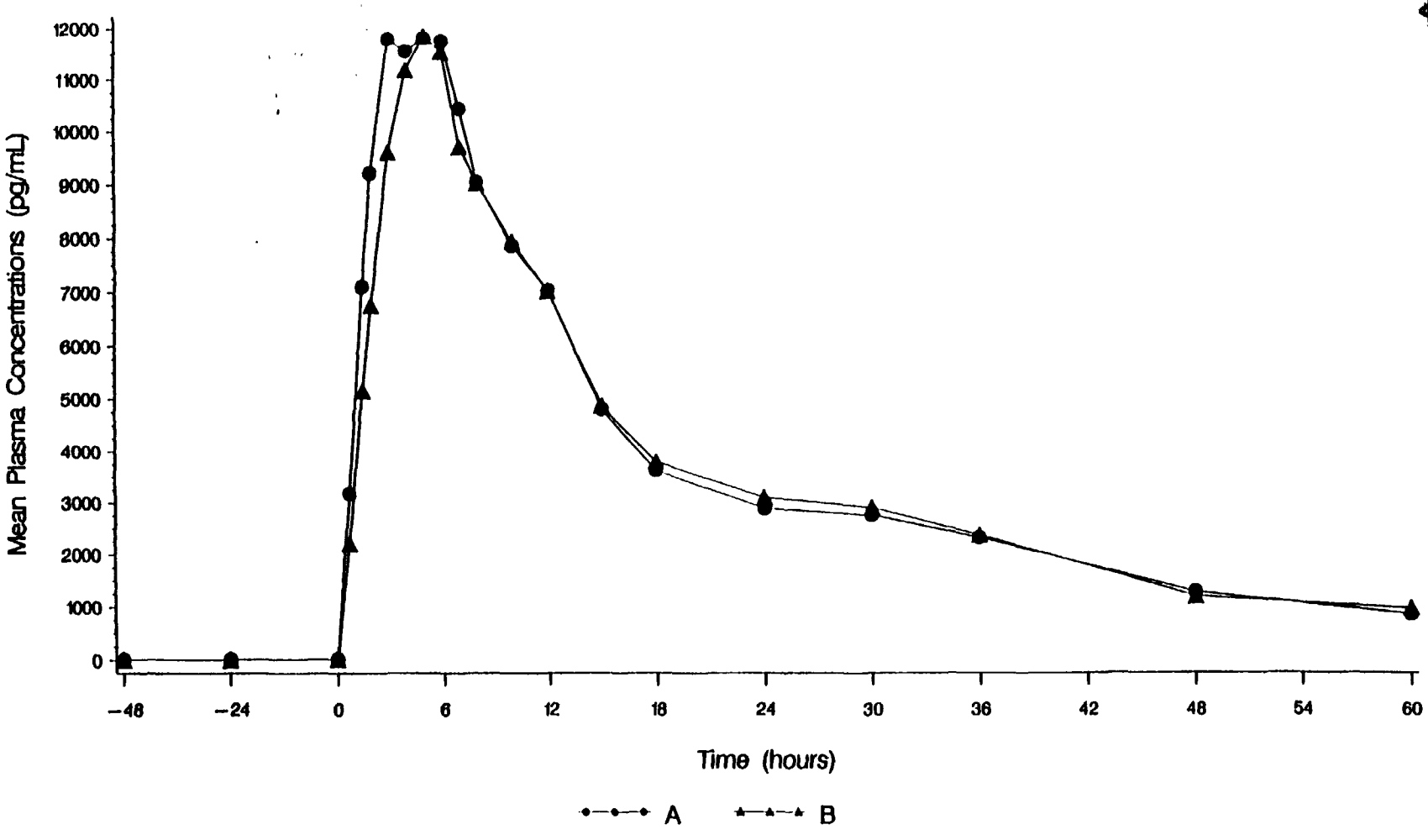


FIG 3

Treatment A is A (Estrace #F6J051A)

Treatment B is B (Estradiol #25D004E)

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