CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-256

BIOEQUIVALENCE REVIEW(S)

AUG 7 ...

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75256 APPLICANT: Duramed Pharmaceuticals

DRUG PRODUCT: Desogestrel (0.15 mg)/Ethinyl Estradiol (0.03 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. You should use the following dissolution method for the comparative dissolution testing:

Apparatus : USP II (paddle)
Medium : Water containing 0.05% sodium lauryl sulfate
900 ml Rotation Speed : 50 rpm
Temperature : 37 ± 0.5 degrees celsius

The dissolution testing should be conducted using 12 individual units of the bio-lots. The mean, percent coefficient of variation and range of the dissolution data should be reported.

2. The study was conducted in two separate groups. You should include the group effect in the statistical model and reanalyze the data.

Sincerely yours,

/S/

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

Desogestrel/Ethinyl Estradiol
0.15 mg/0.03 mg tablet
ANDA 75-256
Reviewer: Pradeep M. Sathe, Ph.D.
WP #75256SD.198

Duramed Pharmaceuticals
Cincinnati, Ohio-45243
Submission Date:
November 19, 1997
January 28, 1998

Review of an *In- Vivo* Bioequivalence Study and *In- Vitro* Dissolution (an electronic submission)

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Figures

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Background Information

Title

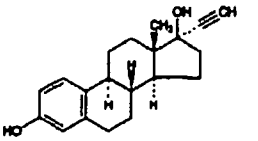
Comparative randomized, single-dose, 2-way crossover bioequivalence study of Duramed and Organon (Desogen®) 21) Tablets containing 150 micrograms desogestrel and 30 micrograms ethinyl estradiol in healthy adult females under fasting conditions.

Objective of the Study

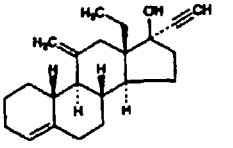
The objective of this study was to determine the bioequivalence of Desogestrel and Ethinyl Estradiol Tablets, manufactured by Duramed Pharmaceuticals, Inc., relative to the listed drug product, Desogen®, manufactured by Organon, in healthy, normal females under fasting conditions.

Chemistry

Ethinyl Estradiol is (17α)-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol. $C_{20}H_{24}O_2$. It has a molecular weight of 296.41.



Desogestrel is (17α)-13-Ethyl-11-methylene-18,19-dinorpregn-4-en-20-yn-17-ol. $C_{22}H_{30}O$. It has a molecular weight of 310.48.



Biochemistry

Ethinyl estradiol is the most orally active estrogenic drug. 3-Ketodesogestrel, the biologically active metabolite of desogestrel, has potent progestational activity and little or no androgenic activity. The combination of an estrogen and progestogen oral contraceptives suppress gonatrophins in females primarily by inhibiting ovulation. They also alter the cervic mucus, so that sperm entry into the uterus is made more difficult, and the endometrium, such that the likelihood of implantation is reduced.

Ethinyl estradiol is mainly metabolized by aromatic hydroxylation to form it major hydroxylated metabolite, 2-hydroxy-ethinyl estradiol. Ethinyl estradiol and its metabolites undergo glucuronide and sulfate conjugation and the glucuronide and sulfate conjugates undergo extensive enterohepatic circulation.
Desogestrel is extensively metabolized in the liver to 3-keto-desogestrel and other metabolites, in much lesser quantities. These other metabolites do not posses any pharmacologic activity.

Ethinyl estradiol and desogestrel are excreted in urine and feces, mainly as the glucuronide and sulfate conjugates of the drugs and their metabolites.

Background Information, Continued

Pharmaco-kinetics

Both estrogen and progestogen are rapidly absorbed from the gastrointestinal tract and undergo extensive first-pass metabolism. The relative bioavailability of ethinyl estradiol (EE) is about 83%. The kinetics of EE are linear. EE is about 98% plasma protein bound. Desogestrel is almost completely converted to 3-keto-desogestrel. The relative serum bioavailability of 3-keto-desogestrel is approximately 84%. 3-ketodesogestrel is about 64% bound to albumin. Since only the unbound fraction of oral contraceptive steroids is biologically active, the kinetics of 3-keto-desogestrel are non-linear when administered in combination with ethinyl estradiol.[1]

The expected mean pharmacokinetic parameters are listed in the following table and are based on a single tablet dose.[1] Based on these estimates, a 2-tablet dose was chosen for increased accuracy and precision and the last blood draw was scheduled at 120 hours. The washout of 28 days exceeds the usual 5 times half-life in order to minimize any influence of the woman's cycle on the study.

Expected Mean Parameters		
Pharmacokinetic Parameter	**3-Ketodesogestrel**	**Ethinyl Estradiol**
C_{max} (pg/mL)	3500 (CV % 19)	196 (CV% 38)
T_{max} (hours)	1.6 (CV% 38)	1.5 (CV% 27)
$T_{1/2}$ (hours)	38 (CV%)	26 (CV% 26)

Indications and Safety Considerations

Oral contraceptives are indicated for the prevention of pregnancy in women who elect this form of contraception. For this study, the primary safety concerns were the possible exposure to a fetus, if present and cardiovascular effects. Thus, a pregnancy test was performed prior to initiation of each period and an EKG was performed along with normal clinical laboratory profiles.

Strengths Available

Desogen® is available in tablets containing 150 micrograms Desogestrel and 30 micrograms Ethinyl Estradiol.

Dosage and Administration

Desogen® is available in two formats, either a 21-day or 28-day dispensing packet. The 28-day packet includes 21 tablets containing active and 7 tablets containing inert ingredients (placebo). The usual dose is one active tablet per day for 21 days followed either by no tablet (21-day pack) or placebo (28-day pack) for 7 days. However, in the event that 2 days on active tablet are missed, 2 tablets are to be administered for each of two days. Thus, the 2 tablet dose administered in this study is within the labeled administration schedule.

[1] Based on the data submitted in NDA for Desogen®

Study Conduct

Products Tested The test and reference preparations were:

Treatment	Preparation
A	Desogestrel and Ethinyl Estradiol Tablets, Lot C0024, Expiration Date: 03/99, Duramed Pharmaceuticals, Inc. Batch Size: [illegible] tablets, which, after sampling and processing yields, was entirely packaged in blister packs.
B	Desogestrel and Ethinyl Estradiol Tablets, Desogen®, Lot E551321, Expiration Date: 11/97, Organon.

Drug Product The following formulation compositions provide the per tablet and per batch quantities of the bio-batch and the production size batch

Component	**Per Tablet Calculated**		**Per Batch Measured**	
Tablet Core	bio-lot	production lot	bio-lot	production lot
Desogestrel	0.15 mg	0.15 mg		
Ethinyl Estradiol	0.03 mg	0.03 mg		
Lactose Monohydrate				
Pregelatinized Starch				
Vitamin E				
Povidone				
Alcohol				
Colloidal Silicon Dioxide				
Stearic Acid				
Total Theoretical Core Weight				
Color Coat				
[illegible] **02**				
[illegible]				
Clear Coat				
Total Theoretical Tablet Weight	**105.04 mg**	**105.04 mg**		

Study Conduct, Continued

Study Facility and Investigators

The clinical portion of this study and the pharmacokinetic and statistical analyses were performed by Inc. (U.S) at its facility at 45224. The principal investigator was

Clinical Design

This was an open-label, randomized, two period crossover study in healthy, normal females to compare the single dose bioavailability of Duramed and Organon Desogestrel and Ethinyl Estradiol Tablets under fasting conditions. Single, oral, 2 tablet doses were separated by a washout period of 28 days. Twenty-four (24) subjects were initially enrolled in the study (Subject Nos. 01-16, 18-21 and 23-26). Of these 24 subjects, 4 did not complete the crossover. Sixteen (16) additional subjects were enrolled (Subject Nos. 17, 22 and 27-40). Of these 16 subjects, 3 did not complete the crossover. See page 13 of this Summary for details of the seven subjects which did not complete the crossover. Thus a total of 33 subjects completed the crossover.

Period	# of Subjects (Start/Complete)	Dates
1	24/22	5/16/97 - 5/21/97
2	20/20	6/13/97 - 6/18/97
1'	16/16	6/13/97 - 6/18/97
2'	13/13	7/11/97 - 7/16/97

' = additional periods 1 and 2 for the 16 subjects dosed as a second group

Continued on next page

Study Conduct, Continued

Inclusion/ Exclusion Criteria

The following inclusion/exclusion criteria were used to qualify volunteer subjects for acceptance into the study:

Inclusion	Exclusion

• Healthy female of any race
• Menstruating
• Age 18-35
• Weight at least 45 kg and within 15% of ideal body weight
• No clinically significant abnormalities
• Normal clinical laboratory values and EKGs
• Able to understand and sign informed consent
	• History or presence of significant disease of the following systems
	  • cardiovascular
	  • pulmonary
	  • hepatic
	  • renal
	  • hematologic
	  • gastrointestinal
	  • endocrine
	  • immunologic
	  • dermatologic
	  • neurologic
	  • psychiatric
	  • neoplastic
	• History or presence of:
	  • alcoholism or drug abuse within past year
	  • hypersensitivity or idiosyncratic reaction to ethinyl estradiol, norethindrone (*sic*) or other hormonal agents
	• Subjects who are pregnant or lactating
	• Within 1 year of the start of study:
	– used a medroxyprogesterone acetate contraceptive injection
	• Within 3 months of the start of study:
	– used tobacco in any form
	• Within 28 days of the start of the study:
	– participated in a previous clinical trial
	– used pharmacologic agents known to significantly induce or inhibit drug-metabolizing enzymes
	– used an oral contraceptive containing estrogens, or any form of hormonal therapy
	– have been on an abnormal diet (for whatever reasons)
	• Within 7 days of the start of the study:
	– used medication (including OTC products), except vitamins used as nutritional supplements

Continued on next page

Study Conduct, Continued

Drug Administration

Volunteer subjects were randomized to receive the two treatments, test preparation (Treatment A) and reference preparation (Treatment B), during two different dosing periods. The two dosing sequences were AB and BA, where A is the test drug product and B is the reference drug product.

This was an open label study in which both the investigator and the volunteer subjects were able to distinguish whether the study medication was the test or the reference drug product. The study medication was dispensed in a manner so as to obscure the identity of the drug product to the volunteer subject.

Blood Collection

During each period, plasma samples were obtained from blood drawn into EDTA-containing tubes at 0 (pre-dose) and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48, 72, 96 and 120 hours after administration of the dose. The blood samples were centrifuged under refrigeration, the plasma collected and promptly frozen and stored at -12°C or lower and forwarded to ı for assay. See the for exceptions to draw times in excess of 2 minutes, which were incorporated into the pharmacokinetic and statistical analyses.

Period of Confinement

Subjects were admitted to the research center the evening prior to each dosing and were discharged after the 36-hour post-dose blood sample was obtained. Subjects returned for all subsequent blood draws. Subjects were discharged at the end of Period 2 following receipt of a post-study physical examination. There were 28 days between the start of each of the dosing periods.

Food and Fluid Restriction

Prior to each period there was an overnight fast of at least 10 hours. Water was consumed ad libitum except within 1 hour before and after dosing. Water at room temperature) was consumed at the time of dosing. Standard meals were provided at four (4) and nine (9) hours post-dose. No other food or beverage was allowed from 12 hours pre-dose until 4 hours post-dose. Meals plans were identical for all periods. See ,r exceptions which were judged insignificant.

Safety Assessments

Blood pressure (sitting) and heart (pulse) rate were measured before each dosing. The Investigator considered the measurements of all subjects clinically acceptable for dosing. Blood pressure and pulse rate measurements (sitting) were also obtained approximately 10 minutes prior to the blood draws at 1 and 2 hours after each dose. Measurements were repeated if clinically warranted.

A blood sample was collected during the 24 hours prior to dosing in Period 2 for a hematocrit and hemoglobin determination. All values were within the normal range.

Bioanalytical Methodology

Analytical Facility Investigator(s)

The bioanalytical portion of this study was performed in the laboratories of

Analytical Method Description

Ethinyl Estradiol and 3-Ketodesogestrel were determined separately, in two analytical studies, from different aliquots of plasma prepared at the clinical site.

Ethinyl Estradiol was determined by high resolution with The internal standard was e method is validated over a range of 2.00 - 399.20 pg/mL.

3-Ketodesogestrel was determined by with The internal standard was he method is validated over a range of 49.91 - 7985.61 pg/mL.

Sample accountability and storage conditions

Samples received from the clinical site were stored at a nominal -22°C for a maximum of 80 days for 3-Ketodesogestrel and 122 days for Ethinyl Estradiol prior to assay. The validated stability of plasma samples is 98 days (3-Ketodesogestrel) and 627 days (Ethinyl Estradiol). The following table indicates that all but one sample were analyzed for both analytes.

Source	Identity	# Samples
Theoretical (Protocol)	(36 subjects + 4 alternates) * 2 periods * 23 draws	1840
Dropouts	Subjects Nos. 7, 12, 13, 23, 33, 35, 36 7 subjects * 2 periods * 23 draws	322
Samples not received	Subject 14, 48 hr, period 2	1
Samples analyzable		1517
Samples analyzed		1517

Continued on next page

Bioanalytical Methodology, Continued

Pre-Study Assay
Validation

Page(s) 3

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

assay validation

Study Results

Subjects

The mean age of the 40 female subjects was 25.4 (Range: 18 - 35) comprising 5 African-Americans, 1 Hispanic and 34 Caucasians. All subjects gave written, informed consent prior to their entry into the study. Seven (7) subjects did not complete the crossover as follows:

Subject	Withdrew/Withdrawn	Period	Time	Reason
7	Withdrew	1	post 8hr draw	Blood draw discomfort
12	Withdrawn	1	post 0.75 hr draw	Difficult venous access
13	Withdrawn	1	6 d post dose	Out-of-range lab result
23	Withdrawn	2	before dosing	Positive pregnancy result
33	Withdrawn	1	7 d post dose	Adverse event
35	Withdrew	2	-1d pre-dose	Personal reasons
36	Withdrawn	2	before dosing	Positive pregnancy result

Per the Study Protocol, plasma samples were analyzed only for those subjects who completed the crossover. Thus, plasma samples for 33 subjects were analyzed for the 3-Ketodesogestrel and Ethinyl Estradiol concentrations which were incorporated in the pharmacokinetic and statistical analyses.

Adverse Events

No serious medical events were reported post-dose. The total number of reported events was 39 which are categorized in Table 5 and enumerated in Table 6. The full report of adverse events is presented in the :

Table 5

Summary of Adverse Events

Relationship to Study Drug Treatments					
Treatment	**Unlikely**	**Possibly**	**Probably**	**Definitely**	**Total**
Test	7	1	13	0	21
Reference	6	5	7	0	18
Totals	13	6	20	0	39

Continued on next page

Study Results, Continued

Table 6

Adverse Events

Subj	Drug	Adverse Event	Onset	End	Relationship	Treatment/ Comment
02	Test	Headache	5/16 @ 0630	5/17 @0700	Unlikely related to drug	Mild: back of head & neck
02	Test	Nausea	5/16 @ 2210	5/17 @ 0700	Possibly related to drug	Mild
02	Test	Started period early	5/22 @1230	5/27 @ 1200	Probably related to drug	Mild
02	Refer.	Headache /Nausea	6/13 @ 2300	6/14 @ 0500	Probably related to drug	Moderate: vomited 6/14 @ 0321
03	Refer.	Lightheaded	5/16 @ 0703	5/16 @ 0718	Unlikely related to drug	Placed in reclined position
03	Refer.	Nausea	5/16 @ 0919	5/16 @ 0922	Possibly related to drug	Placed in reclined position
05	Refer.	Headache	6/11 @ 1000	6/13 @ 0600	Unlikely related to drug	Given dinner
07	Test	Headache	5/16 @ 0630	5/17 @ 2000	Unlikely related to drug	lay down w/cold towel
07	Test	Nausea	5/16 @ 1800	5/16 @ 2030	Probably related to drug	lay down w/cold towel
09	Refer.	Bruise on left inner thigh	5/17 @ 1850	5/20 @ 1400	Probably related to drug	Mild
11	Refer.	Lightheaded	5/16 @ 1123	5/16 @ 1125	Unlikely related to drug	Placed in reclined position
13	Test	Headache	5/16 @ 1026	5/16 @ 1115	Probably related to drug	Mild
13	Test	Nausea	5/16 @ 1110	5/16 @ 1216	Probably related to drug	Mild
13	Test	Dizzy	5/16 @ 1205	5/16 @ 1216	Probably related to drug	Moderate
13	Test	Vomiting (x3)	5/16 @ 1214	5/16 @ 1216	Probably related to drug	Moderate
13	Test	Bruise on rt. buttock	5/16 @ 1700	5/20 @ 1400	Probably related to drug	Not painful
15	Test	Nausea	5/16 @ 1810	5/16 @ 2030	Probably related to drug	Mild; placed cold rag on head
15	Refer.	Nausea	6/13 @ 1810	6/13 @ 2200	Probably related to drug	Moderate
17	Refer.	Rt hand swollen	6/13 @ 1016	6/14 @ 1300	Unlikely related to drug	Mild; 2° to catheter and keeping arm straight
17	Refer.	Lightheaded	6/14 @ 2001	6/14 @ 2010	Unlikely related to drug	Mild; 2° to blood draw; placed in reclined position
18	Test	Nausea	5/16 @ 1430	5/16 @ 1525	Probably related to drug	Mild; laid down after blood draw

Continued on next page

Study Results, Continued

Adverse Events (continued)

Subj	Drug	Adverse Event	Onset	End	Relationship	Treatment/ Comment
18	Test	Vaginal itching	5/26 @ unk	6/4 @ unk	Unlikely related to drug	Mild: symptom stopped after discontinuing soap
20	Test	Headache	5/16 @ 0915	5/16 @ 1155	Probably related to drug	Mild
20	Test	Darting pain in rt lower quadrant ("Rt ovary")	5/16 @ 1300	5/16 @ 2200	Probably related to drug	Mild
20	Test	Pulsing pain in rt. lower quadrant	5/16 @ 2330	5/17 @ 0000	Probably related to drug	Mild
20	Test	Congestion	6/09 @ 0800	6/09 @ 2200	Unlikely related to drug	Mild: on 6/09 @ 1615 took 1 x 60 mg pseudephedrine 2.5 mg triprolidine
21	Refer.	Sick to stomach	5/16 @ 1006	5/16 @ 1010	Probably related to drug	Mild
23	Test	Lightheaded	5/16 @ 0752	5/16 @ 0803	Unlikely related to drug	Mild: associated w/ blood draw; placed in reclined position
24	Refer.	Headache	5/16 @ 1730	5/17 @ 0700	Possibly related to drug	Mild
24	Refer.	Nausea	5/16 @ 1730	5/17 @ 0700	Possibly related to drug	Moderate
24	Refer.	Diarrhea	5/16 @ 2015	5/16 @ 2015	Possibly related to drug	Mild
24	Refer.	Headache	5/20 @ 0700	5/22 @ 0300	Possibly related to drug	Mild: took 1 x Midrin at 5/20 @ 1100 & 5/20 @ 11:30
24	Test	Vomited/Rash	6/13 @ 2255	6/13 @ 2340	Probably related to drug	Mild
26	Test	Cough	6/13 @ 0800	6/15 @ 1200	Unlikely related to drug	Mild: subject states she gets a seasonal cough each year); chamomile teas w/ two 9g packs of honey

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Study Results, Continued

Adverse Events (continued)

Subj	Drug	Adverse Event	Onset	End	Relationship	Treatment/ Comment
31	Refer.	Menstrual spotting	6/12 @ 2130	6/15 @ unk	Probably related to drug	Mild: menstruation started 1.5 weeks early
33	Refer.	Rash on arms, legs, hands	6/14 @ 0929	7/09 @ 0850	Probably related to drug	Moderate: Initial diagnosis: poison ivy; Benadryl lotion (dose NR) 6/14 @ 1100; 50 mg Diphedryl 6/18 @ 0845; Hydrocortisone cream 1% at 6/17 @ 1330, 1800, 2200 and 6/18 @ 0345; Prednisone 2 x 100 mg for 7 days (6/19 - 25);Prednisone 2 x 10 mg for 3 days (7/2-4) and 1 x 10 mg for 3 days (7/5-7)
34	Test	Cramps	6/26 @ 1500	6/26 @ 2300	Unlikely related to drug	Moderate: Tylenol 2 x 500 mg 6/26 @ 1500 & 2100
34	Refer.	Fainted during blood draws	7/11 @ 0738	7/11 @ 0750	Unlikely related to drug	Moderate; placed in reclined position
36	Refer.	Breakthrough menstrual bleeding	6/13 @ 1300	6/17 @ 0800	Probably related to drug	Mild

Continued on next page

Study Results, Continued

Concentration-Time Data

The mean plasma concentration data for 3-Ketodesogestrel are plotted for each time period in Figures 1 and 2. On the next page, in Table 7, these same data are tabulated along with a statistical significance test. Only minor differences are found near the T_{max}. Similarly, the mean time-plasma concentration data for Ethinyl Estradiol is presented Figures 3 and 4 (page 19) and tabulated in Table 8 (page 20).

Figure 1

Mean Plasma 3-Ketodesogestrel Concentrations (Semi-Log Plot)

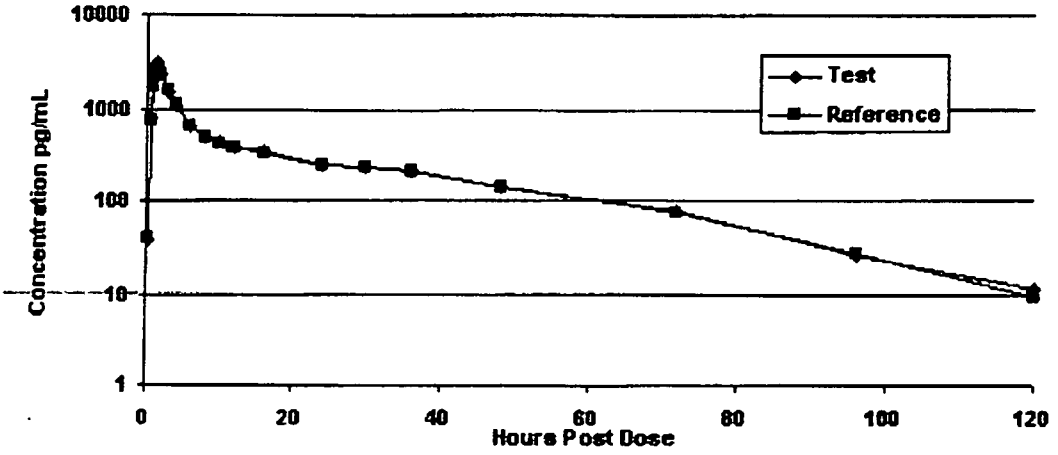
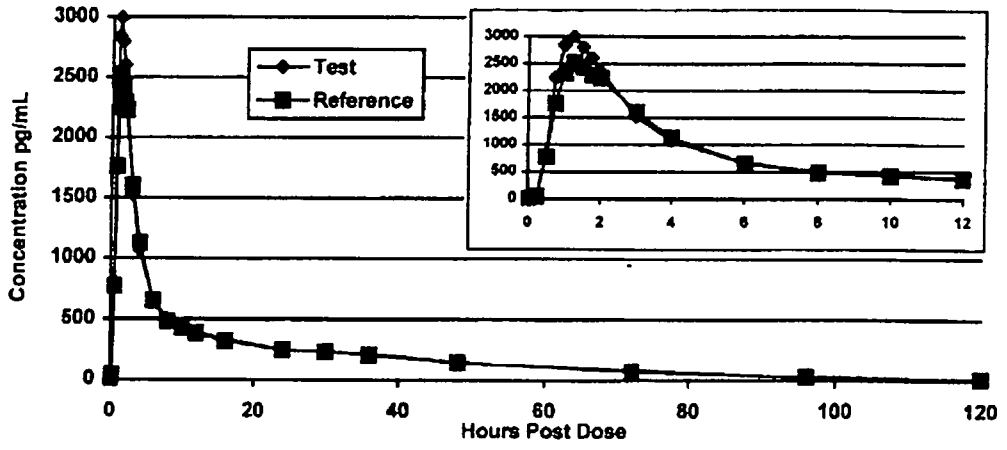


Figure 2

Mean Plasma 3-Ketodesogestrel Concentrations (Linear Plot)



Study Results, Continued

Table 7

Mean Plasma Concentrations (pg/mL) of 3-Ketodesogestrel Following a 2 x 1 Tablet Dose of Desogestrel and Ethinyl Estradiol Tablets Under Fasting Conditions (N=33)

Collection Time (Hr)	Least Square Means (pg/mL)		Statistical Significance
	Test	Reference	
0	0.000	0.000	-
0.25	38.382	40.99	NS
0.5	806.428	771.237	NS
0.75	2233.590	1758.007	0.0204 A > B
1	2837.196	2327.714	0.0021 A > B
1.25	2996.074	2525.530	0.0006 A > B
1.5	2796.499	2438.963	0.0021 A > B
1.75	2598.913	2289.301	0.0066 A > B
2	2342.242	2227.376	NS
3	1521.819	1599.435	NS
4	1068.705	1128.161	NS
6	659.321	647.547	NS
8	499.467	481.297	NS
10	445.329	426.919	NS
12	386.124	382.143	NS
16	336.820	321.104	NS
24	249.092	245.232	NS
30	231.096	232.339	NS
36	214.370	206.427	NS
48	141.131	142.193	NS
72	79.423	73.115	NS
96	25.824	28.147	NS
120	11.126	9.345	NS

NS= Not significant at the p = 0.05 level

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Study Results, Continued

Figure 3

Mean Plasma Ethinyl Estradiol Concentrations (Semi-Log Plot)

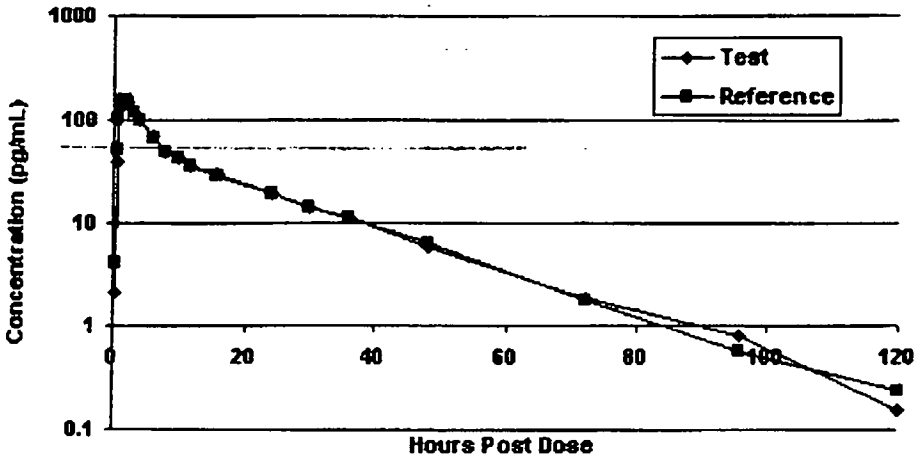
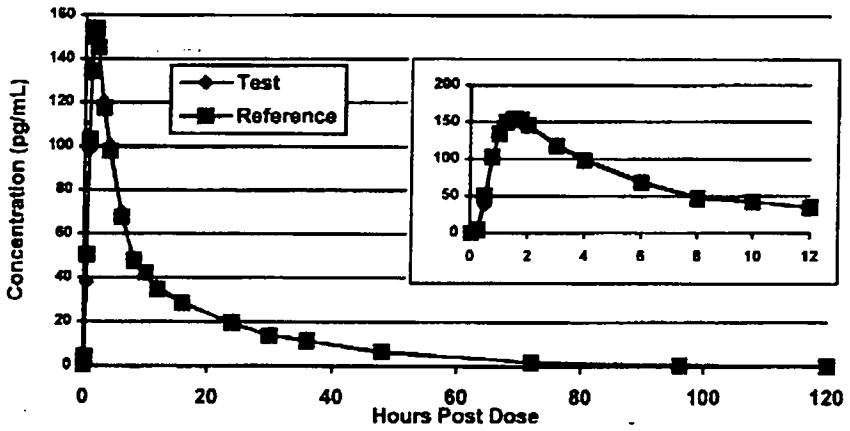


Figure 4

Mean Plasma Ethinyl Estradiol Concentrations (Linear Plot)



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Study Results, Continued

Table 8

Mean Plasma Concentrations (pg/mL) of Ethinyl Estradiol Following a 2 x 1 Tablet Dose of Desogestrel and Ethinyl Estradiol Tablets Under Fasting Conditions (N=33)

Collection Time (Hr)	Least Square Means (pg/mL)		Statistical Significance
	Test	Reference	
0	0.000	0.000	NS
0.25	2.187	4.260	NS
0.5	38.016	50.408	0.0160 A < B
0.75	98.388	103.086	NS
1	133.066	134.571	NS
1.25	151.565	150.234	NS
1.5	151.285	154.166	NS
1.75	148.841	153.703	NS
2	146.462	145.121	NS
3	120.161	117.247	NS
4	100.294	97.632	NS
6	69.871	67.712	NS
8	48.949	47.732	NS
10	42.105	42.113	NS
12	35.883	35.071	NS
16	29.173	28.369	NS
24	19.054	19.483	NS
30	14.100	13.899	NS
36	11.397	11.404	NS
48	6.077	6.693	NS
72	1.878	1.785	NS
96	0.810	0.555	NS
120	0.156	0.234	NS

NS= Not significant at the p = 0.05 level

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Pharmacokinetic & Statistical Analysis

Pharmacokinetic Analysis

All of the available data from 33 subjects with reported 3-Ketodesogestrel concentrations were used in the pharmacokinetic analyses except for Subject 24, Period 2, test preparation at the 48 hour time point. This point was omitted from both the statistical and pharmacokinetic analyses since it was flanked by concentrations more than 122% higher.

Pharmacokinetic parameters were calculated using the actual rather than the scheduled times of sample collection. Graphical presentations of mean results used the scheduled times of sample collection.

Peak concentration (Cmax) was the observed maximum value during the collection period of 0 to 120 hours. The time to peak concentration (Tmax) was the time at which Cmax was observed (or first observed, if more than one peak was present).

The apparent first-order elimination rate (K_{el}) was estimated as the absolute value of the slope of the regression line for the terminal log-linear concentration-time values. The values included in the regression analyses were determined by examination of the individual subject plots of the natural log of concentration against time. The elimination half-life was calculated as $0.693/K_{el}$.

Analysis of Variance

ANOVA was performed on untransformed $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, T_{max}, k_{el} and $T_{1/2}$. Additionally, log-transformed data were used for the analysis of $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max}. The ANOVA model included sequence, subjects nested within sequence, period and treatment as factors. The significance of the sequence effect was tested using subjects nested within sequence as the error term. Firm's statistical analysis was varified by the reviewer.

Confidence Intervals and Ratio Analysis

Consistent with the two one-sided test for bioequivalence[2], 90% confidence intervals for the difference between drug formulation least-square means (LSM) were calculated for both the untransformed and log-transformed $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max}. The confidence intervals are expressed as a percentage relative to the LSM of the reference formulation.

Ratios of means were calculated using the LSM for untransformed and log-transformed $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max}. The geometric mean values are reported for log-transformed parameters. Ratios of means are expressed as a percentage of the LSM for the reference formulation.

Continued on next page

[2] Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm* 1987(15): 657-80.

Pharmacokinetic & Statistical Analysis, Continued

Table 9

Pharmacokinetic Parameters of 3-Ketodesogestrel Following a 2 x 1 Tablet Dose of Desogestrel and Ethinyl Estradiol Tablets Under Fasting Conditions (N=33)

Parameter	Test Mean*	Reference Mean*	Test/Reference Ratio	90% Confidence Interval	Statistical Significance**
$AUC_{(0-t)}$ hr•pg/mL	24215.2	23202.8	104.4	100.2 - 108.5	0.0823
$AUC_{(0-\infty)}$ hr•pg/mL	27193.0	26468.0	102.7	98.5 - 106.9	0.2761
C_{max} (pg/mL)	3293.66	2911.72	113.1	105.9 - 120.3	0.0042
T_{max} (hr)	1.308	1.721	-	-	-
K_{el} (hr^{-1})	0.0269	0.0251	-	-	-
$T_{1/2}$ (hr)	28.759	31.045	-	-	-
ln $AUC_{(0-t)}$	22414.2	21696.6	103.3	90.0 - 107.8	0.2026
ln $AUC_{(0-\infty)}$	25342.3	24961.2	101.5	97.7 - 105.5	0.5125
ln C_{max}	3156.67	2771.54	113.9	105.9 - 122.5	0.0048

*For ln-transformed parameters, the antilog of the mean (i.e., the geometric mean) is reported. Note: AUC_{0-inf}, kel and $T_{1/2}$ could not be estimated for certain subjects. See Tables 1 & 2 for exceptions.
**p-value (ANOVA)

Table 10

Pharmacokinetic Parameters of Ethinyl Estradiol Following a 2 x 1 Tablet Dose of Desogestrel and Ethinyl Estradiol Tablets Under Fasting Conditions (N=33)

Parameter	Test Mean*	Reference Mean*	Test/Reference Ratio	90% Confidence Interval	Statistical Significance**
$AUC_{(0-\infty)}$ hr•pg/mL	1671.029	1663.291	100.5	97.3 - 103.6	0.0813
$AUC_{(0-t)}$ hr•pg/mL	1596.514	1585.270	100.7	97.6 - 103.8	0.6990
C_{max} (pg/mL)	164.085	167.452	98.0	94.0 - 101.9	0.3953
T_{max} (hr)	1.759	1.659	-	-	-
K_{el} (hr^{-1})	0.0466	0.0459	-	-	-
$T_{1/2}$ (hr)	16.060	16.442	-	-	-
ln $AUC_{(0-t)}$	1485.31	1483.35	100.1	97.0 - 103.4	0.9447
ln $AUC_{(0-\infty)}$	1561.00	1564.07	99.8	96.7 - 103.0	0.9159
ln C_{max}	154.318	157.838	97.8	93.3 - 102.5	0.4202

*For ln-transformed parameters, the antilog of the mean (i.e., the geometric mean) is reported. Note: AUC_{0-inf}, kel and $T_{1/2}$ could not be estimated for certain subjects. See *rt*, Tables 3 & 4 for exceptions
**p-value (ANOVA)

Conclusion

Conclusion of Study

The area under the concentration-time curves (AUC) were similar for the test (Duramed) and reference (Organon) preparations for both 3-Ketodesogestrel and Ethinyl Estradiol. The 90% confidence intervals for the mean ratio of the logarithmic transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within 80% to 125%.

The test preparation, therefore, is bioequivalent to the reference drug preparation under fasting conditions in accordance with bioequivalence criteria established by the FDA.

Summary of In Vitro Testing

Dissolution Method

The subject product, Desogestrel and Ethinyl Estradiol Tablets, is a non-compendial item and thus, a dissolution method was developed for this product. Duramed Pharmaceuticals, Inc. has applied the following dissolution method during development of the test preparation as well as to characterize both the test and reference preparations prior to the bioequivalence study. A full description of the method and a validation report is provided in the Appendix.

USP Apparatus:	USP Method II, Paddle
Medium:	500 mL of degassed, deionized water containing 0.3% sodium dodecyl sulfate
Rotation Speed:	100 rpm
Detection:	

Individual Dissolution Results

Dissolution profile results for individual tablets (N=12) for both the test and reference preparation are presented in Table 11 on the following page.

Continued on next page

Summary of In Vitro Testing, Continued

Table 11

Dissolution Profile of Desogestrel and Ethinyl Estradiol in Desogestrel and Ethinyl Estradiol Tablets Using the Proposed Dissolution Method

Percent Desogestrel Dissolved						
	Test Preparation (Lot C0024)			Reference Preparation Lot E551321		
Tablet	10 min.	20 min.	30 min.	10 min.	20 min.	30 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12	97.5					
Mean	97.5	97.3	97.5	85.8	100.4	100.9
% RSD	2.3	2.5	3.1	17.8	1.1	1.7

Percent Ethinyl Estradiol Dissolved						
	Test Preparation Lot C0024			Reference Preparation Lot E551321		
Tablet	10 min.	20 min.	30 min.	10 min.	20 min.	30 min.
1						
2						
3	1					
4						
5	1					
6	1					
7	1					
8	1					
9						
10						
11						
12	100.5					
Mean	99.8	100.1	100.2	85.6	100.3	100.8
% RSD	1.8	2.2	2.2	17.6	0.8	1.0

Continued on next page

Summary of In Vitro Testing, Continued

Proposed Dissolution Specifications

Duramed Pharmaceuticals, Inc. proposes to use the following L_1 dissolution limits for the Duramed Desogestrel and Ethinyl Estradiol Tablets:

Sampling Time (Minutes)	Proposed Limits (% Label)

Product Analysis: Assay & Content Uniformity

The two drug treatments (test and reference products) were analyzed prior to the start of the bioequivalence study. Both assay and content uniformity results, presented in Table 12, indicate that the drug content of the two drug treatments did not differ by more than 5%. Individual content uniformity results are presented in Table 13.

Table 12

Results Obtained for Assay and Content Uniformity of Both the Test and Reference Preparations Prior to the Bioequivalence Study

	Test Preparation (Duramed) Lot C0024		Reference Preparation (Organon) Lot E551321	
Desogestrel				
Assay %	99.3		100.6	
Content Uniformity	Mean %	RSD %	Mean %	RSD %
	100.1	1.9	96.9	2.9
Ethinyl Estradiol				
Assay %	99.3		101.6	
Content Uniformity	Mean %	RSD %	Mean %	RSD %
	96.7	2.0	101.3	1.5

Continued on next page

Summary of In Vitro Testing, Continued

Individual content uniformity results

Table 13

Individual Content Uniformity Results for Desogestrel and Ethinyl Estradiol in Desogestrel and Ethinyl Estradiol Tablets

	Desogestrel		Ethinyl Estradiol	
Tablet	**Duramed Lot C0024**	**Organon Lot E551321**	**Duramed Lot C0024**	**Organon Lot E551321**
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17		92.4		
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				
Mean	100.1	96.9	96.7	101.3
Maximum	104.1	103.6	101.0	105.6
Minimum	96.6	92.4	93.8	98.4
%RSD	1.9	2.9	2.0	1.5

DIVISION COMMENTS :

1. Currently the Orange Book lists RW Johnson's ORTHO-CEPT (Desogestrel/Ethinyl Estradiol 0.15mg/0.03 mg, 21 day regimen) as the Reference Listed Drug. Desogen, was the RLD as per the Orange Book in 1995. The 1996 Orange Book does not list RLD for this combination product. The firm has clarified this issue with the OGD and obtained concurrence for the use of Desogen in these studies. The orange book does not list any other generic formulation besides the one being reviewed, implying that this formulation if approved may be considered as a first generic.

2. The study was conducted using two separate groups. The firm has not reported whether the group effect was studied.

3. The firm's proposed dissolution testing method using 500 ml of degassed, deionized water containing 0.3% sodium dodecyl sulfate, at 100 rpm speed of USP apparatus II (paddle), may not be acceptable. The firm should use the following dissolution method and specifications for the comparative dissolution testing:

Apparatus : USP II (paddle)
Medium : 500 ml water containing 0.05% sodium lauryl sulfate
Rotation Speed : 50 rpm
Temperature : 37 degrees celsius

4. The labelling information does not mention the dosing in relation to food precluding the requirement of a 'food challenge' scenario of the bioequivalence assessment.

DEFICIENCIES:

1. The firm should use the following dissolution method and specifications for the comparative dissolution testing:

Apparatus : USP II (paddle)
Medium : Water containing 0.05% sodium lauryl sulfate
Volume : 500 ml
Rotation Speed : 50 rpm
Temperature : 37 $\pm$ 0.5 degrees celsius

The dissolution testing should be conducted using 12 individual units of the bio-lots. The mean, percent coefficient of variation and range of the dissolution data should be reported.

2. The study was conducted in two separate groups. The firm should include the group effect in the statistical model and reanalyze the data.

RECOMMENDATIONS:

1. The bioequivalence study conducted by Duramed Pharmaceuticals on its Desogestrel/Ethinyl Etsradiol 0.15 mg/0.03 mg tablet, **Lot C0024**, comparing it to Organon's Desogen Desogestrel/Ethinyl Etsradiol 0.15 mg/0.03 mg tablet, **Lot E551321** has been found incomplete by the Division of Bioequivalence. The firm should submit additional data as suggested in Deficiencies 1-2.

/S/ 8/7/98
Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY YCHUANG
FT INITIALED BY YCHUANG 7/28/98

Concur: Date: 8/4/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75256 APPLICANT: Duramed Pharmaceuticals

DRUG PRODUCT: Desogestrel (0.15 mg)/Ethinyl Estradiol (0.03 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. You should use the following dissolution method for the comparative dissolution testing:

Apparatus : USP II (paddle)
Medium : Water containing 0.05% sodium lauryl sulfate
900 ml Rotation Speed : 50 rpm
Temperature : 37 $\pm$ 0.5 degrees celsius

The dissolution testing should be conducted using 12 individual units of the bio-lots. The mean, percent coefficient of variation and range of the dissolution data should be reported.

2. The study was conducted in two separate groups. You should include the group effect in the statistical model and reanalyze the data.

Sincerely yours,

/S/

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

CC:

Endorsements: (Draft and Final with Dates)
HFD-652/Reviewer (P.Sathe) 7/28/98
HFD-652/Bio Team Leader (YCHuang)
HFD-617/Project Manager (Sanchez)
HFD-650/Dale Conner 8/4/98

Path and File Name x:\new\firmsam\duramed\ltr&rev\75256sd.198
BIOEQUIVALENCY - DEFICIENCIES Submission Dates:
1. **FASTING STUDY** (STF) Strengths: 0.15 mg/0.03 mg Desogestrel/Ethinyl Estradiol

Clinical: F **Outcome: IC**
Analytica

WinBio Comments: Application deficient and incomplete.

AUG 7 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75256 APPLICANT: Duramed Pharmaceuticals

DRUG PRODUCT: Desogestrel (0.15 mg)/Ethinyl Estradiol (0.03 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. You should use the following dissolution method for the comparative dissolution testing:

Apparatus : USP II (paddle)
Medium : Water containing 0.05% sodium lauryl sulfate
900 ml Rotation Speed : 50 rpm
Temperature : 37 ± 0.5 degrees celsius

The dissolution testing should be conducted using 12 individual units of the bio-lots. The mean, percent coefficient of variation and range of the dissolution data should be reported.

2. The study was conducted in two separate groups. You should include the group effect in the statistical model and reanalyze the data.

Sincerely yours,

/S/

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

DURAmed

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The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

November 24, 1998

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA [illegible] AMENDMENT
AB

RE: **ANDA #75-256 Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg**
Subject **BIOEQUIVALENCE AMENDMENT**

Dear Dr. Conner:

Reference is made to your correspondence dated August 7, 1998 from the Division of Bioequivalence concerning deficiencies in our abbreviated new drug application (ANDA) #75-256 for Desogestrel/Ethinyl Estradiol Tablets. Reference is also made to a September 1, 1998 telephone call between Dr. Nerurkar and Duramed requesting an expanded dissolution investigation.

We have noted the deficiencies cited and are amending the application, having responded to all of the deficiencies. For each item we first restate the deficiency then present our response or explanation.

This amendment is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

RECEIVED
NOV 25 1998
GENERIC DRUGS

MAR 4 1999

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-256 APPLICANT: Duramed Pharmaceuticals

DRUG PRODUCT: Desogestrel/Ethinyl Estradiol, 0.15 mg/0.03 mg tablet

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

1. Your problem relates to the solubility of Desogestrel. The information available to the Agency, pertaining to the dissolution of the innovator's product indicates that the Division recommended dissolution method has been successfully used in the past. It is suggested that you may try to dissolve Desogestrel using a suitable organic solvent and retry the comparative dissolutions using the Division specified method and specifications.

2. The statistical model mentioned by you includes the 'Group' as a factor. The model however does not include the 'Sequence' as a factor. In the opinion of the Division statistician, the model should have used 'Sequence' as a factor in assessing the 'Group' effect. Please clarify this issue.

Sincerely yours,

/S/

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

Desogestrel/Ethinyl Estradiol
0.15 mg/0.03 mg tablet
ANDA 75-256
Reviewer: Pradeep M. Sathe, Ph.D.
W# 75256O.N98

Duramed Pharmaceuticals
Cincinnati, Ohio-45243
Submission Date:
November 24, 1998

Review of an Amendment

Background

The firm had submitted an application (as electronic submission) on January 28, 1998. The application consisted of a single dose crossover fasting study conducted using two sub-groups and dissolution data comparing the test product with the reference Organon's Desogen[R] Desogestrel/Ethinyl Etsradiol 0.15 mg/0.03 mg tablet. The firm had proposed the following dissolution method and specifications for its product:

Dissolution Method

The subject product, Desogestrel and Ethinyl Estradiol Tablets, is a non-compendial item and thus, a dissolution method was developed for this product. Duramed Pharmaceuticals, Inc. has applied the following dissolution method during development of the test preparation as well as to characterize both the test and reference preparations prior to the bioequivalence study. A full description of the method and a validation report is provided in the Appendix.

USP Apparatus:	USP Method II, Paddle
Medium:	500 mL of degassed, deionized water containing 0.3% sodium dodecyl sulfate
Rotation Speed:	100 rpm
Detection:	

Proposed Dissolution Specifications

Duramed Pharmaceuticals, Inc. proposes to use the following L_1 dissolution limits for the Duramed Desogestrel and Ethinyl Estradiol Tablets:

Sampling Time (Minutes)	Proposed Limits (% Label)

The application was found to be incomplete and the Division conveyed deficiencies to the firm. In the current application, the firm has responded to the deficiencies. The Deficiencies, Firm's Responses and Division's Comments to Firm's Responses are given in that order.

DEFICIENCIES:

"1. The firm should use the following dissolution method and specifications for the comparative dissolution testing:

Apparatus: USP II (paddle)
Medium: Water containing 0.05% sodium lauryl sulfate (SLS)
Volume: 500 ml
Rotation Speed: 50 rpm
Temperature: 37 ± 0.5 degrees Celsius

The dissolution testing should be conducted using 12 individual units of the bio-lots. The mean, percent coefficient of variation and range of the dissolution data should be reported.

2. The study was conducted in two separate groups. The firm should include the group effect in the statistical model and reanalyze the data".

Subsequently, in a telephone conversation on 09/01/98, the Division asked the firm to conduct dissolutions using either 0.1% or 0.3% SLS, at 50 and 75 rpm in up to 900 ml using the paddle apparatus, if desogestrel cannot be dissolved using 0.05% SLS.

FIRM'S RESPONSES:

The firm's responses are listed in the same order as that of deficiencies:

1.

	Paddle Speed

2. The firm states that "the data has been reanalyzed to include the group effect". Specifically, the firm used the following statistical model to analyze the data:

Response Y = Group Subject(Group) Period(Group) Formulation Formulation*Group

Of these, Subject(Group) was a random effect and the remaining were fixed effects, on data pooled from these two groups.

The ANOVA generated the following 'P' values for the (formulation*Group) term, corresponding to various bioequivalence parameters.

values for the (formulation*Group) term, corresponding to

3-Keto-Desogestrel

*(Formulation*Group) for PK parameter*	*P-Value*
LAUCt	**0.2485**
LAUCinf	**0.5882**
Lcmax	**0.8734**

Ethinyl Estradiol

*(Formulation*Group) for PK parameter*	*P-Value*
LAUCt	**0.3600**
LAUCinf	**0.4356**
Lcmax	**0.7009**

DEFICIENCY COMMENTS:

1. The firm's problem relates to the solubility of Desogestrel. The in-house information pertaining to the dissolution of the innovator's product indicates that the Division recommended dissolution method has been successfully used in the past. It is suggested that the firm may try to dissolve Desogestrel using a

suitable organic solvent and retry the comparative dissolutions using the Division specified method and specifications.

2. The statistical model stated by the firm includes the 'Group' as a factor. The model however does not include the 'Sequence' as a factor. In the opinion of the Division statistician, the model should have used 'Sequence' as a factor in assessing the 'Group' effect. The firm should clarify this issue.

RECOMMENDATION:

1. Deficiency Comments 1 and 2 should be forwarded to the firm.

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

1/25/1999

RD INITIALED BY SGNERURKAR
FT INITIALED BY SGNERURKAR

Concur: /S/

Date: 2/16/99

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

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-256 APPLICANT: Duramed Pharmaceuticals

DRUG PRODUCT: Desogestrel/Ethinyl Estradiol, 0.15 mg/0.03 mg tablet

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

1. Your problem relates to the solubility of Desogestrel. The information available to the Agency, pertaining to the dissolution of the innovator's product indicates that the Division recommended dissolution method has been successfully used in the past. It is suggested that you may try to dissolve Desogestrel using a suitable organic solvent and retry the comparative dissolutions using the Division specified method and specifications.

2. The statistical model mentioned by you includes the 'Group' as a factor. The model however does not include the 'Sequence' as a factor. In the opinion of the Division statistician, the model should have used 'Sequence' as a factor in assessing the 'Group' effect. Please clarify this issue.

Sincerely yours,

/S/

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

CC:

Endorsements: (Draft and Final with Dates)
HFD-655/Reviewer (P.Sathe) 1/25/99
HFD-655/Bio Team Leader (SG Nerurkar)
HFD-617/Project Manager
HFD-650/Dale Conner 2/16/99

1/25/99

Path and File Name: (X:\NEW\FIRMSAM\DURAMED\LTRS&REV\75256O.n98)
BIOEQUIVALENCY - DEFICIENCIES Submission Date: 11/24/98

1. **STUDY AMENDMENT** (STA) Strengths: 0.15 mg/0.03 mg Desogestrel/Ethinyl Estradiol
Outcome: IC

WinBio: Application has two deficiencies.

Table 3

Comparison of Individual Tablet Dissolution Results for Desogestrel @ 50 rpm
Bio-batch C-0024 vs. Innovator RD 8333

	C-0024			RD 8333		
	10	20	30	10	20	30
Tablet	min	min	min	min	min	min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	88.9	94.1	93.2	83.9	104.5	102.0
SD	9.298	6.625	3.468	18.423	9.377	3.830
RSD	10.5	7.0	3.7	22.0	9.0	3.8
High	111.9	114.1	101.9	122.8	123.9	111.9
Low	72.3	89.9	89.1	55.3	93.3	97.3

Table 4
Comparison of Individual Tablet Dissolution Results for Desogestrel @ 75 rpm
Bio-batch C-0024 vs. Innovator RD 8333

	C-0024			RD 8333		
	10	20	30	10	20	30
Tablet	min	min	min	min	mir	min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	94.7	94.2	94.2	90.2	100.4	101.6
SD	5.079	4.058	2.489	15.818	2.109	1.557
RSD	5.4	4.3	2.6	17.5	2.1	1.5
High	107.1	104.8	98.6	101.2	103.6	104.8
Low	89.1	89.8	90.2	53.4	96.7	99.4

Table 5

Comparison of Individual Tablet Dissolution Results for Ethinyl Estradiol @ 50 rpm
Bio-batch C-0024 vs. Innovator RD 8333

	C-0024			RD 8333		
	10	20	30	10	20	30
Tablet	min	min	min	min	min	min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	96.7	101.9	102.7	77.8	101.0	101.8
SD	5.211	1.742	2.061	14.086	1.396	1.472
RSD	5.4	1.7	2.0	18.1	1.4	1.4
High	100.9	104.2	105.8	96.4	102.5	104.5
Low	82.9	98.2	99.5	51.9	98.4	100.2

Table 6
Comparison of Individual Tablet Dissolution Results for Ethinyl Estradiol 75 rpm

Bio-batch C-0024 vs. Innovator RD 8333

	C-0024			RD 8333		
	10	20	30	10	20	30
Tablet	min	min	min	min	min	min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	100.6	101.7	101.6	91.4	101.8	102.3
SD	1.169	1.761	1.580	16.978	1.300	1.436
RSD	1.2	1.7	1.6	18.6	1.3	1.4
High	102.6	106.1	105.0	102.4	103.2	105.3
Low	98.7	99.3	99.2	53.7	99.3	100.2

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The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

AB

April 21, 1999

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-256 Desogestrel and Ethinyl Estradiol Tablets, 0.15 mg/0.03 mg
Subject BIOEQUIVALENCE AMENDMENT

Dear Dr. Conner:

Reference is made to your correspondence dated August 7, 1998 and March 4, 1999 from the Division of Bioequivalence concerning deficiencies in our abbreviated new drug application (ANDA) #75-256 for Desogestrel/Ethinyl Estradiol Tablets. Reference is also made to an April 16, 1999 telephone call between Drs. Nerurkar and Sanchez and Duramed. In this telephone call, Dr. Nerurkar requested that we submit a diskette containing the bioequivalence information with the Group assignment for each subject. Previously, Dr. Nerurkar had indicated that deficiency # 2 in the March 4, 1999 letter would be addressed by the Division. This diskette is designed to facilitate calculation of the Group effect.

Also in this telephone call Duramed presented new information regarding the dissolution testing (deficiency #1 in the March 4, 1999 deficiency letter). In the August 7, 1998 deficiency letter, the Division recommended that Duramed revise its dissolution test to be the same as that used by sponsor of the listed drug product, Ortho-Cept. In our Amendment of November 24, 1998 we presented evidence that desogestrel is not sufficiently soluble in the proposed media of 900 ml of 0.05% sodium lauryl sulfate. Dr. Nerurkar indicated in the telephone call that he is investigating this apparent discrepancy within the Agency. In an attempt to provide additional supporting dissolution data, we recently performed dissolution testing on the listed drug product, Ortho-Cept. The purpose of this investigation was to demonstrate the effect of the low solubility of desogestrel in the proposed media. Maximum dissolution of 40.4% of the labeled amount of desogestrel was attained (see attached Table1). For comparison, at the same time we also performed dissolution testing on the bio-batch. Results similar to those obtained for Ortho-Cept were obtained (Table 2 attached). This new information confirms that the dissolution conditions

proposed in the August 7, 1998 deficiency letter are inappropriate for either our product or the listed reference drug product. It can be seen from the percent of ethinyl estradiol released in Tables 1 & 2 that complete disintegration of the tablets was achieved. The low results for desogestrel reflect incomplete solubility of this active drug substance in 900 ml of 0.05% sodium lauryl sulfate. Based on this new evidence, we urge that the Division reconsider its proposed dissolution conditions and accept our proposed ANDA dissolution conditions.

This amendment is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy. A diskette is contained in both copies.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Encl. Form 365h

Desogestrel/Ethinyl Estradiol
0.15 mg/0.03 mg tablet
ANDA 75-256
Reviewer: Pradeep M. Sathe, Ph.D.
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Duramed Pharmaceuticals
Cincinnati, Ohio-45243
Submission Date:
April 21, 1999

Review of an Amendment

Background:

The firm had submitted an application (as electronic submission) on January 28, 1998. The application consisted of a single dose crossover fasting study conducted using two sub-groups and dissolution data comparing the test product with the reference Organon's Desogen[R] Desogestrel/Ethinyl Etsradiol 0.15 mg/0.03 mg tablet. The firm had proposed the following dissolution method and specifications for its product:

USP Apparatus:	USP Method II, Paddle
Medium:	500 mL of degassed, deionized water containing **0.3%** sodium dodecyl sulfate
Rotation Speed:	**100 rpm**
Detection:	

Sampling Time (Minutes)	Proposed Limits (% Label)

The application was found to be incomplete with respect to statistical analysis and dissolution. The Division conveyed deficiencies to the firm. The firm was asked to use the following FDA dissolution method

Apparatus: USP II (paddle)
Medium: Water containing **0.05%** sodium lauryl sulfate (SLS)
Volume: 500 ml
Rotation Speed: **50 rpm**
Temperature: 37 + 0.5 degrees Celsius

In an amendment dated November 24, 1998, the firm responded to these deficiencies. The amendment was found to be incomplete by the Division. In the current amendment, the firm has provided 1) the diskette containing new statistical analysis and 2) information stating that it cannot dissolve the desogestrel component using the FDA dissolution method (Attachment I).

COMMENTS:

1. The Division has conducted an "in-house" statistical analysis of the provided plasma level data for 3-keto-desogestrel and ethinyl estradiol. The analysis is provided in Attachment II. As per the analysis no "group" effect was noticed and based on the 90% confidence interval results, the test and reference product could be considered bio-equivalent. The summary results, using the Division recommended model are shown in the following Tables. Units: AUC: hr*pg/ml, Cmax: pg/ml, Tmax, T1/2: hr.

3-Keto-Desogestrel

Pharmacokinetic Parameter	**Test Product**	**Reference Product**	**90% Confidence Interval**
LnAUCt, *Geometric Mean	9.9934, 21881.6*	9.9639, 21245.5*	98.8-107.4
~~LnAUCinf,~~ *Geometric Mean	~~10.1213,~~ 24867.1*	~~10.1062,~~ 24494.4*	97.7-105.5
LnCmax, *Geometric Mean	8.0581, 3159.3*	7.9306, 2781.1*	105.5-122.3
Tmax	1.308	1.721	
T1/2	28.7	31.0	

Intra-Subject %CV's: LnAUCt: 10.0% LnAUCinf: 8.7% LnCmax: 17.5%

Ethinyl-Estradiol

Pharmacokinetic Parameter	**Test Product**	**Reference Product**	**90% Confidence Interval**
LnAUCt, *Geometric Mean	7.2894, 1464.7*	7.2909, 1466.9*	96.8-103.0
LnAUCinf, *Geometric Mean	7.3412, 1542.6*	7.3448, 1548.1*	96.6-102.8
LnCmax, *Geometric Mean	5.0409, 154.6*	5.0705, 159.3*	93.2-101.1
Tmax	1.759	1.659	
T1/2	16.1	16.4	

Intra-Subject %CV's: LnAUCt: 7.4% LnAUCinf: 7.0% LnCmax: 9.7%

2. The firm was asked to conduct the dissolution testing as per the method used by the innovator. The Division is in touch with the Chemistry Divisions regarding the evaluation of the provided dissolution data. **Until the Chemistry evaluates the descrepancy regarding desogestrel dissolution, the firm's proposed method and specifications may be used as an interim dissolution method and specifications. (Dissolution testing data from earlier review is provided in Attachment III).**

3. Attachment IV is a memorandum from a supervisory chemist in the Northeast regional laboratory. This report identifies a difficulty in dissolution testing of desogestrel from the RLD.

RECOMMENDATIONS:

1. The bioequivalence study conducted by Duramed Pharmaceuticals on its Desogestrel/Ethinyl ~~Estradiol, 0.15 mg/0.03 mg tablet, lot #~~ C0024, comparing it to Desogen[R] Desogestrel/Ethinyl Estradiol, 0.15 mg/0.03 mg tablet (Lot # E551321 by Organon), has been found acceptable by the Division of Bioequivalence. The study demonstrates that Duramed's Desogestrel/Ethinyl Estradiol, 0.15 mg/0.03 mg tablet, is bioequivalent to the reference product Desogen[R] Desogestrel/Ethinyl Estradiol, 0.15 mg/0.03 mg tablet manufactured by Organon.
2. For the evaluation of the dissolution issue, the application should be forwarded to the Chemistry Division.
3. Until the Chemistry Division evaluates the discrepancy of Desogestrel dissolution, the firm's proposed dissolution method and specification may be used in the interim.
4. The following ***interim dissolution testing method*** should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of degassed, deionized water containing **0.3%** sodium dodecyl sulfate at 37°C using USP Apparatus II, (Paddle) at **100 rpm**. The test product should meet the following specifications:

~~[illegible] dissolved in 30 minutes.~~

5. From the bioequivalence point of view, the firm has met the requirements of in-vivo bioequivalence and the application is acceptable.

/S/ 5/14/99
Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch II.

/S/ 5/17/99

RD INITIALED BY SGNERURKAR
FT INITIALED BY SGNERURKAR

Concur: /S/ Date: 5/26/99
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA 75-256 (original, duplicate), HFD-650 (Director), HFD-652 (Sathe), Division File, Drug File.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-256 APPLICANT: Duramed Pharmaceuticals

DRUG PRODUCT: 0.15 mg/0.3 mg Desogestrel/Ethinyl Estradiol Tablet

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

The following ***interim*** 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 0.3% Sodium Lauryl Sulfate, at 37° C using USP Apparatus II (paddle) at 100 rpm. The test product should meet the following specifications:
>
> and Ethinyl estradiol in the dosage form are dissolved in 30 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,

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

CC:

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Printed in final on 05/05/99

Endorsements: (Final with Dates)
HFD-655/ Reviewer (P.Sathe)
HFD-655/ Bio team Leader (SG Nerurkar)
HFD-650/ D. Conner for NM /S/

BIOEQUIVALENCY - ACCEPTABLE submission date: April 21, 1999

1. **STUDY AMENDMENT** (STA) ✓ Strengths: 0.15 mg/0.3 mg Tablet
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments:
Bio-study acceptable. Dissolution interim. Application approved based on bio-equivalence study.

CC:

e)

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Printed in final on 05/05/99

Endorsements: (Final with Dates)
HFD-655/ Reviewer (P.Sathe) 5/14/99
HFD-655/ Bio team Leader (SG Nerurkar)
HFD-650/ D. Conner

BIOEQUIVALENCY - ACCEPTABLE submission date: April 21, 1999

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Bio-study acceptable. Dissolution interim. Application approved based on bio-equivalence study.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-256 APPLICANT: Duramed Pharmaceuticals

DRUG PRODUCT: 0.15 mg/0.3 mg Desogestrel/Ethinyl Estradiol Tablet

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

The following ***interim*** 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 0.3% Sodium Lauryl Sulfate, at 37° C using USP Apparatus II (paddle) at 100 rpm. The test product should meet the following specifications:

[redacted]
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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-256 SPONSOR: Duramed Pharmaceuticals

DRUG AND DOSAGE FORM: **Desogestrel/Ethinyl estradiol tablet**

STRENGTH(S): 0.15 mg/0.3 mg

TYPES OF STUDIES: Single Dose fasting study

CLINICAL STUDY SITE(S):

ANALYTICAL SITE(S):

STUDY SUMMARY: Fasting study results acceptable

DISSOLUTION: **Dissolution INTERIM and acceptable until finalized by the agency**

DSI INSPECTION STATUS

Inspection needed: YES	Inspection status:	Inspection results:
First Generic Possible New facility _____ For cause _____ Other _____	Inspection requested: (date) 5/11/99 Inspection completed: (date)	

PRIMARY REVIEWER: Pradeep M. Sathe, Ph.D. BRANCH: II

INITIAL: /S/ _____ DATE: 5/14/99

TEAM LEADER: Shrinivas G. Nerurkar, Ph.D. BRANCH: II

INITIAL: /S/ DATE: 5/17/99

for DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.

INITIAL: /S/ _____ DATE: 5/26/99