CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75288

BIOEQUIVALENCY REVIEW(S)

Ethinyl Estradiol/Norgestrel	**G.D. Searle**
0.03 mg/ 0.3 mg Tablet	**Skokie, IL**
ANDA # 75-288	**Submission Date:**
Reviewer: Lin-Whei Chuang	**May 18, 1998**

Review of an Amendment to a Bioequivalence Study and Dissolution Data

The *in vivo* bioequivalence study and dissolution testing conducted by G.D. Searle on its ethinyl estradiol(EE)/norgestrel (NG) tablet, 0.03 mg/0.3 mg (Low-Ogestrel tablet), lot #RCT10242, comparing to Lo/Ovral tablet (EE/NG tablet, 0.03 mg/0.3 mg), lot #9958097, manufactured by Wyeth Ayerst, has been found incomplete due to the following 8 deficiencies:

1. Please provide report of analytical study conducted for the assay of EE and NG in the study samples, including site, date, name(s) of investigator(s), analytical procedure, method validation, re-assay report, and chromatograms or raw data for at least % of the subjects randomly selected.

Firm's Response: Analytical methods conducted by were submitted and reviewed below.

a. Analytical Method of EE -- **Not Releasable through FOI** --

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Analytical method

Reviewer's Comment:

The analytical data submitted by the firm are acceptable.

2. The clinical study was conducted over a period of 7 months (11/8/96-6/1/97). Please provide the exact date of study drug treatments for each subject.

Firm's Response:

Dates of period 1 were between 11/8/96 and 4/28/97, and period 2 between 12/6/96 and 5/30/97.

Reviewer's Comment:

The clinical dates indicated that, at least for those subjects whose chromatograms were submitted, the analysis were conducted within the time range of validated long-term stability (180 days for EE and 287 days for NG).

3. Please provide evidence of approval of the study by an IRB.

Firm's Response:

IRB approval was granted on 7/16/96 by L. A. Meyer of the Research Consultants' Review Committee.

Reviewer's Comment:

The firm's response is adequate.

4. Please provide the potencies of test and reference drugs, the lot size of the test drug, and the expiration date of the reference drug.

Firm's Response:

The lot size of study lot #PT-142-96 was approximately tablets and its potency was 99.9% for EE and 97.2% for NG. The potency of the reference lot, LoOvral #9958097, was 98.9% for EE and 99.1% for NG. The expiration date of the reference drug is 5/99.

Reviewer's Comment:

The firm's response is adequate.

5. Please provide reason(s) for completing only one period of the study for each of the following subjects: subjects #10, 15, 17, 20, 103 & 915.

Firm's Response:

Three of them (subjects #10, 17 & 103) dropped due to irregular menstrual cycles; subject #15 had positive pregnancy test at check-in of period 2, #20 violated protocol during wash-out

period, and #915 dropped because she was not needed (24 subjects already completed the study before she had to start period 2).

Reviewer's Comment:

The firm's response is adequate.

6. Please provide any possible clinical significance of changes in clinical laboratory test results obtained from pre- and post-study periods. Please provide discussion of any possible effect of these changes on the outcome of the study.

Firm's Response:

The principal investigator, reviewed the results and determined they were not clinically significant.

Reviewer's Comment:

The firm's response is adequate.

7. Please provide the components and composition of the test product.

Firm's Response:

Following information were provided by the firm:

Composition of 0.3 mg NG and 0.03 mg EE Tablets --
(Not Releasable Through FOI)

Core Tablet	Amount (mg/tablet)
Norgestrel, USP	0.30
Ethinyl Estradiol, USP	0.03
Lactose Monohydrate, NF	
Microcrystalline Cellulose, NF	
Povidone, USP	
Croscarmellose Sodium, NF	
Magnesium Stearate, NF	
Total Weight	100.0

Reviewer's Comment:

The firm's response is adequate.

8. Please conduct *in vitro* dissolution testing on the same lot of test and reference products used for the *in vivo* bioequivalence study.

Firm's Response:

The *in vitro* dissolution data provided in the original submission (12/24/97) were conducted on the same lot of test and reference products used for the *in vivo* bioequivalence study. Lot #PT-142-96 reported in the dissolution testing is the packaging lot number for clinical lot 10242.

Reviewer's Comment:

The firm's response is adequate. The firm had conducted the dissolution with the method and medium, which are paddle apparatus at 75 rpm in 500 mL of water with in accordance with those recommended by the Agency.

Recommendation:

1. The bioequivalence study conducted by G.D. Searle on its ethinyl estradiol/norgestrel 0.03 mg/0.3 mg tablets, lot #RCT10242, comparing it to Lo/Ovral 0.03 mg/0.3 mg tablets, lot #9958097, has been found acceptable by the Division of Bioequivalence.

2. The dissolution testing conducted by G.D. Searle on its ethinyl estradiol/norgestrel 0.03 mg/0.3 mg tablets has been found acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 500 mL of distilled water with at 37° C using USP 23 apparatus 2 (paddle) at 75 rpm. The test products should meet the following specifications:

"Not less than % of the labeled amount of both ethinyl estradiol and norgestrel should be dissolved in 60 minutes."

/S/ 9/15/98

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED-YHUANG /S/ 9/15/98
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Concur: /S/ Date: 10/19/98
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-288 APPLICANT: G.D. Searle

DRUG PRODUCT: Ethinyl Estradiol/Norgestrel Tablet, 0.03 mg/0.3 mg

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

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

The dissolution testing should be conducted in 500 mL of water with . at 37° C using USP Apparatus 2 at 75 rpm. The test product should meet the following specifications:

"Not less than % (Q) of the labeled amount of both ethinyl estradiol and norgestrel in the dosage form are dissolved in 60 minutes."

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

CC: ANDA 75-288
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ L. Chuang

Printed in final on 9/15/98

Endorsements: (Final with Dates)
HFD-652/ L. Chuang 9/15/98
HFD-652/ Y. Huang 9/15/98
HFD-650/ D. Conner 10/19/98

BIOEQUIVALENCY - ACCEPTABLE submission date: 5/18/98 & 9/3/98

STUDY AMENDMENT (STA) Strength: 0.03 mg/0.3 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

Ethinyl Estradiol/Norgestrel	**G.D. Searle**
0.03 mg/ 0.3 mg Tablet	**Skokie, IL**
ANDA # 75-288	**Submission Date:**
Reviewer: Lin-Whei Chuang	**December 24, 1997**

Addendum to a Previous Review

It has been noted that in the previous review (4/29/98) for the 12/24/97 submission, the reviewer erroneously described the dissolution medium and method conducted by the firm as paddle method at 50 rpm in 900 mL of 0.05 M phosphate buffer. The firm actually conducted the dissolution with the method and medium, which are paddle apparatus at 75 rpm in 500 mL of water with in accordance with those recommended by the Agency.

Recommendation:

No action is needed.

/S/ 9/15/98

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG /S/ 9/15/98

Concur /S/ Date: 10/19/98
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-288 APPLICANT: G.D. Searle

DRUG PRODUCT: Ethinyl Estradiol/Norgestrel Tablet (0.03/0.3 mg)

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

1. Please provide report of analytical study conducted for the assay of EE and NG in the study samples, including site, date, name(s) of investigator(s), analytical procedure, method validation, re-assay report, and chromatograms or raw data for at least 20% of the subjects randomly selected.

2. The clinical study was conducted over a period of 7 months (11/8/96-6/1/97). Please provide the exact date of study drug treatments for each subject.

3. Please provide evidence of approval of the study by an IRB.

4. Please provide the potencies of test and reference drugs, the lot size of the test drug, and the expiration date of the reference drug.

5. Please provide reason(s) for completing only one period of the study for each of the following subjects: subjects #10, 15, 17, 20, 103 & 915.

6. Please provide any possible clinical significance of changes in clinical laboratory test results obtained from pre- and post-study periods. Please provide discussion of any possible effect of these changes on the outcome of the study.

7. Please provide the components and composition of the test product.

8. Please conduct *in vitro* dissolution testing on the same lot of test and reference products used for the *in vivo* bioequivalence study.

Sincerely yours,

/S/

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

CC: ANDA #75-288
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-652/L. Chuang LWC 4/22/98
HFD-652/Y. Huang YH 4/24/98
HFD-617/L. Sanchez
HFD-650/Dale Conner DRC 4/29/98

BIOEQUIVALENCY - DEFICIENCIES Submission Date: 12/24/97

1. **FASTING STUDY** (STF) Strengths: 0.03mg/0.3 mg
Clinical: _____ **Outcome:** **IC**
Analytical: Not Given

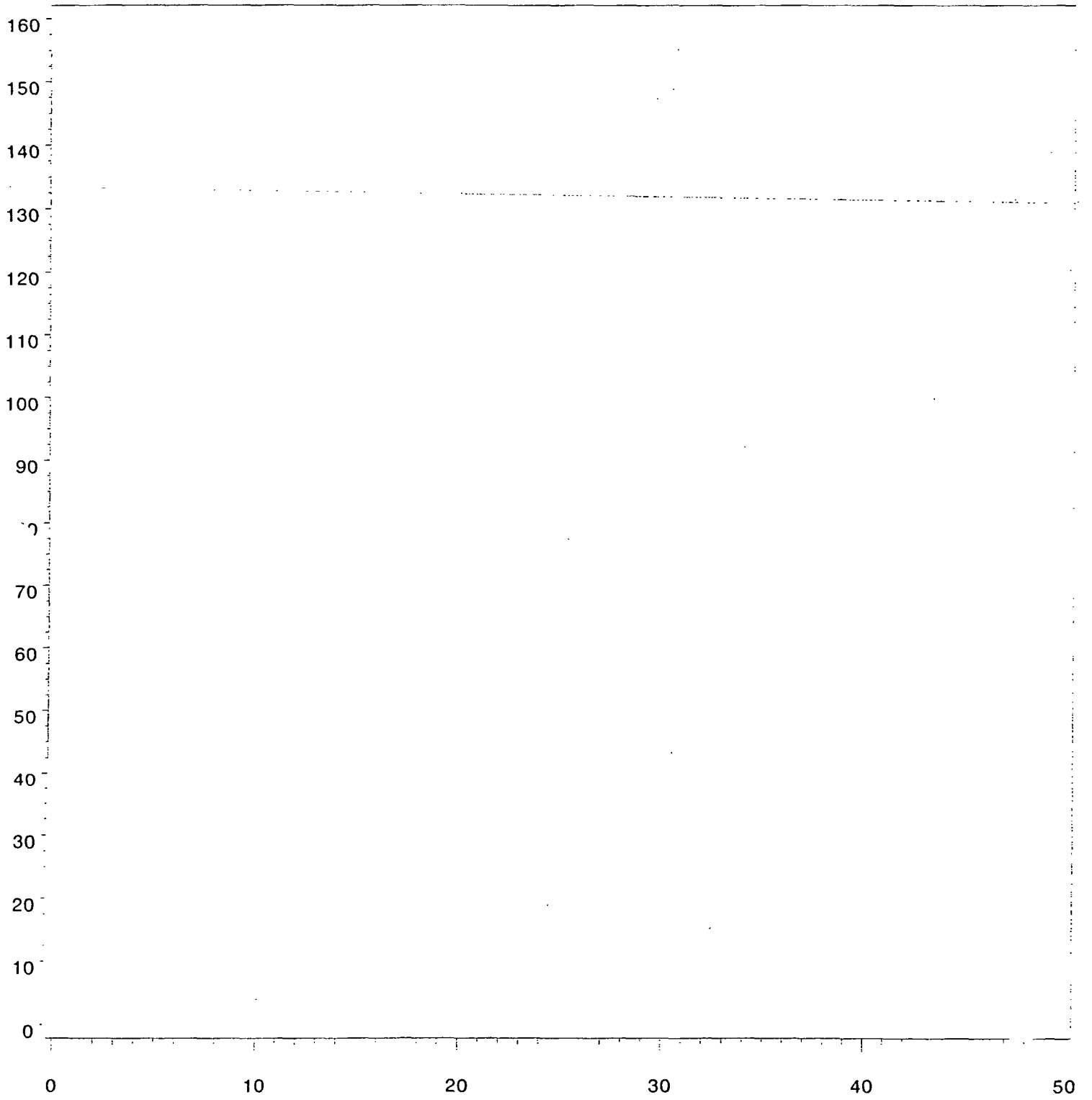
2. ~~**DISSOLUTION DATA** (DIS)~~ All Strengths
~~**Outcome: IC**~~ NC
XD

Outcome Decisions: **IC** - Incomplete

WinBio Comments: Both *in vivo* bioequivalence *in vitro* dissolution testing are incomplete due to 8 deficiencies.

IG 1 . PLASMA ETHINYL ESTRADIOL LEVELS

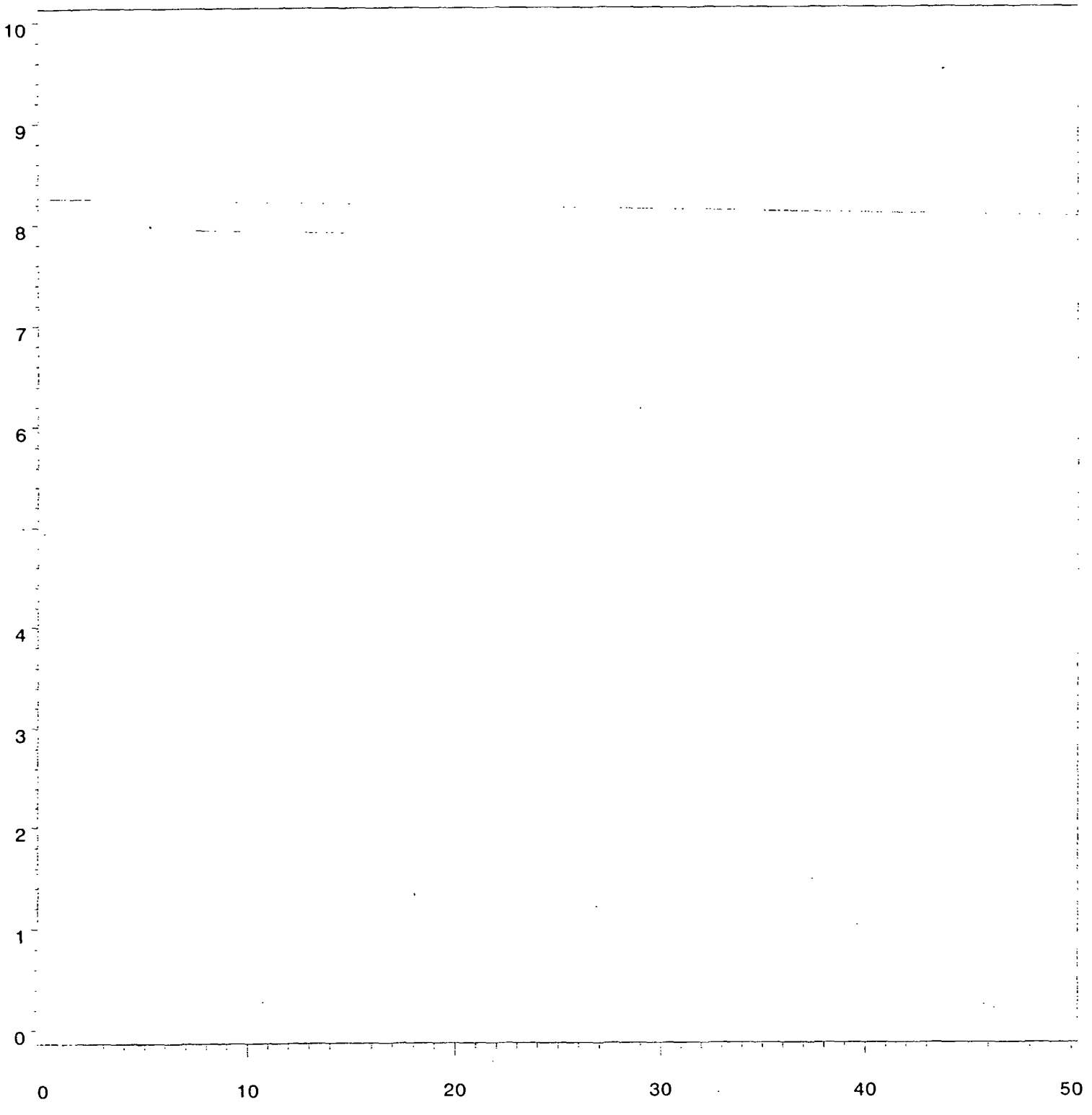
LOW-OGESTREL TABLETS, 0.3/30 MG, ANDA #75-288
UNDER FASTING CONDITIONS
DOSE=1 X 0.3/30 MG



1=TEST(GDSEARLE) 2=REF(WYETH-AYERST)

FIG 2 . PLASMA NORGESTREL LEVELS

LOW-OGESTREL TABLETS, 0.3/30 MG, ANDA #75-288
UNDER FASTING CONDITIONS
DOSE=1 X 0.3/30 MG



1=TEST(GDSEARLE) 2=REF(WYETH-AYERST)

Ethinyl Estradiol/Norgestrel
0.03 mg/ 0.3 mg Tablet
ANDA # 75-288
Reviewer: Lin-Whei Chuang

G.D. Searle
Skokie, IL
Submission Date:
December 24, 1997

Review of a Bioequivalence Study and Dissolution Data

Introduction:

The drug product is an oral, combination contraceptive. The estrogenic component, ethinyl estradiol (EE), is semisynthetic while the progestin component, norgestrel (NG) is totally synthetic.

Orally administered EE shows extensive first pass metabolism (bioavailability 40 to 50%) while NG (as racemate, and two enantiomers separately) doesn't have the first pass effect (bioavailability 85-100%). EE undergoes reduction of ring A and sulfate conjugation to yield inactive metabolites. Norgestrel undergoes A ring reduction, 16 carbon hydroxylation, sulfation and glucuronidation. The existing data show that the two enantiomers may not be metabolized identically in humans but they are metabolized almost to same extent and their metabolites are inactive. EE and NG show 2 compartment pharmacokinetics. The elimination half life has been reported to be 6-20 hours for EE and 11-45 hours for levonorgestrel (LNG).

The drug product should be taken same time every day, preferably after evening meal or at bedtime. It is repeated cyclically every 28 day period (21 active tablets for 21 days followed by either no tablets for 7 days or one a day placebo tablet for 7 days). Wyeth Ayerst markets these combination drug products as LO/OVRAL and LO/OVRAL-28 (21 day Tablet and 28 day Tablet). The "Orange Book" describes LO/OVRAL as reference product which was approved by the Agency through NDA #17802. Wyeth Ayerst also markets LO/OVRAL and LO/OVRAL-28 in the strength of 0.05 mg/0.5 mg.

In Vivo Bioequivalence Study

The primary objective of the study is to show bioequivalency of the test product (Low-Ogestrel) and Lo/Ovral, manufactured by

Wyeth Ayerst, after a single oral dose under fasting conditions.

The clinical portion of the study was conducted at
during 11/8/96-6/1/97.
The report of analytical method and validation was not included in this submission.

The design was a single-dose, 2-way crossover study. Subjects received study drugs on either day 2, 3, or 4 of their menstrual cycle. The protocol of the study (#N5L-96-02-001) was dated 7/18/96, however, evidence of its approval by the institutional review board,
was not included in the submission.

Thirty-one (31) subjects were enrolled to ensure 24 evaluable subjects would complete the study, they were 19-34 years old consisted of 25 Caucasians, 4 Hispanics, and 2 blacks. The inclusion and exclusion criteria were:

Inclusion Criteria:

1. 18-35 years old women.
2. Weight within 15% of ideal weight.
3. Good health based on medical history, physical examination, abdominal and pelvic examination, and laboratory screen tests during pre-dose.
4. Negative hepatitis B and HIV-1 & HIV-2 tests.
5. Negative alcohol test and urine drug screen result.
6. Negative serum HCG pregnancy test and agreed to practice an effective means of birth control.
7. Normal values of SHBG and CBG.
8. Provided written informed consent.

Exclusion Criteria

1. Amenorrhea in the cycle preceding the first study cycle.
2. Intake of any investigation medication within 30 days prior to the first dose of study medication and during the course of the study.
3. Consumption of grapefruit-, xanthine-, or caffeine-containing products within 48 hours prior to each dose of study medication.
4. Intake of tobacco products within 90 days, oral

contraceptive within 60 days, prescription medication within 14 days, or OTC medication within 7 days prior to study drug administration and during the study.

5. Known hypersensitivity to the test product.
6. Being previously admitted to the same study.

Qualified subjects were instructed to notify the clinical team immediately following the onset of menses and were scheduled to receive study medications on day 2, 3, or 4 of menses. After an 10-hour fast, each subject received one of the following treatments:

Treatment A (Test Drug): Two Low-Ogestrel (EE/NG) tablets, 2 X 0.03 mg/0.3 mg, Searle lot #RCT 10242, lot size and potency not given.

Treatment B (Reference Drug): Two Lo/Ovral (EE/NG), tablets, 2 X 0.03 mg/0.3 mg, Wyeth-Ayerst lot #9958097, potency and expiration date not given.

Each treatment was taken with 240 mL of water. Subjects remained fasted for 4 hours. They were not allowed any fluid during the 1 hour before to 1 hour after drug administration except the 240 mL of water taken with the study drug.

Blood samples were obtained at 0, 0.5, 1, 1.25, 1.5, 1.75, 2, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36, and 48 hours post-dose. Plasma samples were prepared and stored at -70°C until shipped to Searle. It was stated in the protocol that the plasma samples would be assayed for plasma EE and NG.

The washout period was the time until the next menses and within 25-32 days unless approved by the medical monitor and the investigator.

Blood pressure and heart rate were monitored before dosing and at 5, 24, and 48 hours post-dose. Post-study treatment included physical examination and clinical laboratory tests. Blood and urine were also taken for the determination of baseline clinical laboratory parameters prior to each study drug administration.

Analytical Method:

This submission did not include any analytical information.

Results:

Among the 31 subjects enrolled, 24 completed the study without protocol violation or adverse events warranting discontinuation (subjects #23 discontinued during treatment A, period 1, due to pharyngitis). Subjects #17 & 23 completed only treatment A and subjects #10, 15, 20, 103, & 915 completed only treatment B; and that resulted in 26 subjects providing plasma samples from treatment A and 29 subjects from treatment B. However, the firm did not provide reasons why these subjects completed only 1 treatment (except that subject #23 had pharyngitis during treatment A).

During the study period, 24 subjects reported 88 adverse events, 31 during treatment A and 57 during treatment B. Nineteen (19) of these events were determined possibly related to test drug and 26 possibly related to reference drug. The nature of these events were nausea, vomiting, emesis, dysmenorrhea, menstrual cramps and disorder, metrorrhagia, rhinitis/cold, headache, rigors/cold sensation, muscle hypertonia, nasal congestion, abdominal pain, flatulence/bloating, delayed menses, pharyngitis, dyspepsia, conjunctivitis, dizziness, dry mouth, breast pain, pallor, sinus congestion, sweating, emotional lability, somnolence/drowsiness, syncope, and chest pain/chest pressure.

Four (4) subjects had concomitant medicine (nasal saline spray, acetaminophen, dexatrim, vitamin C, pseudoephedrine, zinc, Sudafed and penicillin) due to cold symptoms, headache, weight loss, sinus congestion, or streptococcus throat.

The mean and range of changes of vital signs from baseline to post-treatment were comparable between the 2 treatments as indicated below:

	Mean (Range) of change	
Parameter	Treatment A (n=26)	Treatment B (n=29)
Pulse Rate (bpm)	5.84	4.34

Systolic Pressure	2.08	4.21
Diastolic Pressure	0.16	-1.45

The results of pre- and post-treatment clinical laboratory tests indicated following statistically significant changes: decrease of alkaline phosphatase U/L), increase of chloride mmol/L), decrease of creatinine kinase U/L), decrease of eosinophils decrease of hematocrit decrease of hemoglobin g/dl), decrease of red blood cell L), decrease of phosphorus mmol/L), increase of SCBG umol/L), and decrease of gamma-glutamyl transferase U/L). However, the clinical significance of these changes and their possible effect on the outcome of the study were not discussed in the final report.

Although the analytical procedure and validation was not reported in this submission, the plasma concentrations of EE and NG were reported in both hard copy and diskette. Using the data diskette provided by the firm, the reviewer calculated the mean plasma concentrations and pharmacokinetic parameters of EE and NG at each sampling time point after both treatments. Results are presented in Figures 1&2 and Tables 1-4. The EE plasma concentrations of subject #910 were only measurable for 4 of the 18 time points in treatment A and 2 of the 18 time points in treatment B. In addition, the observed Tmax of this subject was adjacent to missing data points for both treatments. Therefore the EE data of subject #910 is deleted for following pharmacokinetic and statistical evaluation.

Table 1: ARITHMETIC MEAN OF PLASMA EE LEVELS (PG/ML) AND RATIOS OF MEANS --- 2 X 0.03 MG/0.3 MG of EE/NG, UNDER FASTING CONDITION --- (N=25 FOR TEST AND N=28 FOR REFERENCE EXCEPT WHEN INDICATED)

	TEST MEAN	SD	REF. MEAN.	SD	RATIO T/R
TIME HR					
0	0.00	0.00	0.00b	0.00	.
0.5	69.93	33.78	81.35	34.59	0.86
1	137.05	50.93	137.82	52.12	0.99
1.25	150.45	50.75	156.22	55.47	0.96
1.5	149.61	51.89	151.62	55.60	0.99
1.75	146.24a	43.11	151.88	55.74	0.96
2	139.42	42.52	143.94	51.85	0.97
4	100.35	26.19	94.36c	27.42	1.06
6	68.04	20.38	63.97	17.21	1.06
8	48.72a	15.15	45.55	13.23	1.07
10	40.29	12.41	38.28	11.87	1.05

12	37.21	13.18	34.19	9.98	1.09
15	28.83	9.95	26.95	8.41	1.07
18	24.17	7.87	23.56	6.94	1.03
24	17.07a	6.53	17.30	7.94	0.99
30	12.96	5.84	11.02c	4.32	1.18
36	10.46	4.66	21.47c	59.26	0.49
48	5.34	3.09	4.53	3.10	1.18

a = (n=24), b = (n=26), c = (n=27)

TABLE 2: PHARMACOKINETIC PARAMETERS OF EE FOR TEST AND REFERENCE PRODUCTS
- ARITHMETIC MEANS AND RATIOS OF MEANS -
--- 2 X 0.03 MG/0.3 MG of EE/NG, UNDER FASTING CONDITION ---
(N=25 FOR TEST AND N=28 FOR REFERENCE)

	TEST MEAN	SD	REF. MEAN	SD	RATIO T/R
PARAMETER					
AUCI (HR*PG/ML)	1598.03	452.95	1641.32	649.56	0.97
AUCT (HR*PG/ML)	1465.53	408.34	1510.41	632.17	0.97
CMAX (PG/ML)	160.54	46.07	177.54	66.56	0.90
KE	0.05	0.02	0.05	0.02	1.04
LAUCI	1536.62	---	1543.87	---	1.00
LAUCT	1411.67	---	1412.63	---	1.00
LCMAX	154.37	---	165.71	---	0.93
THALF	15.18	5.50	15.39	5.77	0.99
TMAX	1.60	0.55	2.69	6.54	0.60

Table 3: ARITHMETIC MEAN OF PLASMA NG LEVELS (PG/ML) AND RATIOS OF MEANS
--- 2 X 0.03 MG/0.3 MG of EE/NG, UNDER FASTING CONDITION ---
(N=26 FOR TEST AND N=29 FOR REFERENCE)

	TEST MEAN	SD	REF. MEAN.	SD	RATIO T/R
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	6640.60	3223.50	4633.32	2019.92	1.43
1	9163.54	2993.41	6518.50	1845.17	1.41
1.25	8893.42	2732.84	7514.07	2178.97	1.18
1.5	8587.35	2871.43	7475.48	2254.29	1.15
1.75	8297.86	3251.44	7606.05	2086.69	1.09
2	7397.60	2494.24	7375.14	1901.79	1.00
4	3735.01	1389.02	4056.00	1375.28	0.92
6	2434.13	1089.71	2480.55	849.38	0.98
8	1887.10	745.93	1918.06	621.59	0.98
10	1710.66	673.25	1682.87	565.91	1.02
12	1594.88	687.78	1550.88	456.03	1.03
15	1333.42	493.61	1363.09	389.66	0.98
18	1166.89	418.37	1193.19	383.05	0.98
24	1026.15	360.82	959.12	302.80	1.07
30	846.13	318.72	835.07	284.15	1.01
36	755.13	306.65	724.92	275.14	1.04
48	516.42	207.95	521.08	205.96	0.99

TABLE 4: PHARMACOKINETIC PARAMETERS OF NG FOR TEST AND REFERENCE PRODUCTS
- ARITHMETIC MEANS AND RATIOS OF MEANS -
--- 2 X 0.03 MG/0.3 MG of EE/NG, UNDER FASTING CONDITION ---
(N=26 FOR TEST AND N=29 FOR REFERENCE)

PARAMETER	TEST MEAN	SD	REF. MEAN	SD	RATIO T/R
AUCI (HR*PG/ML)	98508.29	32381.02	97025.78	31482.99	1.02
AUCT (HR*PG/ML)	75466.59	23639.38	72740.60	19197.02	1.04
CMAX (PG/ML)	10305.80	3130.80	8703.23	2134.49	1.18
KE	0.03	0.01	0.03	0.01	1.10
LAUCI	93479.38	---	92748.53	---	1.01
LAUCT	72100.40	---	70632.85	---	1.02
LCMAX	9827.36	---	8454.94	---	1.16
THALF	28.67	17.35	30.11	16.37	0.95
TMAX	1.32	0.66	1.55	0.30	0.85

The ratios of test to reference products of 3 major pharmacokinetic parameters for both EE and NG are presented in Tables 5-6:

TABLE 5: RATIOS OF TEST TO REFERENCE OF THREE MAJOR PHARMACOKINETIC PARAMETERS OF EE
--- 2 X 0.03 MG/0.3 MG of EE/NG, UNDER FASTING CONDITION ---

SUB	SEQ	AUCT	AUCI	CMAX
1	2	0.79	0.78	1.07
2	1	1.02	1.05	1.35
3	1	1.19	1.19	0.94
4	2	0.84	0.77	1.10
5	1	1.11	0.95	0.99
6	2	0.69	0.68	0.71
7	2	0.95	0.94	0.99
8	1	0.91	0.94	0.93
9	1	1.12	1.10	1.27
10	2	.	.	.
11	2	0.91	0.99	0.57
12	1	1.07	1.07	0.88
13	2	0.86	0.89	0.81
14	1	1.08	1.19	1.19
15	2	.	.	.
16	1	0.90	0.86	0.81
17	1	.	.	.
18	1	0.91	0.90	0.77
19	2	1.02	0.99	0.87
20	2	.	.	.
21	2	1.21	0.97	1.24
22	1	0.90	0.90	0.84
23	1	.	.	.
24	2	0.93	0.92	0.98
101	2	1.14	1.13	0.96
102	1	1.38	1.28	1.03
103	2	.	.	.
104	1	1.06	1.12	1.21
105	2	1.25	1.25	1.13
915	2	.	.	.
MEAN		1.01	0.99	0.98
N		23	23	23
MINIMUM				
MAXIMUM				

TABLE 6 RATIOS OF TEST TO REFERENCE OF THREE MAJOR PHARMACOKINETIC PARAMETERS OF NG
--- 2 X 0.03 MG/0.3 MG of EE/NG, UNDER FASTING CONDITION ---

SUB	SEQ	AUCT	AUCI	CMAX
1	2	1.05	1.12	1.43
2	1	0.97	0.77	1.06
3	1	1.07	0.93	1.33
4	2	1.17	1.07	1.49
5	1	0.90	0.86	0.91
6	2	0.99	0.92	0.96
7	2	0.89	0.89	1.12
8	1	0.94	0.83	0.72
9	1	1.20	0.97	1.27
10	2	.	.	.
11	2	1.16	1.18	1.48
12	1	0.95	0.91	1.38
13	2	1.04	1.30	1.15
14	1	0.70	0.69	0.89
15	2	.	.	.
16	1	0.78	0.40	0.90
17	1	.	.	.
18	1	0.84	0.75	1.25
19	2	1.16	1.17	1.12
20	2	.	.	.
21	2	0.70	0.76	0.89
22	1	0.96	0.94	1.49
23	1	.	.	.
24	2	0.86	0.84	1.52
101	2	0.95	0.96	1.28
102	1	1.36	1.32	1.58
103	2	.	.	.
104	1	0.93	1.13	0.47
105	2	1.04	1.05	1.09
910	2	1.13	1.08	1.33
915	2	.	.	.
MEAN		0.99	0.95	1.17
N		24	24	24
MINIMUM				
MAXIMUM				

The mean AUCT/AUCI ratio of EE was 0.92 (0.82-1.00) for treatment A and 0.92 (0.72-0.98) for treatment B; and the same ratio of NG was 0.79 (0.55-0.92) for treatment A and 0.76 (0.40-0.92) for treatment B.

Analysis of Variance was conducted by the reviewer on the untransformed and log-transformed data of AUCT, AUCI and CMAX. The model included sequence, subject within sequence, treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term with a 10% level of significance. The treatment and period effect were tested against the residual mean square error with a level of significance of 5%. No significant effects were detected for any of the parameters.

The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of reference product versus test product for both EE and NG are presented in Tables 7-8.

TABLE 7: LS MEANS (LSM), RATIOS, AND 90% CONFIDENCE INTERVALS (CI) OF EE --- 2 X 0.03 MG/0.3 MG of EE/NG, UNDER FASTING CONDITION --- (N=23)

PARAMETER	TEST LSM	REF.LSM	RATIO T/R	90% CI
AUCI (HR*PG/ML)	1633.08	1665.33	0.98	93.36 - 102.77
AUCT (HR*PG/ML)	1511.24	1523.75	0.99	94.42 - 103.94
CMAX (PG/ML)	168.14	177.95	0.94	87.89 - 101.08
LAUCI	1534.76	1566.79	0.98	93.00 - 103.17
LAUCT	1422.56	1428.04	1.00	94.37 - 105.15
LCMAX	160.49	166.65	0.96	89.73 - 103.37

TABLE 8: LS MEANS (LSM), RATIOS, AND 90% CONFIDENCE INTERVALS (CI) OF NG --- 2 X 0.03/0.3 MG of EE/NG, UNDER FASTING CONDITION --- (N=24)

PARAMETER	TEST LSM	REF.LSM	RATIO T/R	90% CI
AUCI (HR*PG/ML)	95107.23	101585.03	0.94	85.41 - 101.84
AUCT (HR*PG/ML)	73159.59	73944.48	0.99	93.33 - 104.55
CMAX (PG/ML)	10129.62	8756.20	1.16	106.10 - 125.27
LAUCI	89749.64	96871.42	0.93	85.59 - 100.29
LAUCT	69605.38	71291.13	0.98	92.35 - 103.23
LCMAX	9611.27	8477.63	1.13	103.30 - 124.43

Comments on *In Vivo* Bioequivalence Study:

1. The firm did not provide any information on the analytical study for the assay of EE and NG in human plasma.

2. The dose of EE/NG administered was twice the recommended daily dose. The clinical significance of changes in the results of pre- to post-study clinical laboratory tests and their possible effect on the outcome of the study was not discussed.

3. The evidence of approval of the study by an IRB was not provided.

4. The clinical study was conducted over a period of 7 months (11/8/96-6/1/97). The firm did not report the exact date of study drug treatment for each subject.

5. The potencies of test and reference drugs, the lot size of the test drug, and the expiration date of the reference drug were not reported.

6. Reason(s) for completing only one period of the study was not provided for the following subjects: subjects #10, 15, 17, 20, 103 & 915.

7. The pharmacokinetic parameters and the 90% confidence intervals calculated by the reviewer were mostly consistent with those reported by the firm.

8. The observed Tmax of NG for subject #19 during treatment A (period 2) was the first measurable time point of that period. The estimated Cmax of this subject during treatment A may not be as accurate as others. The data of subject #19 were excluded and ANOVA re-conducted by the reviewer. The results indicate significant difference between treatments for LNCmax (p=0.0395), however, the LS means and 90% confidence intervals presented below in Table 9 are within the acceptable range:

TABLE 9: LS MEANS (LSM), RATIOS, AND 90% CONFIDENCE INTERVALS (CI) OF NG --- 2 X 0.03/0.3 MG of EE/NG, UNDER FASTING CONDITION --- (N=23, DATA FROM SUBJECT #19 WERE EXCLUDED)

PARAMETER	TEST LSM	REF.LSM	RATIO T/R	90% CI
AUCI (HR*PG/ML)	94976.98	101899.30	0.93	84.74 - 101.68
AUCT (HR*PG/ML)	72937.95	74126.15	0.98	92.66 - 104.13
CMAX (HR*PG/ML)	10165.56	8747.66	1.16	106.29 - 126.13
LAUCI	89396.78	97125.06	0.92	84.84 - 99.86
LAUCT	69285.47	71427.10	0.97	91.66 - 102.66
LCMAX	9631.22	8463.12	1.14	103.35 - 125.32

***In Vitro* Dissolution Testing:**

Dissolution data provided by the firm are presented below in Table 10:

Table 10 - In Vitro Dissolution Testing

Drug (Generic Name): Ethinyl Estradiol/Norgestrel (Low-Ogestrel)
Dosage Form: Tablet
Dose Strength: 0.03 mg/0.3 mg
ANDA No.: 75-288
Firm:
Submission Date: 12/24/97

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 50 No. Units Tested: 12
Medium: 0.05 Mphosphate Buffer, pH 7.5 Volume: 900 mL
Tolerance: NLT % (Q) of norgestrel in 30 minutes
NLT % (Q) of ethinyl estradiol in 60 minutes
Reference Drug: Lo-Ovral Tablet (Wyeth Ayerst)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (minute)	Test Product Lot # PT-142-96 Strength (mg): 0.03/0.3 **Norgestrel**			Reference Product Lot # 9958097 Strength (mg): 0.03/0.3 **Norgestrel**		
	Mean %	Range	%CV	Mean %	Range	%CV
15	88		3	61		8
30	94		1	81		4
45	95		1	88		3
60	96		1	92		1
	Ethinyl Estradiol			**Ethinyl Estradiol**		
15	99		3	89		5
30	100		2	97		2
45	101		2	96		2
60	99		2	97		1

Comments on Dissolution Testing:

The lot number reported for the test product used in the *in vivo* bioequivalence study (#RCT10242) and that used in the *in vitro* dissolution testing (#PT-142-96) are different.

Overall Deficiencies:

1. The firm did not provide any information on the analytical study for the assay of EE and NG in human plasma.

2. The clinical study was conducted over a period of 7 months (11/8/96-6/1/97). The firm did not report the exact date of study drug treatment for each subject.

3. The evidence of approval of the study by an IRB was not provided.

4. The potencies of test and reference drugs, the lot size of the test drug, and the expiration date of the reference drug were not reported.

5. Reason(s) for completing only one period of the study was not provided for the following subjects: subjects #10, 15, 17, 20, 103 & 915.

6. The clinical significance of changes in the results of pre- to post-study clinical laboratory tests and their possible effect on the outcome of the study was not discussed

7. The components and composition of the test product were not provided.

8. The lot number reported for the test product used in the *in vivo* bioequivalence study (#RCT10242) and that used in the *in vitro* dissolution testing (#PT-142-96) are different. The same lot of test and reference products should be used in both *in vivo* and *in vitro* studies.

Recommendation:

1. The *in vivo* bioequivalence study conducted by G.D. Searle on its ethinyl estradiol/norgestrel tablet, 0.03 mg/0.3 mg (Low-Ogestrel tablet), lot #RCT10242, comparing to Lo/Ovral tablet (ethinyl estradiol/norgestrel tablet, 0.03 mg/0.3 mg), lot #9958097, manufactured by Wyeth Ayerst, has been found incomplete due to deficiencies #1-7.

2. The *in vitro* dissolution testing conducted by G.D. Searle on its ethinyl estradiol/norgestrel tablet, 0.03 mg/0.3 mg (Low-Ogestrel tablet), lot #PT-142-96 , comparing to Lo/Ovral tablet (ethinyl estradiol/norgestrel tablet, 0.03 mg/0.3 mg), lot #9958097, manufactured by Wyeth Ayerst, has been found incomplete due to deficiency #8.

/S/ 4/23/98

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG /S/ 4/24/98

Concur /S/ Date: 4/29/98
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