F. Human Pharmacokinetics and Bioavailability Summary, Continued

Table 5

Comparative Dissolution of Cenestin™ 1.25- and 2.5 mg Tablets

Cenestin™ 1.25 mg Tablets, Lot C-0015 (Biobatch)

Tablet	Percent Sodium Estrone Sulfate Released			
	2 Hours	5 Hours	8 Hours	10 Hours
Mean	40.4	75.0	92.5	97.5
Max				
Min				
%RSD	4.7	3.2	1.8	1.4

Cenestin™ 2.5 mg Tablets, Lot S-0006

Tablet	Percent Sodium Estrone Sulfate Released			
	2 Hours	5 Hours	8 Hours	10 Hours
Mean	33.6	70.9	90.2	95.9
Max				
Min				
%RSD	5.4	2.1	1.6	1.7

Continued on next page

Attachment I

	Cenestin™ Tablets Comparative Dissolution: F2 Calculations Mean Percent Sodium Estrone Sulfate Released			
	2 Hour	5 Hour	8 Hour	F2
0.625 mg, C-0005 (Reference)	40.3	74.6	90.7	N/A
0.3 mg, X-0323	37.5	73.9	93.9	79
0.9 mg, X-0335	43.5	79.3	95.5	68
1.25 mg, C-0015	40.4	75.0	92.5	92
2.5 mg, S-0006	33.6	70.9	90.2	67

MAR 2 3 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
NDA:	**20992 (BB)**
Compound:	Synthetic Conjugated Estrogens, A (Cenestin™)
Sponsor:	Duramed Pharmaceuticals, Inc.
Type of Submission:	New Drug Product
Date of Submission:	December 8, 1998 (amendment)
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.

Addendum to the January 27, 1999 Review

Background

On January 27, 1999, a review was performed for a submission dated December 8, 1998 that provided in vitro sodium equilin sulfate dissolution data for the 0.3, 0.625, and 0.9 mg strength Cenestin™ tablets. In the January 27, 1999 review, it is also noted that the Sponsor withdrew the 1.25 and 2.5 mg strength Cenestin™ tablets.

This document is an addendum to the January 27, 1999 review to address the following:

1. To better clarify a specific statement in the review's Recommendation section.

2. To revisit the dissolution specifications as stated in the reviews dated December 4, 1998 (sodium estrone sulfate) and January 27, 1999 (sodium equilin sulfate) for the 0.3, 0.625, and 0.9 mg strength Cenestin™ tablets, in light of the recent decision of not approving the 0.3 mg strength Cenestin™ tablet by the Division of Reproductive and Urologic Drug Products (DRUDP).

Clarification of the Recommendation Section of January 27, 1999 review:

Currently the January 27, 1999 review states the following:

"The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the 2 amendments of NDA 20992 dated December 8, 1998 and December 9, 1998. OCPB/DPEII is of the opinion that the sponsor has provided appropriate information to satisfy the BA and BE waiver requirements in 21 CFR 320.22 for Cenestin™ 0.3, 0.625, and 0.9 mg strength tablets."

For clarification, the above statements should be replaced with the following:

"The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the 2 amendments of NDA 20992 dated December 8, 1998 and December 9, 1998. OCPB/DPEII is of the opinion that the sponsor has provided appropriate information to satisfy the bioavailability requirements (21 CFR 320) for the 0.3, 0.625, and 0.9 mg strength Cenestin™ tablets."

Reassessment of the Dissolution Specifications Based on the In Vitro Dissolution Data for the 0.625 and 0.9 mg Strength Cenestin™ Tablets

Since only the 0.625 and 0.9 mg strength Cenestin™ tablets will be approved by DRUDP, the following in vitro dissolution method and specifications are recommended, which are modified from the recommendations in the reviews dated December 4, 1998 and January 27, 1999.

Method:

The recommended in vitro dissolution method for both sodium estrone sulfate and sodium equilin sulfate is

Specifications:

The dissolution specifications for the 0.625 and 0.9 mg strength Cenestin™ tablets should be:

Time, hour	Sodium Estrone Sulfate, % dissolved	Sodium Equilin Sulfate, % dissolved
2		
5		
8		

Note: The above Method and Specifications have been conveyed to the Sponsor via a telephone conference on March 15, 1999.

S.W. Johnny Lau, R.Ph., Ph.D.

Ameeta Parekh, Ph.D. 3/23/99

Final Draft
John Hunt

cc: NDA 20992, HFD-870 (M. Chen, J. Hunt, A. Parekh, S.W.J. Lau), HFD-580 (T. van der Vlugt, D. Moore), CDR (B. Murphy for Drugs)

JAN 27 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	**20992 (BB)**
Compound:	Synthetic Conjugated Estrogens (Cenestin™)
Sponsor:	Duramed Pharmaceuticals, Inc.
Type of Submission:	New Drug Product
Date of Submissions:	December 8, 1998 (amendment)
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.

Background:

The sponsor submitted this 505 (b)(2) NDA on March 27, 1998 for oral synthetic conjugated estrogens (Cenestin™) to treat postmenopausal symptoms. Five Cenestin™ tablet strengths (0.3, 0.625, 0.9, 1.25, and 2.5 mg) were proposed for approval in this NDA. The sponsor claimed that Cenestin™ has 3 primary estrogenic substances (sodium estrone sulfate, sodium equilin sulfate, and sodium 17 α-dihydroequilin sulfate) and 6 minor estrogens. The sponsor submitted an amendment on December 8, 1998 to include the in vitro dissolution data and f_2 analysis for sodium equilin sulfate for Cenestin™ 0.3, 0.625, and 0.9 mg strength tablets. On December 9, 1998, the sponsor submitted another amendment to withdraw Cenestin™ 1.25 and 2.5 mg strength tablets for approval in NDA 20992.

Summary:

1. Cenestin™ 0.625 and 0.3 mg strength tablets were studied in the pivotal clinical study (2x0.625, 1x0.625, and 1x0.3 mg strength tablets).

2. The sponsor requested a bioavailability (BA) and bioequivalence (BE) study waiver for Cenestin™ 0.3, 0.9, and 2.5 mg strength tablets.

3. The formulation composition of Cenestin™ 0.3, 0.625, and 0.9 mg strength tablets are proportionally similar. The formulation composition of Cenestin™ 1.25 and 2.5 mg strength tablets are also proportionally similar but different from that of Cenestin™ 0.3, 0.625, and 0.9 mg strength tablets.

4. The to-be-marketed Cenestin™ 0.3 mg strength tablet is green-colored. Whereas the clinically-tested 0.3 mg strength tablet is red-colored. This color change is to maintain blinding for the clinically-tested 0.625 mg strength tablet, which is red-colored. The green- and red- colored 0.3 mg strength tablets are the same in formulation composition and processing.

5. Only in vitro dissolution data for sodium estrone sulfate for all 5 strength tablets were provided in the original NDA.

6. During a telephone conference on December 4, 1998, the sponsor was requested to provide the in vitro comparative dissolution data for sodium equilin sulfate for the to-be-marketed Cenestin™ 0.3, 0.625, and 0.9 mg strength tablets. In support of the color change for the to-be-marketed 0.3 mg strength tablet, in vitro comparative dissolution data for sodium equilin sulfate for the clinically-tested (red-colored) and to-be-marketed (green-colored) 0.3 mg strength tablets are also needed.

7. In the same telephone conference, the sponsor was notified that the 1.25 and 2.5 mg strength tablets do not meet the BA and BE waiver requirements in 21 CFR 320.22. This decision is based on that the proposed to-be-marketed 1.25 and 2.5 mg strength tablets are not compositionally similar to the to-be-marketed 0.3, 0.625, 0.9 mg strength tablets. Moreover, Cenestin™ 1.25 and 2.5 mg strength tablets were not clinically tested.

8. The f_2 for clinically-tested lots of 0.625 and 0.3 mg strength tablets to the to-be-marketed lot of 0.625 mg strength tablet as well as the f_2 for the to-be-marketed lots of 0.3 and 0.9 mg strength tablets to the to-be-marketed lot of 0.625 mg strength tablet were all within 57.4 and 96.1. The f_2 for the clinically-tested lot of 0.3 mg strength tablet to the to-be-marketed lot of 0.3 mg strength tablet was 69.6. These data demonstrated similar sodium equilin sulfate dissolution profiles between the to-be-marketed 0.3, 0.625, and 0.9 mg strength tablets. (See Attachment for sodium equilin sulfate dissolution data.)

Cenestin™ Strength Tablets	f_2	f_2
to-be-marketed 0.625 mg	reference	
clinically-tested 0.625 mg	70.9	
to-be-marketed 0.3 mg (green)	57.4	reference
clinically-tested 0.3 mg (red)	72.5	69.6
to-be-marketed 0.9 mg	96.1	

9. The sponsor proposed that the dissolution requirements for sodium estrone sulfate and sodium equilin sulfate to be the same. Therefore, the proposed in vitro dissolution method for sodium equilin sulfate is USP Method I, 50 rpm, 900 ml deaerated purified water at 37+/-0.5°C.

10. Per the original NDA submission, the proposed sodium estrone sulfate dissolution limit at 5 hours is and not as stated in the December 8, 1998 amendment.

11. Per the December 8, 1998 amendment, the proposed dissolution limits for sodium equilin sulfate follow:

Time (hours)	Cenestin™ 0.3, 0.625, 0.9 mg Strength Tablets
2	
5	
8	

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the 2 amendments of NDA 20992 dated December 8, 1998 and December 9, 1998. OCPB/DPEII is of the opinion that the sponsor has provided appropriate information to satisfy the BA and BE waiver requirements in 21 CFR 320.22 for Cenestin™ 0.3, 0.625, and 0.9 mg strength tablets. The sponsor's proposed in vitro dissolution method is acceptable. However, the in vitro dissolution specifications for sodium equilin sulfate for Cenestin™ 0.3, 0.625, and 0.9 mg strength tablets should be and not less than at 2, 5, and 8 hours, respectively.

S.W. Johnny Lau, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

FT signed by Ameeta Parekh, Ph.D., Team Leader 1/27/99

cc:
NDA 20992, HFD-870 (M. Chen, A. Parekh, S.W.J. Lau), HFD-580 (T. van der Vlugt, D. Moore), CDR (B. Murphy for Drugs)

Attachment

Individual Dissolution Data for Equilin

LOT#C-0005

0.625 mg NDA bioavailability lot

SAMPLE	2HR	5HR	8HR
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean %	41.2	77.4	93.3
SD %	5.9	2.6	1.6
High %	44.6	80.0	95.5
Low %	37.2	73.9	91.0

LOT# 94850

0.625 mg pivotal clinical trial lot

SAMPLE	2HR	5HR	8HR
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean %	35.6	74.4	94.0
SD %	7.5	3.4	2.4
High %	40.4	78.2	97.5
Low %	31.5	70.6	90.2

Attachment

Individual Dissolution Data for Equilin

LOT#X-0328
0.3 mg NDA submission lot

SAMPLE	2HR	5HR	8HR
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean %	34.0	68.5	89.1
SD %	9.2	3.6	2.9
High %	40.2	72.0	92.3
Low %	28.4	64.4	83.4

LOT#C-0034
0.3 mg pivotal clinical trial lot

SAMPLE	2HR	5HR	8HR
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean %	36.6	73.8	92.5
SD %	11.5	4.4	4.1
High %	46.2	78.7	100.4
Low %	32.0	66.8	86.3

Attachment

Individual Dissolution Data for Equilin

LOT#X-0335
0.9 mg NDA submission lot

SAMPLE	2HR	5HR	8HR
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean %	42.1	76.9	92.8
SD %	4.1	2.4	2
High %	44.0	79.8	97.0
Low %	38.7	74.1	90.4

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10:29 AM

Attachment

CALCULATION OF f_2 VALUES (Similarity Factor) [1]

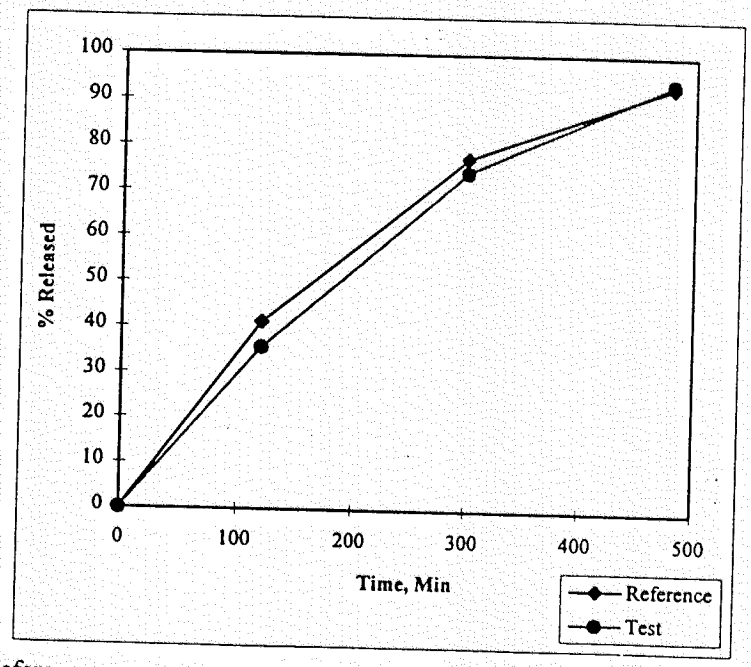
Reference C-0005 Product: Conjugated Estrogens Tablet, USP
Test: 94850 Component: Equilin

Time	R_t	T_t	$R_t - T_t$	$(R_t - T_t)^2$
120	41.2	35.6	5.60	31.36
300	77.4	74.4	3.00	9.00
480	93.3	94.0	0.70	0.49
Sum	211.90	204.00	9.30	40.85
n	3			

$f_1 = [(\text{sum} \mid R_t - T_t \mid) / (\text{sum } R_t)] \times 100$

$f_2 = 50 \times \log\{[1 + (1/n) \text{ sum } (R_t - T_t)^2]^{-0.5} \times 100\}$

f1 =	4.4
f2 =	70.9



Reference:

1. J. W. Moore and H. W. Flanner, Pharm. Tech., 1996, *20(6)*, 64-74.

F2CALC.XLS
12/8/98
11:16 AM

Attachment

CALCULATION OF f_2 VALUES (Similarity Factor) [1]

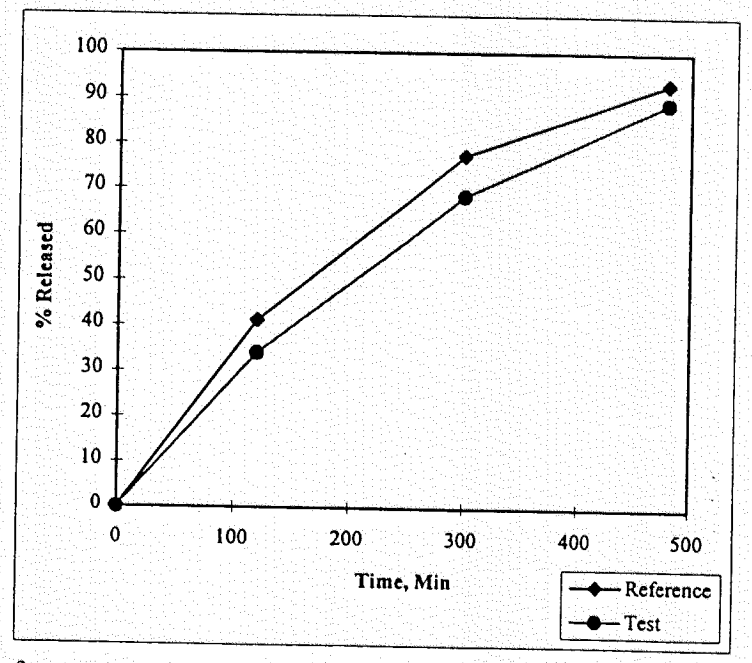
Reference C-0005 Product: Conjugated Estrogens Tablet, USP
Test: X-0328 Component: Equilin

Time	R_t	T_t	$R_t - T_t$	$(R_t - T_t)^2$
120	41.2	34.0	7.20	51.84
300	77.4	68.5	8.90	79.21
480	93.3	89.1	4.20	17.64
Sum	211.90	191.60	20.30	148.69
n	3			

$f_1 = [(\text{sum} \mid R_t - T_t \mid) / (\text{sum } R_t)] \times 100$

$f_2 = 50 \times \log\{[1 + (1/n) \text{ sum } (R_t - T_t)^2]^{-0.5} \times 100\}$

f1 =	9.6
f2 =	57.4



Reference:

1. J. W. Moore and H. W. Flanner, Pharm. Tech., 1996, *20(6)*, 64-74.

F2CALC.XLS
12/8/98
11:15 AM

Attachment

CALCULATION OF f_2 VALUES (Similarity Factor) [1]

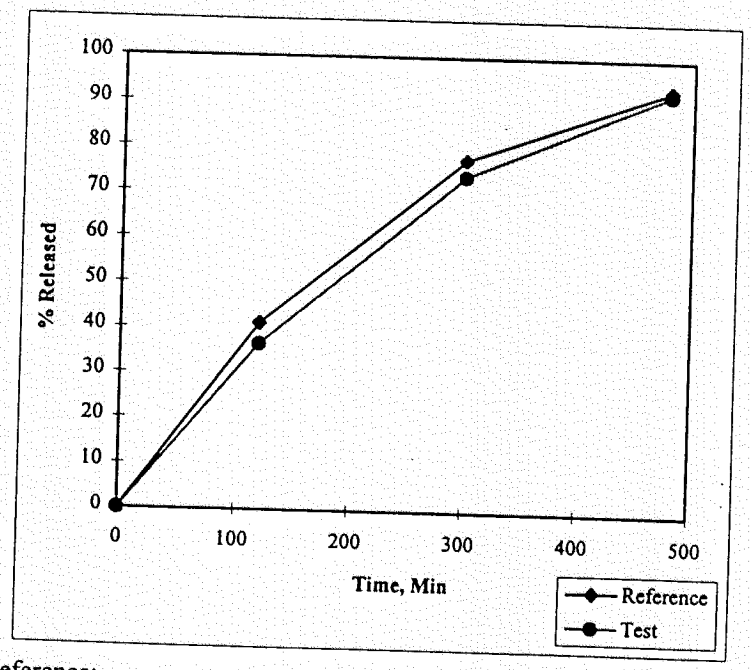
Reference C-0005 Product: Conjugated Estrogens Tablet, USP
Test: C-0034 Component: Equilin

Time	R_t	T_t	$R_t - T_t$	$(R_t - T_t)^2$
120	41.2	36.6	4.60	21.16
300	77.4	73.8	3.60	12.96
480	93.3	92.5	0.80	0.64
Sum	211.90	202.90	9.00	34.76
n	3			

$f_1 = [(\text{sum} \mid R_t - T_t \mid) / (\text{sum } R_t)] \times 100$

$f_2 = 50 \times \log\{[1 + (1/n) \text{ sum } (R_t - T_t)^2]^{-0.5} \times 100\}$

f1 =	4.2
f2 =	72.5



Reference:

1. J. W. Moore and H. W. Flanner, Pharm. Tech., **1996**, *20(6)*, 64-74.

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12/8/98
10:25 AM

Attachment

CALCULATION OF f_2 VALUES (Similarity Factor) [1]

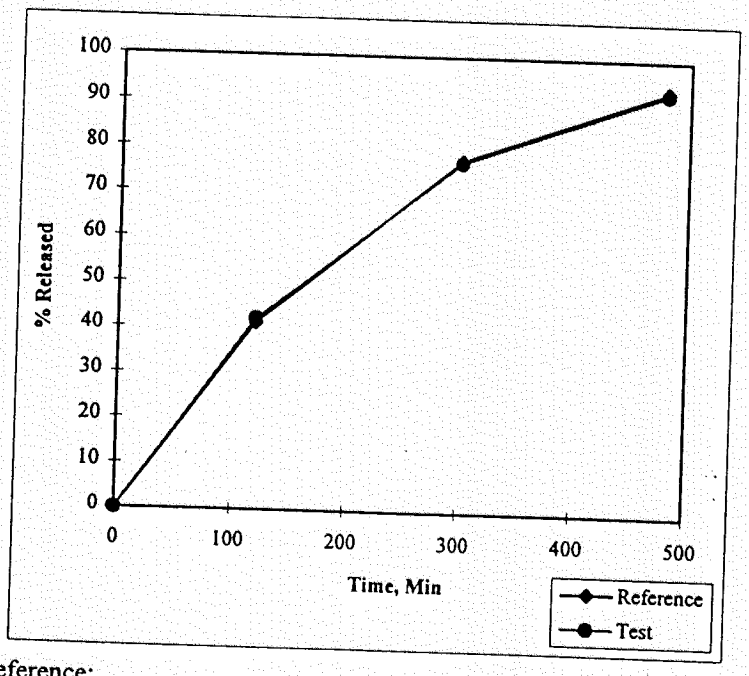
Reference C-0005 Product: Conjugated Estrogens Tablet, USP
Test: X-0335 Component: Equilin

Time	R_t	T_t	$R_t - T_t$	$(R_t - T_t)^2$
120	41.2	42.1	0.90	0.81
300	77.4	76.9	0.50	0.25
480	93.3	92.8	0.50	0.25
Sum	211.90	211.80	1.90	1.31
n	3			

$f_1 = [(\text{sum} \mid R_t - T_t \mid) / (\text{sum } R_t)] \times 100$

$f_2 = 50 \times \log\{[1 + (1/n) \text{ sum } (R_t - T_t)^2]^{-0.5} \times 100\}$

f1 =	0.9
f2 =	96.1



Reference:

1. J. W. Moore and H. W. Flanner, Pharm. Tech., 1996, *20(6)*, 64-74.

F2CALC.XLS
12/8/98
11:31 AM

Attachment

CALCULATION OF f_2 VALUES (Similarity Factor) [1]

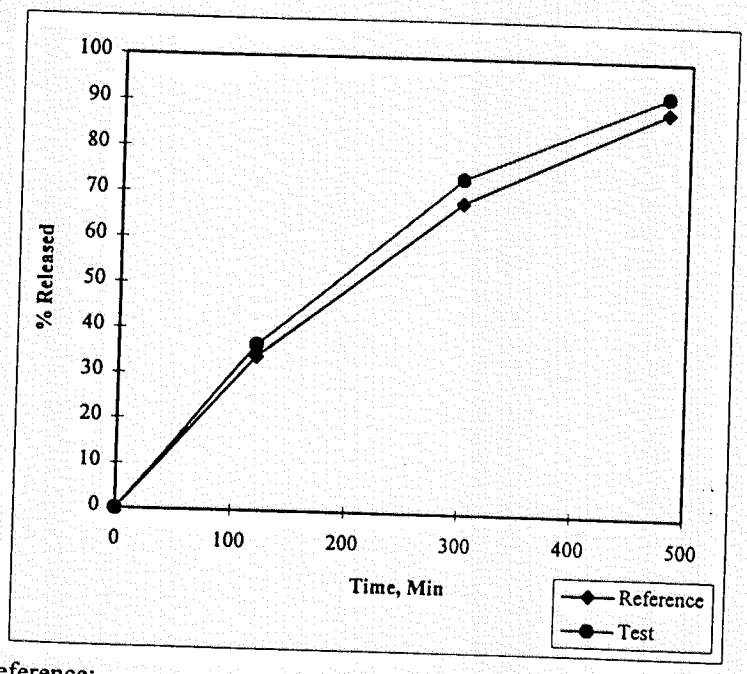
Reference X-0328 Product: Conjugated Estrogens Tablet, USP
Test: G-0034 Component: Equilin

Time	R_t	T_t	$R_t - T_t$	$(R_t - T_t)^2$
120	34.0	36.6	2.60	6.76
300	68.5	73.8	5.30	28.09
480	89.1	92.5	3.40	11.56
Sum	191.60	202.90	11.30	46.41
n	3			

$f_1 = [(\text{sum} \mid R_t - T_t \mid) / (\text{sum } R_t)] \times 100$

$f_2 = 50 \times \log\{[1 + (1/n) \text{ sum } (R_t - T_t)^2]^{-0.5} \times 100\}$

f1 =	5.9
f2 =	69.6



Reference:

1. J. W. Moore and H. W. Flanner, Pharm. Tech., 1996, *20(6)*, 64-74.

MAR 9 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

IND:	(N-009 PN))
Compound:	Synthetic conjugated estrogens (Cenestin™)
Sponsor:	Duramed Pharmaceuticlas, Inc.
Type of Submission:	Phase II clinical study protocol: bioequivalence of 2x0.625 and 1x1.25 mg synthetic conjugated estrogens tablets
Date of Submission:	February 8, 1999
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.

Background:

Conjugated estrogens are used to treat vasomotor symptoms for menopausal women. The Sponsor submitted NDA 20992 for Cenestin™ 0.3, 0.625, 0.9, 1.25, and 2.5 mg tablets. The original formulation of 1.25 and 2.5 mg tablets are different from that of the 0.3, 0.625, and 0.9 mg tablets. The Sponsor has reformulated the 1.25 and 2.5 mg tablets to be similar to the 0.3, 0.625, and 0.9 mg tablets. Thus, this IND includes a protocol to evaluate the bioequivalence of 1 Cenestin™ 1.25 mg tablet versus 2 Cenestin™ 0.625 mg tablets.

PROTOCOL SUMMARY

Protocol Number: DPI 99-01

Study Title:

Comparative, randomized, single-dose, 2-way crossover bioequivalence study of one Duramed (Cenestin™) 1.25 mg tablet versus two Duramed (Cenestin™) 0.625 mg tablets in healthy, post-menopausal female adults under fasting conditions.

Objectives:

To evaluate the single dose bioequivalence of 1 Cenestin™ 1.25 mg tablet versus 2 Cenestin™ 0.625 mg tablets under fasting conditions.

Study Design:

This is an open-label, randomized, 2-period, single dose, crossover study in 36 (18-65 years) postmenopausal or oophorectomized female. Each randomized subject will receive either 2 Cenestin™ 0.65 mg tablets or 1 Cenestin™ 1.25 mg tablet on the first treatment period. On the second treatment period, each subject will receive the treatment she did not receive previously. The washout period between the 2 treatments will be 14 days.

Blood Sampling and Analysis:

Serial blood samples will be collected from each subject at -0, 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 14, 16, 24, 32, 40, 48, 60, and 72 hours postdose. Plasma conjugated and unconjugated estrone, equilin, and estradiol concentrations will be determined.

Pharmacokinetic Analysis:

C_{max}, t_{max}, $AUC_{(0\rightarrow t)}$, $AUC_{(0\rightarrow 72)}$, $AUC_{(0\rightarrow inf)}$, k_{el}, and $t_{1/2}$ will be estimated via standard methods.

Statistical Analysis:

ANOVA will be performed on the log-transformed $AUC_{(0\rightarrow t)}$, $AUC_{(0\rightarrow inf)}$, and C_{max}. The ANOVA model will include sequence, subjects nested within sequence, period and formulation as factors. The significance of the sequence effect will be tested via the subjects nested within sequence as the error term. ANOVA will also be performed via the average baseline value in each period as the covariate.

Comments:

1. Assessment of bioequivalence should be on the same pharmacokinetic parameters as those in the NDA 20992, namely, $AUC_{(0\rightarrow 72)}$, $AUC_{(0\rightarrow inf)}$, and C_{max} of unconjugated and total estrone and equilin.
2. Formulation ingredients of the Cenestin™ tablets should be provided.
3. Complete bioanalytical report to quantitate conjugated and unconjugated estrone, equilin, and estradiol should include specificity, lower limit of quantitation, inter- and intra- day assay precision, accuracy, linearity, and validation. The bioanalytical report should be included in the final study report.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed IND dated February 5, 1999. Comments 1 to 3 should be conveyed to the Sponsor.

S.W. Johnny Lau, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

FT signed by Ameeta Parekh, Ph.D., Team Leader 3/9/99

cc:
IND 53731, HFD-870 (M. Chen, A. Parekh, S.W.J. Lau), HFD-580 (T. van der Vlugt, D. Moore), CDR (B. Murphy for Drugs)