CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-275

BIOEQUIVALENCE

Estradiol
0.5 mg, 1 mg and 2 mg Tablets
ANDA #**40-275**
Reviewer: Z.Z. Wahba
File #40275sd.897

ESI Lederle, Inc.
Philadelphia, PA
Submission Date:
August 29, 1997

REVIEW OF AN IN VIVO BIOEQUIVALENCE STUDY, DISSOLUTION TESTING DATA AND WAIVER REQUESTS

I. **OBJECTIVE**:
Review the following:

1. ESI Lederle's single dose, two-way crossover bioequivalence study under fasting conditions comparing its drug product Estradiol Tablets, 2.0 mg to the reference drug product Bristol-Myers Squibb's Estrace® Tablets, 2.0 mg.

2. Dissolution data for 0.5 mg, 1.0 mg and 2.0 mg strengths of the test and reference drug products.

3. Waiver requests for the 0.5 mg and 1.0 mg strength tablets.

II. **INTRODUCTION**:
17ß-estradiol is a naturally occurring steroidal estrogen and is the principle and most active endogenous estrogen. Estradiol tablets are indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause, treatment of vulval and vaginal atrophy, treatment of hypoestrogenism resulting from certain conditions, prevention of osteoporosis, and palliation of breast and prostate cancer.

In the normal nonpregnant female, estrogens are secreted in major quantities only by the ovaries, though minute amounts are also secreted by the adrenal cortices. In pregnancy, tremendous quantities are also secreted by the placenta. Only three estrogens are present in significant quantities in the plasma of the human female: 17,ß-estradiol, estrone and estriol. The estrogenic potency of 17 ß-estradiol is 12 times that of estrone and 80 times that of estriol (Guyton, A.C, Textbook of Medical Physiology, 8th ed., 1991).

Estrone and estradiol both circulate predominantly in the

conjugated (primarily sulfated) form. Unconjugated estrone represents only 5-10% of total endogenous plasma estrone in pre- and postmenopausal women (O.A. Dada *et al., Acta Clin. Endocrinol., 1978;88:*754; O.A. Towobola *et al., Clin. Endocrinol., 1980;13:*461). Estrone sulfate is biologically inactive and serves as a reservoir for formation of estrone. Unconjugated estradiol represents about 43% of total endogenous estradiol (O.A. Dada *et al., Acta Clin. Endocrinol., 1978;88:*754).

The absorption and metabolism of human estrogens are sensitive to a variety of factors. These include diet, body weight and the use of antibiotics. To date, the kinetics have not been fully established.

Estradiol is currently marketed by Bristol-Myers Squibb Company under the trade name Estrace®, and is available in 0.5 mg, 1 mg and 2 mg tablets. The usual initial dose is 1 or 2 mg daily of estradiol, adjusted as necessary to control present symptoms. The minimum effective dose for maintenance therapy should be determined by titration. Administration should be cyclic (e.g., 3 weeks on and 1 week off). Attempts to discontinue medication should be made at 3 to 6 month intervals.

III. BIOEQUIVALENCE STUDY UNDER FASTING CONDITION CLINICAL STUDY PROTOCOL #96-027-MA

A. STUDY SITES AND INVESTIGATORS

Clinical facility:	PPD Pharmaco, Inc. RTP Clinic 1400 Perimeter Park Drive, Morrisville, N.C. 27560
Medical Director:	Edward A. Kelly, M.D.
Scientific Director:	Edward A. Kelly, M.D.
Dosing Date:	Group 1: 04/26/97, 05/03/97 Group 2: 05/03/97, 05/17/97
Analytical Facility:	PPD Pharmaco, Inc. RTP Clinic
Analytical Investigator:	Amy Pearsall
Analytical Study Date:	05/12/97 to 06/27/97

B. STUDY DESIGN

Single dose, randomized, two-way crossover study under fasting conditions.

C. **SUBJECTS**

Thirty-seven (37) healthy postmenopausal women were recruited and completed the study. The subjects were within 44 to 65 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Selection, Inclusion and Exclusion Criteria

The same as previously provided in the firm's protocol #96-027-MA (protocol #96-027, submission date 5/5/96).

D. **FOOD AND FLUID INTAKE:**

Subjects fasted overnight for at least 10 hours before dosing and 4 hours after dosing. The drug products were administered with 240 mL tap water. Water was not permitted for 1 hour before and 1 hour after the dose, but was allowed at all other times. The subjects received their medication according to randomized dosing schedule. Standard meals were provided at appropriate times thereafter (at 4 and 9 hours after drug administration).

E. **TREATMENT PLAN**

Test product: 1 X 2.0 mg Estradiol Tablets (ESI Lederel), Lot #R971645, Batch size: 1,150,000 Tablets, assay potency: 101.2%, content uniformity: 101.0%, manufacturing date: 3/17/97.

Reference product:1 X 2.0 mg Estrace® Tablets (Bristol-Myers Squibb), Lot #K5K07A, Batch size: (not given), assay potency: 98.1%, content uniformity: 98.6%, expiration date: 9/98.

Washout period: 7 days.

A single 2.0 mg dose was given in each period of the study.

F. **BLOOD SAMPLING:**

Blood samples were collected into lithium heparin vacutainers, at -48, -24, 0, 0.75, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10, 12, 15, 18, 24, 36, 48 and 72 hours post-dosing.

G. **ASSAY METHODOLOGY**: [Not for release under FOI]

1. Methods:

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

methods

Stability:

1. All three analytes (unconjugated estradiol, unconjugated estrone and total estrone) were stable in plasma at -20°C for a period of seven weeks (unconjugated estradiol and unconjugated estrone) and six weeks (conjugated estrone).

2. All three analytes (unconjugated estradiol, unconjugated estrone and conjugated estrone) were stable during 3 freeze/thaw cycles.

H. IN VIVO BE STUDY AND STATISTICAL ANALYSIS:

Thirty-seven (37) healthy postmenopausal women were recruited and completed the study.

Adverse Events:

A total of 11 adverse events (hot flashes, headache etc.) were reported for 26 subjects. These adverse events were reported on pages 109 and 116, volume C1.2. All adverse events were mild. None of the adverse events was considered serious or resulted in terminating any subject from study participation.

The plasma concentration and pharmacokinetic parameters of unconjugated estradiol, unconjugated estrone and conjugated estrone were analyzed using SAS-GLM procedure for analysis of variance. The firm conducted the study in two groups. The group effect was included in the SAS-GLM (Model y= group seq seq*group sub(seq*group) trt per) with an error term sub(seq*group). Reviewer recalculated all the pharmacokinetic parameters and statistics and the results of the recalculation are in agreement with the sponsor's submission. Because unconjugated estradiol, unconjugated estrone and conjugated estrone are endogenous estrogens in human plasma, plasma concentration of these estrogens were examined with and without baseline adjusted concentration data. The following plasma concentration and pharmacokinetic parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are based on baseline adjusted concentration data:

UNCONJUGATED ESTRADIOL DATA

The mean plasma unconjugated estradiol levels for the test and reference products were comparable to each other as shown in Table #1 and Figures #1 and 2. The 90% confidence intervals

for the LSMeans log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #3). The T/R mean ratios (RLSM12) for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25% (Table #3).

Table #1
Mean Plasma Concentrations (Pg/mL)
of Unconjugated Estradiol in 37 Subjects Following a Single Oral Dose of 2.0 mg Estradiol Tablet Under Fasting Conditions
(Test Lot #R971645, Reference Lot #K5K07A)

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
-48	0.31	0.54	0.44	0.67	0.70
-24	0.39	0.82	0.24	0.46	1.59
0	0.49	1.39	0.10	0.28	4.75
0.75	31.69	30.93	23.80	21.30	1.33
1.5	25.56	16.18	23.09	16.60	1.11
2	27.87	15.96	23.64	12.79	1.18
3	33.16	16.23	30.14	13.62	1.10
4	35.23	14.59	33.82	15.47	1.04
5	42.61	19.06	42.56	20.59	1.00
6	44.94	18.91	45.75	20.26	0.98
7	45.64	17.35	45.07	20.04	1.01
8	47.23	18.94	44.91	17.76	1.05
10	46.19	16.55	46.42	16.84	1.00
12	45.66	17.01	44.00	16.32	1.04
15	40.26	14.82	37.91	13.40	1.06
18	36.60	15.07	35.71	14.66	1.02
24	29.69	14.46	28.92	11.84	1.03
36	20.15	9.72	20.07	9.49	1.00
48	12.70	8.37	11.34	5.83	1.12
72	4.81	3.72	4.43	2.87	1.08

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

Table #2
Mean Pharmacokinetic Parameters (Arithmetic)
in 37 Subjects Following a Single Oral
Dose of 2.0 mg Estradiol Tablet Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	1772.07	743.02	1673.58	600.42	1.06
AUCT	1620.55	647.24	1541.86	563.14	1.05
CMAX	59.35	25.10	56.24	22.06	1.06
KE	0.04	0.01	0.04	0.02	0.92
*LAUCI	1620.08	0.44	1559.75	0.40	1.04
*LAUCT	1483.24	0.45	1422.39	0.44	1.04
*LCMAX	54.89	0.40	52.55	0.37	1.04
THALF	18.90	7.82	18.15	8.17	1.04
TMAX	8.40	5.75	7.85	3.52	1.07

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

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

Table #3
LSMeans And The 90% Confidence Intervals in 37 Subjects Following a Single Oral Dose of 2.0 mg Estradiol Tablet Under Fasting Conditions

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	1612.31	1553.71	1.04	97.88	110.01
LAUCT	1469.29	1410.25	1.04	98.94	109.71
LCMAX	53.91	51.73	1.04	98.67	110.06

UNIT: AUC=PG HR/ML CMAX=PG/ML

Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

UNCONJUGATED ESTRONE DATA

The mean plasma unconjugated estrone levels for the test and reference products were comparable to each other as shown in Table #4 and Figures #3 and 4. The 90% confidence intervals for the LSMeans log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #6). The T/R mean ratios (RLSM12) for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25% (Table #6).

Table #4
Mean Plasma Concentrations (Pg/mL) of Unconjugated Estrone in 37 Subjects Following a Single Oral Dose of 2.0 mg Estradiol Tablet Under Fasting Conditions
(Test Lot #R971645, Reference Lot #K5K07A)

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
-48	0.88	1.31	1.12	1.90	0.78
-24	0.84	1.35	1.00	1.69	0.84
0	0.84	1.48	0.48	0.86	1.73
0.75	46.05	35.75	36.88	35.47	1.25
1.5	137.98	94.99	111.38	63.99	1.24
2	195.00	123.33	168.46	95.88	1.16
3	273.61	131.22	252.36	110.11	1.08
4	305.82	131.54	288.78	109.45	1.06
5	374.79	136.17	360.68	141.59	1.04
6	360.54	134.65	341.41	120.02	1.06
7	339.04	128.47	321.34	126.57	1.06
8	332.84	122.07	328.97	134.64	1.01
10	321.02	130.47	314.71	129.91	1.02
12	288.67	116.13	292.98	129.52	0.99
15	226.39	101.71	226.95	106.32	1.00

18	181.05	85.08	184.41	91.45	0.98
24	133.68	68.81	128.95	63.27	1.04
36	88.29	52.48	84.80	46.17	1.04
48	50.79	32.77	46.88	28.12	1.08
72	19.32	16.46	16.93	12.24	1.14

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

Table #5
Mean Pharmacokinetic Parameters (Arithmetic) in 37 Subjects Following a Single Oral Dose of 2.0 mg Estradiol Tablet Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	9207.55	3886.14	8811.84	3703.84	1.04
AUCT	8686.62	3545.79	8379.44	3507.27	1.04
CMAX	410.98	144.49	399.49	140.66	1.03
KE	0.05	0.02	0.05	0.02	0.95
LAUCI	8293.87	0.51	7916.75	0.51	1.05
LAUCT	7861.27	0.50	7530.53	0.51	1.04
LCMAX	384.08	0.39	372.61	0.40	1.03
THALF	16.58	6.48	15.34	4.70	1.08
TMAX	6.76	2.48	6.49	2.46	1.04

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
* The values represent the geometric means (antilog of the means of the logs).

Table #6
LSMeans And The 90% Confidence Intervals in 37 Subjects Following a Single Oral Dose of 2.0 mg Estradiol Tablet Under Fasting Conditions

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	8172.56	7802.29	1.05	99.99	109.73
LAUCT	7744.57	7418.91	1.04	100.06	108.91
LCMAX	378.14	366.69	1.03	97.39	109.19

UNIT: AUC=PG HR/ML CMAX=PG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

CONJUGATED ESTRONE DATA

The mean plasma conjugated estrone levels for the test and reference products were comparable to each other as shown in Table #7 and Figures #5 and 6. The 90% confidence intervals for the LSMeans log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #9). The T/R mean ratios (RLSM12) for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25% (Table #9).

Table #7
Mean Plasma Concentrations (ng/mL) of Conjugated Estrone in 37 Subjects Following a Single Oral Dose of 2.0 mg Estradiol Tablet Under Fasting Conditions
(Test Lot #R971645, Reference Lot #K5K07A)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
-48	0.04	0.08	0.03	0.06	1.34
-24	0.01	0.03	0.02	0.05	0.52
0	0.01	0.03	0.01	0.03	1.70
0.75	37.13	21.78	30.10	20.99	1.23
1.5	42.55	18.40	42.48	19.45	1.00
2	40.33	18.26	38.32	18.74	1.05
3	32.14	10.89	31.85	13.66	1.01
4	28.26	10.28	27.70	10.67	1.02
5	31.76	12.08	30.39	9.80	1.05
6	24.60	9.79	23.94	7.74	1.03
7	21.49	8.58	21.32	7.47	1.01
8	19.64	8.34	19.16	7.19	1.02
10	17.31	7.48	16.99	6.33	1.02
12	14.74	7.57	14.66	6.96	1.01
15	10.07	5.74	10.27	5.93	0.98
18	7.47	4.92	7.65	4.43	0.98
24	5.44	3.10	5.47	2.85	0.99
36	3.73	2.65	3.51	2.36	1.06
48	1.94	1.33	1.83	1.13	1.06
72	0.71	0.56	0.68	0.53	1.05

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

Table #8
Mean Pharmacokinetic Parameters (Arithmetic) in 37 Subjects Following a Single Oral Dose of 2.0 mg Estradiol Tablet Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	544.41	218.88	528.17	195.98	1.03
AUCT	524.92	207.44	510.00	186.22	1.03
CMAX	51.39	19.87	49.92	19.94	1.03
KE	0.05	0.01	0.05	0.01	1.02
*LAUCI	504.23	0.40	492.59	0.39	1.02
*LAUCT	486.94	0.40	476.53	0.38	1.02
*LCMAX	48.20	0.35	46.56	0.37	1.04
THALF	15.93	4.86	16.09	5.28	0.99
TMAX	2.01	1.34	2.03	1.35	0.99

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

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

Table #9

LSMeans And The 90% Confidence Intervals in 37 Subjects Following a Single Oral Dose of 2.0 mg Estradiol Tablet Under Fasting Conditions

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	491.50	480.12	1.02	98.95	105.91
LAUCT	474.59	464.43	1.02	98.92	105.56
LCMAX	48.11	46.53	1.03	97.07	110.12

UNIT: AUC=NG HR/ML CMAX=NG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

IV. FORMULATION COMPARISON

ESI Lederle comparative formulations for its test product, Estradiol Tablets, 0.5 mg, 1.0 mg and 2.0 mg are summarized in the following Table.

Formulation Composition

ESI-Lederle Estradiol Tablets USP, 0.5mg, 1mg and 2mg						
Ingredients	**0.5mg**		**1mg**		**2mg**	
	% w/w	**mg/tablet**	**% w/w**	**mg/tablet**	**% w/w**	**mg/tablet**
Estradiol						
Lactose						
(a)						
Microcrystalline Cellulose		4				
Sodium Starch						
Magnesium						20
Total						

(a) Based on Estradiol USP, Micronized assaying at 100% potency. If the potency of the Estradiol USP, Micronized, is not 100%, the amount used must be adjusted to give the claimed potency and the amount of Lactose Monohydrate NF, Spray Dried, must be adjusted accordingly.

(b) A 2% overage of estradiol is used to compensate for losses incurred during manufacture. A report justifying the 2% overage for the 0.5mg tablet proposed production batch size is included in Section XI 1 of the ANDA application which was submitted on 8/29/97.

V. IN VITRO DISSOLUTION TESTING

USP 23 dissolution method was used for the comparative dissolution testing of the test and reference products of 0.5 mg, 1 mg and 2 mg strengths.

All the test and reference products met the USP dissolution specifications as summarized below.

Method: USP method
Apparatus: 2 (Paddle) at 100 rpm
Medium: 0.3% sodium lauryl sulfate in water; 500 mL
Sampling Time: 15, 30, 45 and 60 minutes
Number of Units: 12 Tablets
Tolerances: NLT of the labeled amount of estradiol in the dosage form is dissolved in minutes.

Test Product: ESI Lederle's Estradiol Tablets
0.5 mg Tablets, Lot #R971663
1.0 mg Tablets, Lot #R971646
2.0 mg Tablets, Lot #R971645
Reference Product: Bristol-Myers Squibb's Estrace® Tablets
0.5 mg Tablets, Lot #M5K13A
1.0 mg Tablets, Lot #B6K64A
2.0 mg Tablets, Lot #K5K07A

The dissolution testing results are shown in the following table.

I. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Lot #R971645 Strength(mg) 2			Reference Product Lot # K5K07A Strength(mg)2		
	Mean %	Range	%CV	Mean %	Range	%CV
15	95.42		0.94	84.92		2.58

30	99.0		1.22	94.67		1.58
45	99.83		1.03	97.25		1.92
60	99.92		1.38	98.92		1.38

Sampling Times (Minutes)	Test Product Lot #R971646 Strength(mg) 1			Reference Product Lot #B6K64A Strength(mg) 1		
	Mean %	Range	%CV	Mean %	Range	%CV
15	94.17		1.0	86.17		2.96
30	97.42		0.92	93.75		2.32
45	97.67		1.10	95.58		2.29
60	98.25		0.98	96.58		1.90

Sampling Times (Minutes)	Test Product Lot #R971663 Strength(mg) 0.5			Reference Product Lot #M5K13A Strength(mg) 0.5		
	Mean %	Range	%CV	Mean %	Range	%CV
15	94.50		0.71	95.00		2.73
30	97.50		0.93	99.25		3.13
45	97.67		0.80	99.75		3.03
60	98.17		0.85	100.42		3.08

1. The dissolution data for the test and reference listed products are acceptable.

VI. COMMENTS:

1. The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, ESI Lederle Estradiol Tablets, USP, 2 mg, lot #R971645 and the reference product, Bristol-Myers Squibb's Estrace® Tablets, 2.0 mg, lot # K5K07A are bioequivalent. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax for unconjugated estradiol, unconjugated estrone and conjugated estrone were all within the acceptable range of 80-125%.

2. The in vitro dissolution data for the 0.5 mg, 1.0 mg and 2.0 mg strengths of the test product are acceptable.

3. Comparative formulations given for the test product show the 0.5 mg and 1.0 mg strength tablets are proportionally similar in their active and inactive ingredients to the 2.0 mg strength.

VII. DEFICIENCIES:

1. The information provided in the submission regarding long term stability data for the three analytes (unconjugated estradiol, unconjugated estrone and conjugated estrogen) mentioned that unconjugated estradiol, and unconjugated estrone are stable for seven weeks and for conjugated estrogen the stability was six weeks. The stability data should cover a period equal to the time from the day each study started (blood sampling) to the day the last sample was analyzed.

   It is not clear from the submission if this period (6 or 7 weeks) covered the entire length of the bio-study. Please submit dates of the blood sampling and analytical assay for all subjects (preferred in tabulated format, if possible).

2. Recovery data was not submitted for conjugated estrone. The recovery data profile should provide the mean, range (high, low), the percentage of coefficient of variation (%CV) and the percentage of change from the quality control theoretical values. The sponsor should also submit the SOP for the recovery procedure.

3. Spot checks for random calculated values of the analytes have shown different values as compared to the firm's reported values in the submission. In particular for high concentration samples, the reported values of response ratios that are represented the division of response of analyte standard (or unknown sample) by response of internal standard are not similar to the values calculated by the reviewer (see some examples, on pages 335 and 381, volume C1.2). Please provide a summary for the method of calculation of the three analytes accompanied by a few examples of the firm's calculations, especially examples of samples that reflect the different

range ~~of~~ concentrations (low, medium and high).

VIII. RECOMMENDATIONS:

The in vivo bioequivalence study conducted under fasting conditions by ESI Lederle Inc. On its Estradiol Tablets, 2.0 mg strength, lot #R971645, comparing it to Bristol-Myers Squibb's Estrace® Tablets, 2.0 mg, lot # K5K07A, has been found incomplete due to the deficiencies #1-3.

The firm should be informed of the recommendation and deficiencies #1-3 .

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #40-275 APPLICANT: ESI Lederle, Inc.

DRUG PRODUCT: Estradiol Tablets, 0.5 mg, 1.0 mg and 2.0 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,

/S/

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

2.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #40-275 APPLICANT: ESI Lederle, Inc.

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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 DEFICIENCIES

ANDA: #40-275 APPLICANT: ESI Lederle Inc.

DRUG PRODUCT: Estradiol Tablets

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

1. The information that you have provided in the submission regarding long term stability data for the three analytes (unconjugated estradiol, unconjugated estrone and conjugated estrogen) mentioned that unconjugated estradiol, and unconjugated estrone are stable for seven weeks and for conjugated estrogen the stability was six weeks. The stability data should cover a period equal to the time from the day each study started (blood sampling) to the day the last sample was analyzed.

   It is not clear from the submission if this period (6 or 7 weeks) covered the entire length of the bio-study. Please submit dates of the blood sampling and analytical assay for all subjects (preferred in tabulated formate, if possible).

2. The recovery data was not submitted for conjugated estrone. You should submit the recovery raw data for conjugated estrone. The recovery data should include the mean, range (high, low), the percentage of coefficient of variation (%CV) and the percentage of change from the quality control theoretical values. You should also submit the SOP for the recovery procedure.

3. Spot checks for random calculated values of the analytes have shown different values as compared to your reported values in the submission. In particular for high concentration samples, the reported values of response ratios that are represented the division of response of analyte standard (or unknown sample) by the response of internal standard are not similar to the values calculated by the reviewer (see some examples on pages 335 and 381, volume C1.2).
   Please provide a summary of the method of calculation for the three analytes accompanied by a few examples of your calculations, especially examples for samples that reflect a different range of concentrations (low, medium and high).

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Sincerely yours,

/S/

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

Figure # 1

ANDA # 40-275

Unconjugated Estradiol

Estradiol (Protocol No. 96–027–MA)

Mean Plasma Concentration Profile

Baseline Adjusted Concentration Values

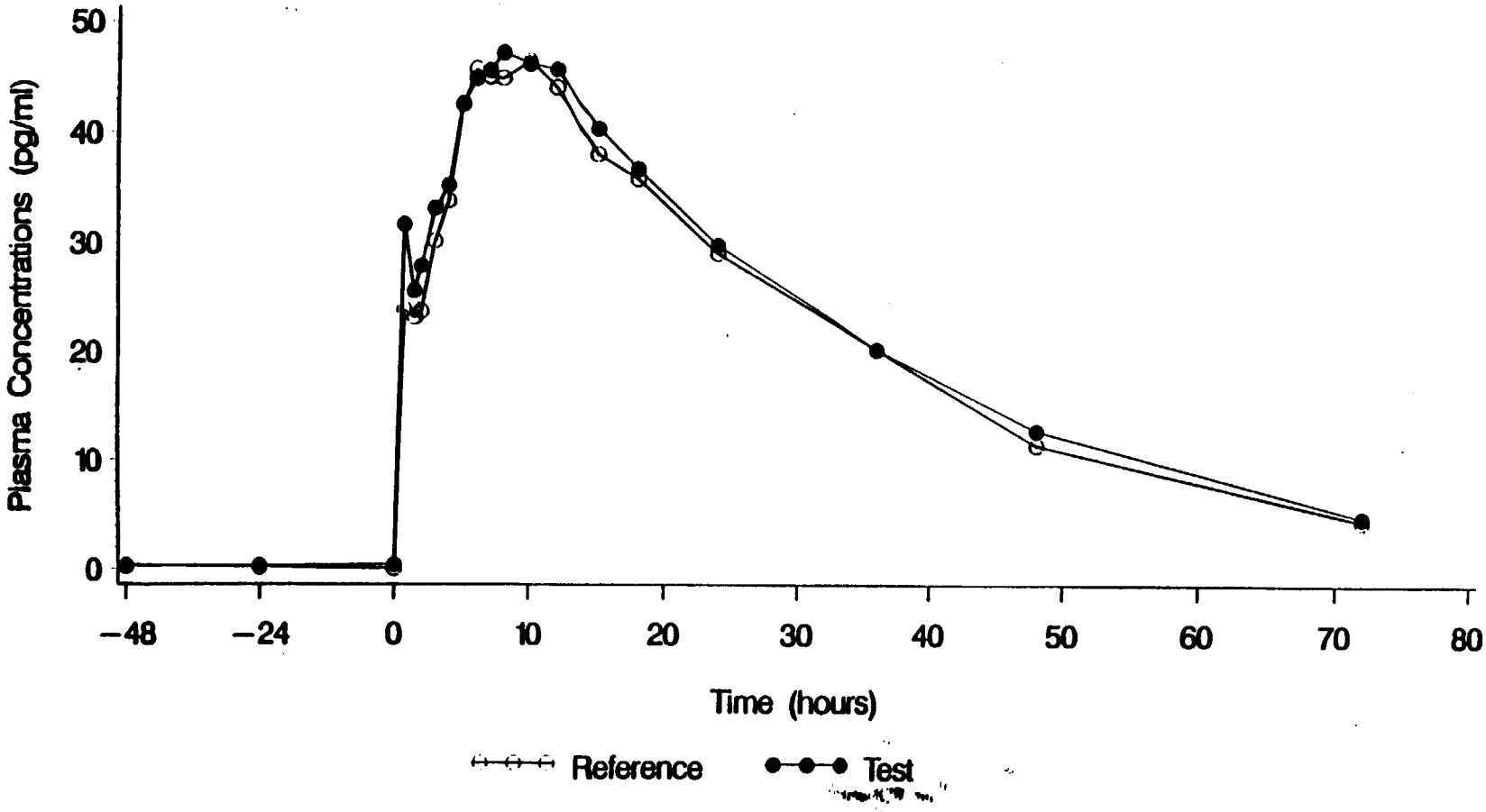

Figure #2

ANDA #40-275

Unconjugated Estradiol

Estradiol (Protocol No. 96–027–MA)
Mean Plasma Concentration Profile
Baseline Adjusted Concentration Values

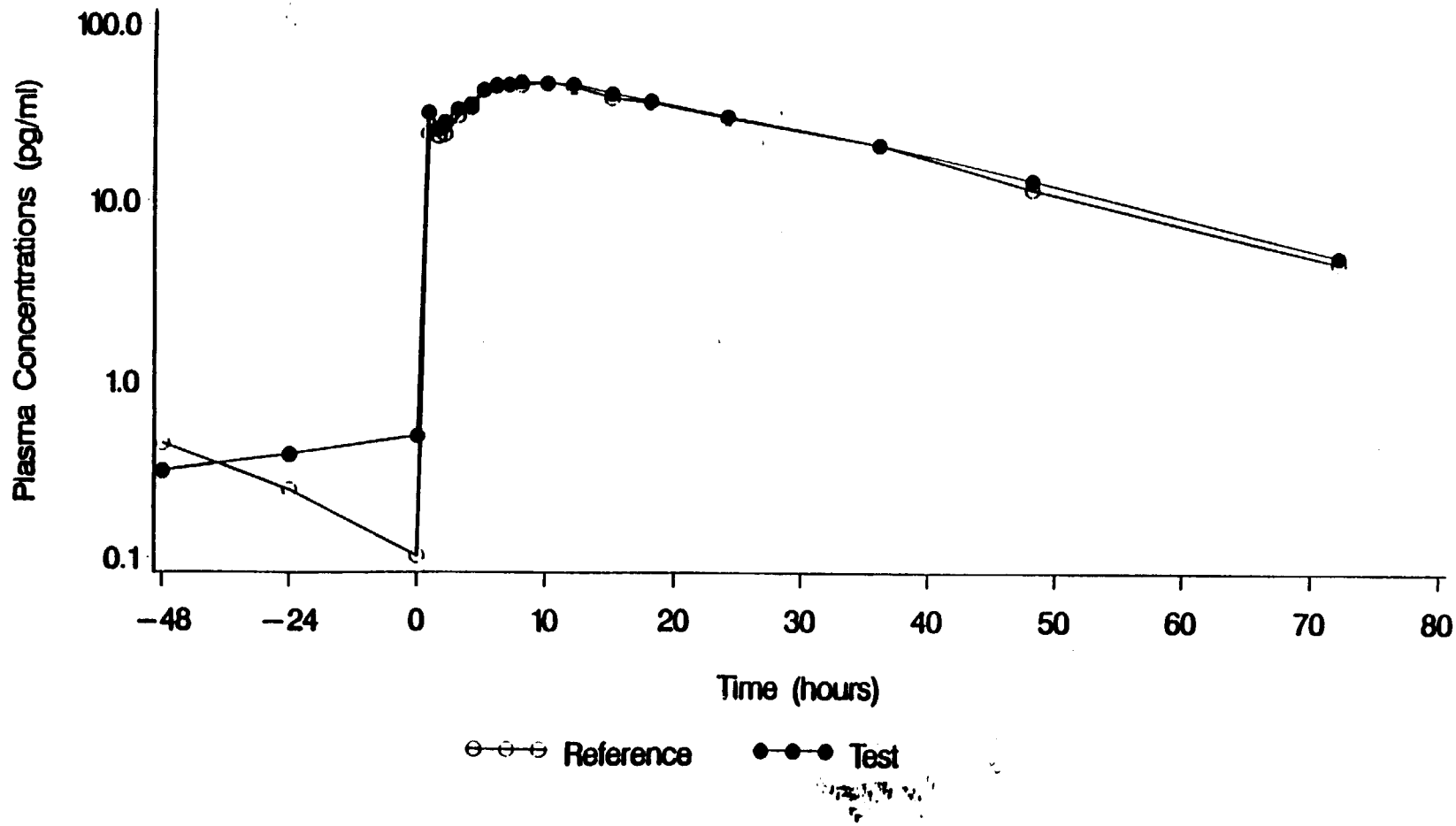

Figure # 3
ANDA #40-275

Unconjugated Estrone

Estradiol (Protocol No. 96–027–MA)
Mean Plasma Concentration Profile
Baseline Adjusted Concentration Values

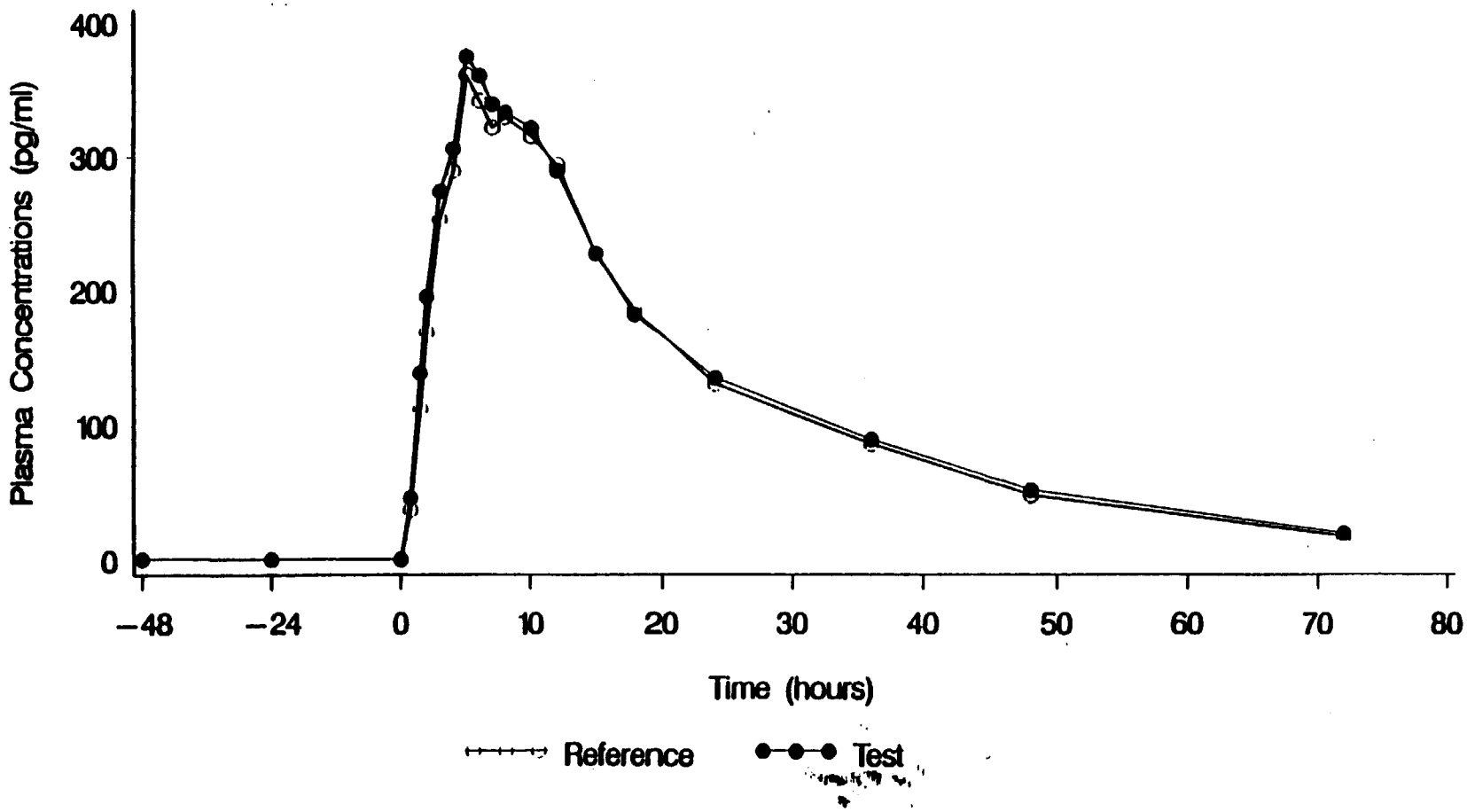

Figure #4
ANDA #40-275

Unconjugated Estrone

Estradiol (Protocol No. 96–027–MA)
Mean Plasma Concentration Profile
Baseline Adjusted Concentration Values

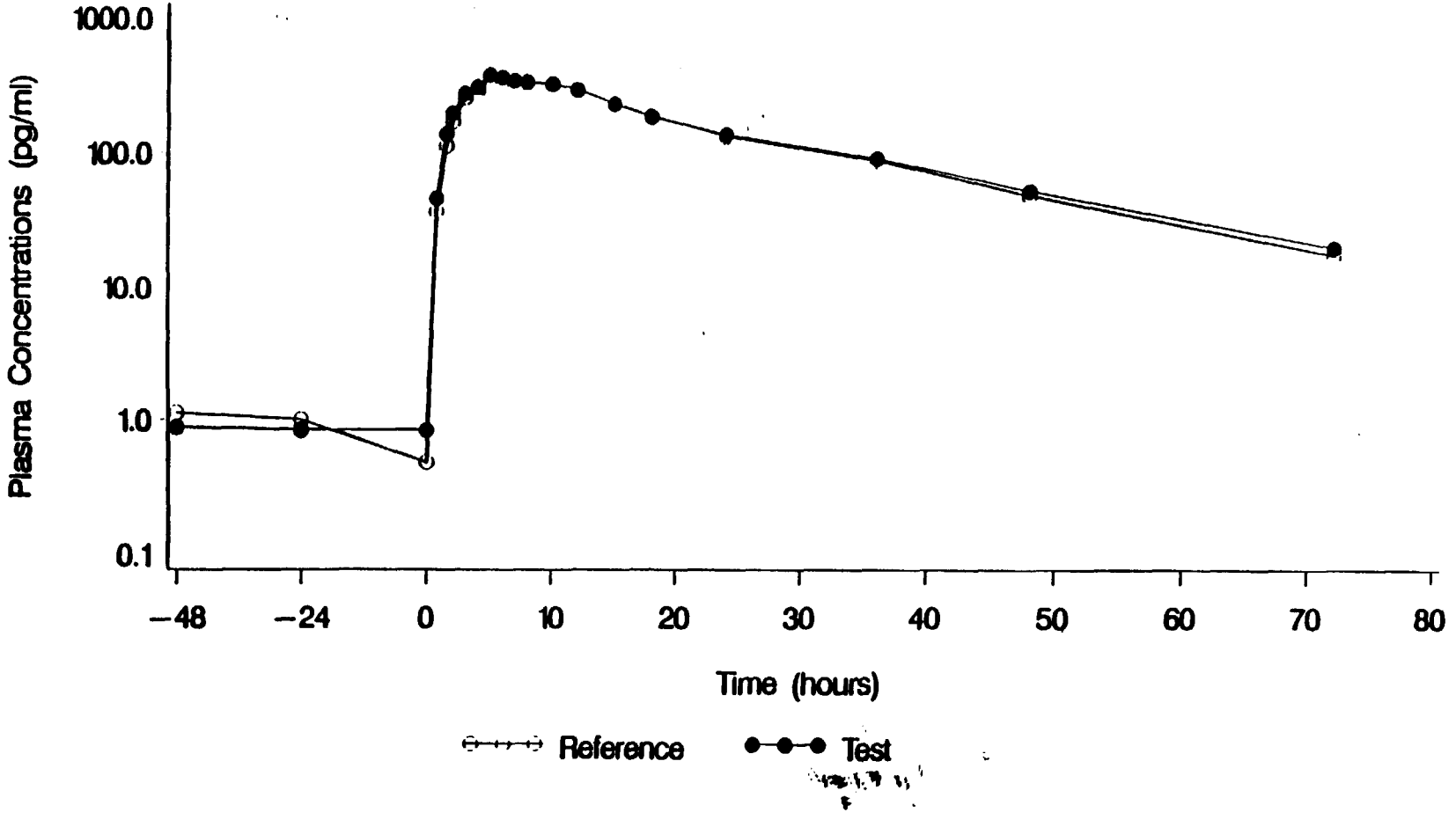

Figure #5

ANDA #40-275

Conjugated Estrone

Estradiol (Protocol No. 96–027–MA)
Mean Plasma Concentration Profile
Baseline Adjusted Concentration Values

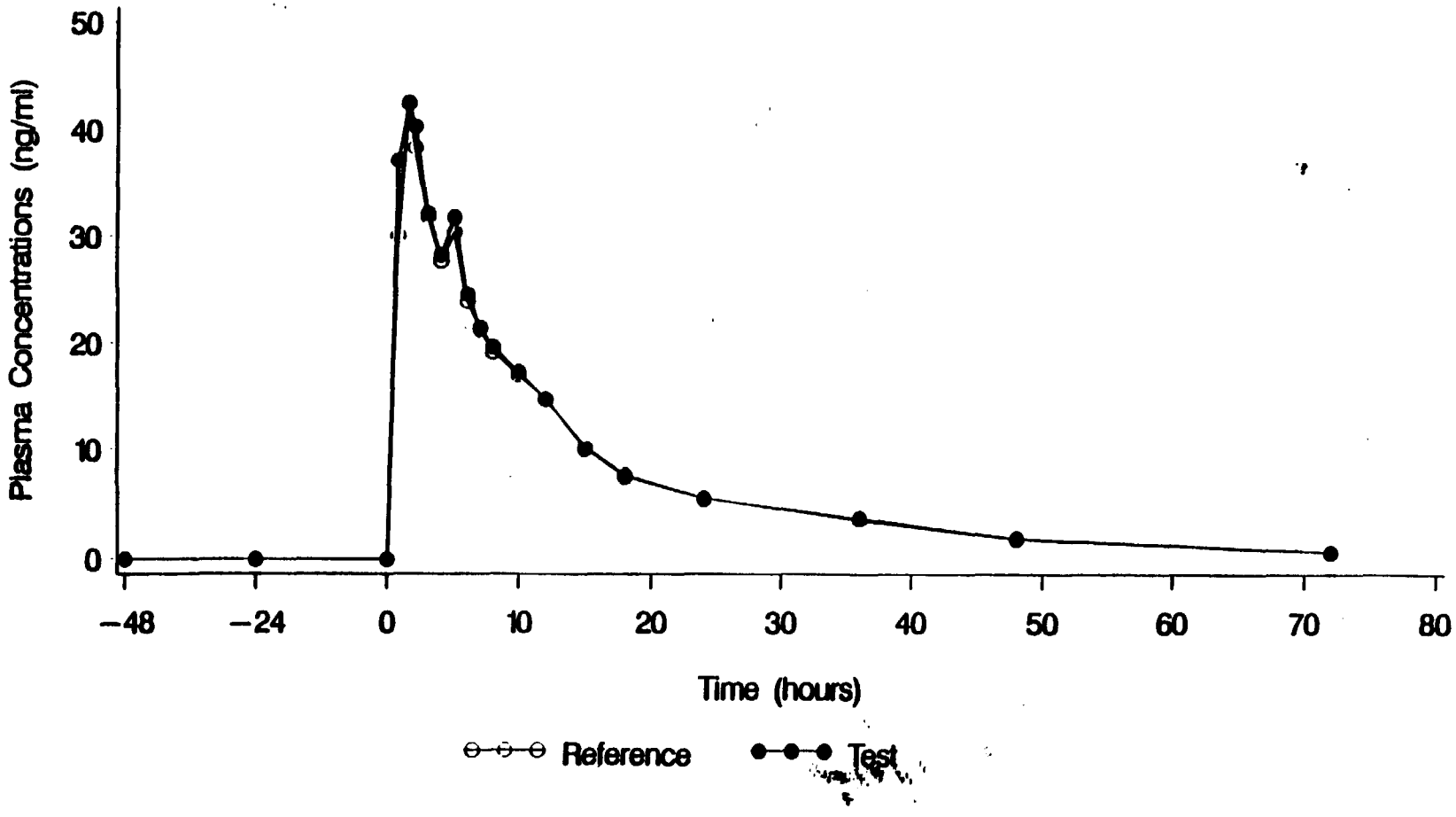

Figure #6

ANDA #40-275

Conjugated Estrone

Estradiol (Protocol No. 96–027–MA)

Mean Plasma Concentration Profile

Baseline Adjusted Concentration Values