CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-417

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-417: N000BB
Submission Dates	December 17, 2001; April 12, 2002
Brand Name	PREMARIN®
Generic Name	conjugated estrogens
Reviewer	S.W. Johnny Lau
Team Leader	Hae-Young Ahn
OCPB Division	DPE II (HFD-870)
ORM division	Metabolic and Endocrine Drug Products (HFD-510)
Sponsor	Wyeth-Averst Research.
Relevant IND(s)	[redacted]
Submission Type: Code	3S
Formulation: Strength(s)	Film-coated tablets (0.3 and 0.45 mg)
Indication	To prevent postmenopausal osteoporosis

Executive Summary

The sponsor submitted NDA 21-417 (related to IND [redacted] for the 0.3 mg and 0.45 mg conjugated estrogens (CE) alone oral tablets on December 17, 2001 to seek approval for the prevention of postmenopausal osteoporosis. The sponsor also submitted NDA 04-782/SE2-115 for the 0.45 mg CE alone tablet for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy. The Human Pharmacokinetics and Bioavailability section for NDA 04-782/SE2-115 was acceptable. However, NDA 04-782/SE2-115 failed the chemistry manufacturing and controls inspection but otherwise was approvable.

The sponsor currently markets PREMARIN®, which contains 0.3, 0.625, 0.9, 1.25, or 2.5 mg CE alone in oral tablets. Hence, PREMARIN® 0.45 mg CE alone oral tablet is the newest strength seeking approval. PREMARIN® 0.625 mg CE alone daily oral tablet has the indication for the prevention of osteoporosis. PREMARIN® 0.3 mg CE alone oral tablet is approved to treat moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy.

The sponsor's proposed in vitro dissolution method and specifications for the 0.3 and 0.45 mg CE alone tablets are acceptable. Briefly,

The sponsor's proposed in vitro dissolution method for CE (the USP 25 method):	
Apparatus	2
In vitro release medium	water
Volume of release medium	900 mL
Medium temperature	37 ± 0.5°C
Stirring speed	50 rpm

CE in vitro dissolution specifications:	
	Proposed, % estrone sulfate released
2 hours	between [redacted]
5 hours	between [redacted]
8 hours	not less than [redacted]

Recommendation –

- The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) reviewed NDA 21-417. OCPB finds that the submitted information supports the Human Pharmacokinetics and Bioavailability section for NDA 21-417.
- Future Clinical Pharmacology section for PREMARIN®, PREMPRO™, and PREMPHASE® labeling should be consistent between products.

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

FT signed by Hae-Young Ahn, Ph.D., Team Leader 10/ /02

Background:
PREMARIN® is derived from pregnant mares' urine, which contains more than 10 estrogens. PREMARIN®'s CE contains at least the sodium sulfate conjugates of estrone, equilin, 17α-dihydroequilin, 17β-dihydroequilin, 17α-estradiol, 17β-estradiol, equilenin, 17α-dihydroequilenin, 17β-dihydroequilenin, and $\Delta^{8,9}$-dehydroestrone.

The sponsor submitted NDA 04-782/SE2-115 for the 0.45 mg CE alone tablet on July 31, 2000 for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy to the Division of Reproductive and Urologic Drug Products.

The sponsor submitted NDA 20-527/SLR-017 for the 0.45 mg CE/1.5 mg MPA [redacted] mg MPA oral tablets on June 15, 2000 for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar atrophy to the Division of Reproductive and Urologic Drug Products. [redacted]

The sponsor submitted NDA 21-396 [redacted] for the 0.45 mg CE/1.5 mg MPA or 0.3 mg CE/1.5 mg MPA oral tablets on September 24, 2001 for the prevention of osteoporosis, to the Division of Endocrine and Metabolic Drug Products.

The sponsor conducted clinical safety and efficacy Study 0713D2-309-US to evaluate the prevention of osteoporosis and relieving postmenopausal symptoms for the 0.3 and 0.45 mg CE alone tablets. The sponsor used the same clinical pharmacology studies (0713D2-119-US and 0713D2-120-US) to support the Human Pharmacokinetics and Bioavailability section for NDA 21417, NDA 04-782/SE2-115, NDA 20-527/SLR-017, and NDA 21-396 [redacted] Therefore, the review for the Human Pharmacokinetics and Bioavailability section of NDA 21-417 for the PREMARIN® 0.45 mg CE alone tablet will be referred to that for the NDA 04-782 SE2-115. The review for the Human Pharmacokinetics and Bioavailability section for NDA 21-417 pertains to the PREMARIN® 0.3 mg CE alone tablet. Synopses for Studies 0713D2-119-US and 0713D2-120-US are in Attachment 1.

The following questions, based on the content of NDA 21-417, guided this review.

1. What study results are submitted to support the Human Pharmacokinetics (PK) and Bioavailability (BA) section of NDA 21-417?

	Study	Review Question
Bioanalytical assay	-	2
PK of 0.3 and 0.45 mg CE tablets	0713D2-119-US and 0713D2-120-US	3
Dose linearity	0713D2-119-US and 0713D2-120-US	4
Multiple dose	-	5
Formulation	-	6
In vitro dissolution	-	7
Proposed labeling	-	8

2. What were the bioanalytical methods for CE used in NDA 21-417?
Because of low doses, 2 tablets of each formulation were administered to provide plasma drug concentrations that could be more accurately measured.

Unconjugated and total estrone (baseline adjusted and unadjusted), equilin, 17β-estradiol (baseline adjusted and unadjusted), 17β-dihydroequilin, $\Delta^{8,9}$-dehydroestrone, and 17β-$\Delta^{8,9}$-dehydroestradiol in plasma were determined via ——————. Total (unconjugated and conjugated) estrone, equilin, $\Delta^{8,9}$-dehydroestrone, 17β-estradiol, 17β-dihydroequilin and 17β-$\Delta^{8,9}$-dehydro-estradiol concentrations in plasma were determined via the same procedure after glusulase hydrolysis. Control samples were also utilized to confirm that the hydrolysis of the conjugated estrogens was complete. The %CV for CE analytes ranged from — to — for both Studies 0713D2-119-US and 0713D2-120-US.

Analyte	[1]LLOQ, pg/mL
2 mL plasma sample:	
unconjugated estrone, $\Delta^{8,9}$-dehydroestrone, 17β-dihydroequilin, and 17β-$\Delta^{8,9}$-dehydroestradiol	—
Unconjugated equilin	—
Unconjugated 17β-estradiol	—
0.4 mL plasma sample:	
Total equilin	—
total estrone, $\Delta^{8,9}$-dehydroestrone, 17β-dihydroequilin, and 17β-$\Delta^{8,9}$-dehydroestradiol	—
Total 17β-estradiol	—

[1]LLOQ = lower limit of quantitation

Overall, the bioanalytical assay for CE in plasma was acceptable. See the clinical pharmacology and biopharmaceutics review for detailed review on bioanalytical methods for Study 0713D2-119-US and Study 0713D2-120-US in NDA 04-6782 SE2-115 and NDA 20-527 SLR-017, respectively. The sponsor did not summarize and report the intra-day variation for CE bioanalytical assays.

3. What are the PK for the 0.3 and 0.45 mg CE alone oral tablets?

See Attachment 2 for CE figures and PK parameters tables for the 0.3 mg CE alone tablets. See NDA 04-6782 SE2-115's clinical pharmacology and biopharmaceutics review for the 0.45 mg CE alone tablet.

4. Are CE dose proportional kinetically?

Most of the components showed linear dose proportionality (Attachment 3), except unconjugated equilin AUC_t, unconjugated 17β-estradiol C_{max}, unconjugated 17β-$\Delta^{8,9}$-dehydroestradiol C_{max} and AUC_t, and total $\Delta^{8,9}$-dehydroestrone C_{max} and AUC. See NDA 20-527 SLR-017's clinical pharmacology and biopharmaceutics review for detailed review of the 0.3 and 0.45 mg CE alone tablets.

5. Do CE accumulate upon multiple dose administration of 0.30 and 0.45 mg CE alone oral tablets?

Study 0713D2-120-US is single dose in design and did not address the dose accumulation potential upon multiple-dose administration. PREMARIN® 0.3, 0.625, 0.9, and 1.25 mg CE alone oral tablets for continuous daily administration were approved for the same indications as that proposed for the 0.45 mg CE oral tablet via this efficacy supplement. No multiple dose CE PK information is in the current PREMARIN® labeling.

The sponsor conducted Study 0713D2-309-US to assess the safety and efficacy of 0.3 mg and 0.45 mg CE oral tablets; though no blood was sampled for CE measurements in this study. See NDA 04-6782 SE2-115's clinical pharmacology and biopharmaceutics review for the 0.45 mg CE alone tablet.

6. What are the formulations used in the clinical studies for NDA 21-417?

The CE present in the tablets are identical to that in the marketed Premarin® products. The 0.45 mg CE tablet uses the same formulation technology as the marketed Premarin® products. The CE formulations (0930329B for the 0.3 mg CE tablet and 0930287B for the 0.45 mg CE tablet) tested in the clinical studies 0713D2-309-US, 0713D2-119-US, and 0713D2-120-US are identical to the market formulations in terms of scale of manufacture and composition except the color coat, which is —— for the clinical formulation. See Attachment 4 for formulation information.

Color coat difference between the clinically-tested and the to-be-marketed 0.3 mg CE oral tablet formulation were evaluated via comparative in vitro dissolution tests. The sponsor submitted the in vitro dissolution data for the 0.3 mg CE oral tablet via N 000BB on April 12, 2002 (see Attachment 4). The sponsor submitted 2 sets of dissolution data for the clinical batches. One set contains data points of 1, 2, 4, 6, and 10 hours and another data set contains data points of 2, 5, and 8 hours. Only the 2, 5, and 8 hours data set for the clinical batch can be used to compare with the 2, 5, and 8 hours data set for the —market batches. Moreover, the clinical batch data resulted from the without sinker method. Whereas the 3 market batches data resulted from the sinker method. Per chemistry team leader, David Lin, the dissolution results from sinker and without sinker methods should be identical. USP 25's dissolution method in Section 7.11 allows sinker to be used anyhow. The f_2 values between the clinical batch and the 3 market batches were 66.1, 77.0, and 84.9. See Attachment 4 for the plots of the dissolution profiles. By overlaying the dissolution profiles between the clinical batch over the market batches, the CE dissolution profiles appear to be similar between the clinical batch and the 3 market batches. Based on the individual dissolution profiles and f_2 values, the clinically tested 0.3 mg CE alone tablets and the to-be-marketed 0.3 mg CE alone tablets are deemed to be similar.

See NDA 04-6782 SE2-115's clinical pharmacology and biopharmaceutics review for the 0.45 mg CE alone tablet.

7. What are the proposed in vitro dissolution method and specifications for the 0.30 and 0.45 mg CE alone tablets?

The sponsor's proposed in vitro dissolution method for CE (the USP 25 method):	
Apparatus	2
In vitro release medium	water
Volume of release medium	900 mL
Medium temperature	37 ± 0.5°C
Stirring speed	50 rpm

CE in vitro dissolution specifications:	
	Proposed, % estrone sulfate released
2 hours	between —
5 hours	between —
8 hours	not less than —

The sponsor's proposed in vitro dissolution method and specifications for the 0.3 and 0.45 mg CE alone tablet are acceptable, which are also identical to the specifications for the marketed 0.625 mg CE alone tablets.

8. What are the sponsor's proposed labeling for products' Clinical Pharmacology section?
The labeling will not be reviewed now pending further discussion on the findings of Women's Health Initiative Study. However, future Clinical Pharmacology section for PREMARIN®, PREMPRO™, and PREMPHASE® labeling should be consistent between products.

Attachment 1

SYNOPSIS

COMPANY NAME: Wyeth NAME OF FINISHED PRODUCT: Premarin, Prempro NAME OF ACTIVE INGREDIENT: conjugated equine estrogens (AY-011152); medroxyprogesterone acetate (AY-011236)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER VOLUME: PAGE:	*(For National Authority Use Only)*

STUDY TITLE: A SINGLE-DOSE, COMPARATIVE BIOAVAILABILITY STUDY OF PREMARIN AND MEDROXYPROGESTERONE ACETATE (MPA) FROM THREE STRENGTHS OF PREMARIN/MPA COMBINATION TABLETS AND ONE STRENGTH OF A PREMARIN-ONLY TABLET IN HEALTHY, POSTMENOPAUSAL WOMEN: FINAL REPORT (Protocol 0713D2-119-US, GMR-32506)

INVESTIGATORS: [redacted]

STUDY CENTERS: [redacted]

PUBLICATION (REFERENCE): N/A

STUDY PERIOD : **CLINICAL PHASE:** I

(DATE OF FIRST ENROLLMENT) 28 Aug 1996
(DATE OF LAST COMPLETION) 20 Jan 1997

OBJECTIVES: To assess the relative bioavailability of Premarin and MPA contained in three different strengths of Premarin/MPA combination tablets and that of a Premarin-only tablet in healthy, hysterectomized, postmenopausal women.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy women 35 to 65 years old who were within ± 20% of ideal body weight for their height and frame. The subjects had to be hysterectomized ambulatory women who were either naturally postmenopausal, with little or no ovarian estrogen production, or who had a bilateral oophorectomy (documented by an operative report) because of benign pathologic findings at least 6 months before the study start.

NUMBER OF PATIENTS (PLANNED, ENROLLED, ANALYZED):
32 planned, 35 enrolled, 32 completed, 31 analyzed.

DURATION OF TREATMENT: Each subject participated in the clinical portion of the study for approximately 99 days, which included four 9-day study periods with at least 30-day washout intervals. Each study period consisted of a 2 ½-day (3 night) inpatient stay and 6 outpatient visits. The duration of the study was 5 months.

STUDY DRUG, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: Treatment A: two tablets of Premarin 0.625 mg/MPA 2.5 mg (combination-tablet formulation), batch no. 2TQA. Treatment B: two tablets of Premarin 0.45 mg/MPA 2.5 mg (combination-tablet formulation), batch no. 3TEN. Treatment C: two tablets of Premarin 0.45 mg/MPA 1.5 mg (combination-tablet formulation), batch no. 3TEM. Treatment D: two tablets of Premarin 0.45 mg, batch no. 3TEL.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: None

SYNOPSIS

COMPANY NAME: Wyeth NAME OF FINISHED PRODUCT: **Premarin, Prempro** NAME OF ACTIVE INGREDIENT: conjugated equine estrogens (AY-011152); medroxyprogesterone acetate (AY-011236)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER VOLUME: PAGE:	*(For National Authority Use Only)*

PHARMACOKINETIC AND STATISTICAL METHODS: Noncompartmental pharmacokinetic methods were used to analyze the plasma concentration data. Statistical comparisons were made by using an analysis of variance (ANOVA) for a four-period crossover design. Pairwise comparisons between treatments were made by using Duncan's Multiple Range Test for p-values ≤ 0.05.

SAFETY ASSESSMENT METHODS: A complete medical, gynecologic, and physical examination, with measurement of vital signs and hematologic, biochemical, renal, hepatic, and urinary laboratory determinations, was done at screening and study completion. During the treatment period, study events and symptoms, as well as vital signs and concomitant medications, were evaluated and recorded in the case report form.

HARMACOKINETIC RESULTS: The comparative bioavailabilities for Premarin components and MPA were evaluated following administration of two Premarin 0.625-mg/MPA 2.5-mg tablets (treatment A), two Premarin 0.45-mg/MPA 2.5-mg tablets (treatment B), two Premarin 0.45-mg/MPA 1.5-mg tablets (treatment C), and two Premarin 0.45-mg tablets (treatment D). All of the Premarin estrogens with estimable peak concentration (C_{max})and area under the concentration-time curve (AUC) showed significant treatment differences for these parameters. In general, results of the Duncan's Multiple Range Test indicated that the three 0.45-mg Premarin treatments produced lower estrogen concentrations than the 0.625-mg Premarin treatment. The ratios of mean C_{max} for estrogens observed following treatments B, C, and D to mean C_{max} following treatment A ranged from 56% to 76%; and the ratios of mean AUC ranged from 57% to 84%, which are reasonably close to the theoretical value of 72%.

Significant treatment differences were seen for C_{max} and AUC of MPA, and the Duncan's Multiple Range Test indicated that the 1.5-mg MPA treatment produced lower MPA concentrations than the two 2.5-mg MPA treatments. The ratios of mean C_{max} following treatment C to mean C_{max} following treatments A and B were 53% and 68%, respectively; and the ratios of mean AUC were 62% and 63%, respectively, which are very close to the theoretical value of 60%.

SAFETY RESULTS: There were no serious or unexpected adverse events. All events were treatment emergent; headache was the most common adverse event. Eight (8) headaches were reported by 7 subjects; all but 1 of these were considered to be possibly drug related. One (1) headache (drug-related) was severe. There were isolated increases and decreases from baseline in laboratory values, vital signs, and weight, but none of these were considered clinically important.

SYNOPSIS

COMPANY NAME: Wyeth NAME OF FINISHED PRODUCT: Premarin, Prempro NAME OF ACTIVE INGREDIENT: conjugated equine estrogens (AY-011152); medroxyprogesterone acetate (AY-011236)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER VOLUME: PAGE:	*(For National Authority Use Only)*

CONCLUSION: The two Premarin 0.45-mg/MPA 2.5-mg combination tablets, two Premarin 0.45-mg/MPA 1.5-mg combination tablets, and two Premarin 0.45-mg tablets produced lower estrogen concentrations than the two Premarin 0.625-mg/MPA 2.5-mg combination tablets, in line with the relative doses. The two Premarin 0.45-mg/MPA 1.5-mg combination tablets produced lower MPA concentrations than the two Premarin 0.625-mg/MPA 2.5-mg combination tablets, or the two Premarin 0.45-mg/MPA 2.5-mg combination tablets—approximately 60% of the larger MPA dose. The various dose strengths of Premarin and MPA behave pharmacokinetically in a dose-proportional manner.

DATE OF THE REPORT: 09 Jul 1999

SYNOPSIS

COMPANY NAME: Wyeth NAME OF FINISHED PRODUCT: Premarin, Prempro NAME OF ACTIVE INGREDIENT: conjugated equine estrogens (AY-011152); medroxyprogesterone acetate (AY-011236)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER VOLUME: PAGE:	*(For National Authority Use Only)*

STUDY TITLE: A SINGLE-DOSE, COMPARATIVE BIOAVAILABILITY STUDY OF PREMARIN AND MEDROXYPROGESTERONE ACETATE (MPA) FROM THREE STRENGTHS OF PREMARIN/MPA COMBINATION TABLETS AND ONE STRENGTH OF A PREMARIN-ONLY TABLET IN HEALTHY, POSTMENOPAUSAL WOMEN: FINAL REPORT (Protocol 0713D2-120-US, GMR-32507)

INVESTIGATORS: [redacted]

STUDY CENTERS: [redacted]

PUBLICATION (REFERENCE): N/A

UDY PERIOD : **CLINICAL PHASE:** I

(DATE OF FIRST ENROLLMENT) 14 Sep 1996
(DATE OF LAST COMPLETION) 14 Feb 1997

OBJECTIVES: To assess the relative bioavailability of Premarin and MPA contained in three different strengths of Premarin/MPA combination tablets and that of a Premarin-only tablet in healthy, hysterectomized, postmenopausal women.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy women 35 to 65 years old who were within ± 20% of ideal body weight for their height and frame. The subjects had to be hysterectomized ambulatory women who were either naturally postmenopausal, with little or no ovarian estrogen production, or who had a bilateral oophorectomy (documented by an operative report) because of benign pathologic findings at least 6 months before the study start.

NUMBER OF PATIENTS (PLANNED, ENROLLED, ANALYZED):
32 planned, 34 enrolled, 30 completed, 30 analyzed.

DURATION OF TREATMENT: Each subject participated in the clinical portion of the study for approximately 99 days, which included four 9-day study periods with at least 30-day washout intervals. Each study period consisted of a 2 ½-day (3 night) inpatient stay and 6 outpatient visits. The duration of the study was 5 months.

STUDY DRUG, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: Treatment A: two tablets of Premarin 0.625 mg/MPA 2.5 mg (combination-tablet formulation), batch no. 2TQA. Treatment B: two tablets of Premarin 0.45 mg/MPA 1.5 mg (combination-tablet formulation), batch no. 3 TEM. Treatment C: two tablets of Premarin 0.30 mg/MPA 1.5 mg (combination-tablet formulation), batch no. 3 THN. Treatment D: two tablets of Premarin 0.30 mg, batch no. 3THP.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: None

SYNOPSIS

COMPANY NAME: Wyeth NAME OF FINISHED PRODUCT: Premarin, Prempro NAME OF ACTIVE INGREDIENT: conjugated equine estrogens (AY-011152); medroxyprogesterone acetate (AY-011236)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER VOLUME: PAGE:	*(For National Authority Use Only)*

PHARMACOKINETIC AND STATISTICAL METHODS: Noncompartmental pharmacokinetic methods were used to analyze the plasma concentration data. Statistical comparisons were made by using an analysis of variance (ANOVA) for a four-period crossover design. Pairwise comparisons between treatments were made by using Duncan's Multiple Range Test for p-values ≤ 0.05.

SAFETY ASSESSMENT METHODS: A complete medical, gynecologic, and physical examination, with measurement of vital signs and hematologic, biochemical, renal, hepatic, and urinary laboratory determinations, was done at screening and study completion. During the treatment period, study events and symptoms, as well as vital signs and concomitant medications, were evaluated and recorded in the case report

PHARMACOKINETIC RESULTS: The comparative bioavailabilities for Premarin estrogen components and MPA were evaluated following administration of two Premarin 0.625-mg/MPA 2.5-mg tablets (treatment A), two Premarin 0.45-mg/MPA 1.5-mg tablets (treatment B), two Premarin 0.30-mg/MPA 1.5-mg tablets (treatment C), and two Premarin 0.30-mg tablets (treatment D). All of the Premarin estrogens with estimable peak concentrations (C_{max}) and areas under the concentration-time curve (AUC) showed significant treatment differences for these parameters, as expected. In general, results of the Duncan's Multiple Range Test indicated that the lower-dose treatments with Premarin (B, C, and D) produced lower rank-order estrogen concentrations than the Premarin 0.625-mg treatment (A). The ratio of the estrogen concentrations for the Premarin 0.45-mg dose and the 0.625-mg dose, respectively, is 72%. The Premarin estrogen ratios of mean C_{max} for treatment B (0.45 mg) to those of mean C_{max} for treatment A (0.625 mg) ranged from 56% to 63%, and the ratios of mean AUC ranged from 64% to 75%. The ratio of the estrogen concentrations for the Premarin 0.30-mg dose and the 0.625-mg dose, respectively, is 48%. The Premarin estrogen ratios of mean C_{max} for treatments C and D (0.30 mg) to those of mean C_{max} for treatment A (0.625 mg) ranged from 46% to 54%, and the ratios of mean AUC ranged from 45% to 59%. These ratios are similar to the theoretical values, especially for the more reliable AUC values, and thus demonstrate that the estrogen components are dose proportional in this dose range.

Significant treatment differences were seen for C_{max} and AUC of MPA, as expected; the Duncan's Multiple Range Test indicated that the two 1.5-mg MPA treatments produced lower MPA concentrations than the 2.5-mg MPA treatment. The ratios of mean C_{max} following treatments B and C to the mean C_{max} for treatment A were 70% and 77%, respectively; and the ratios of mean AUC were 72% and 70%, respectively, which are reasonably close to the theoretical value of 60%.

Comparison of estrogen pharmacokinetic parameters following administration of 2 x Premarin 0.30-mg/MPA 1.5-mg combination tablets and 2 x Premarin 0.30-mg tablets demonstrates that there is no effect of MPA on Premarin estrogen pharmacokinetics.

Attachment 2

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FIG. 36 UNCONJUGATED 17BETA-ESTRADIOL PLASMA CONCENTRATIONS ADJUSTED FOR BASELINE: TWO PREMARIN 0.30 MG TABLETS

Figure 36
Unconjugated 17Beta – Estradiol Plasma Concentrations Adjusted for Baseline
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg Tablets
Protocol 0713D2 – 120 – US

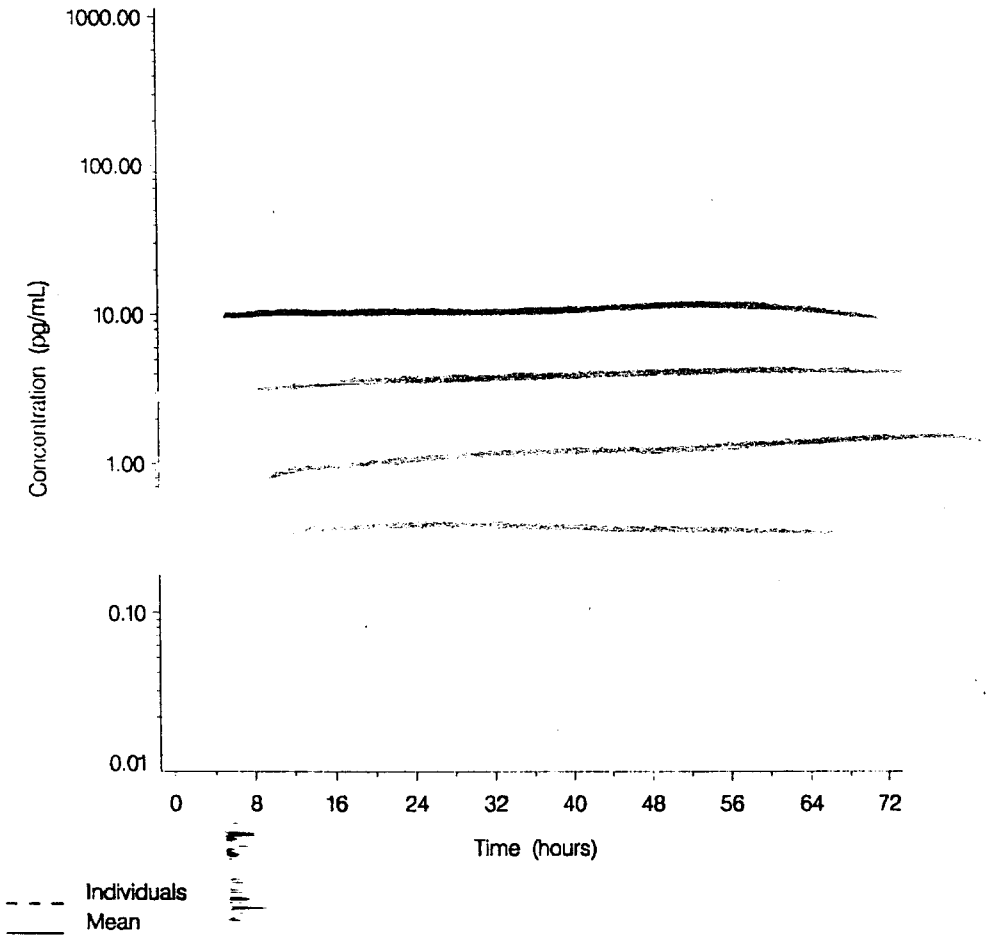

FIG. 44 UNCONJUGATED 17BETA-DIHYDROEQUILIN PLASMA CONCENTRATIONS: TWO PREMARIN 0.30 MG TABLETS

Figure 44
Unconjugated 17Beta – Dihydroequilin Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg Tablets
Protocol 0713D2 – 120 – US

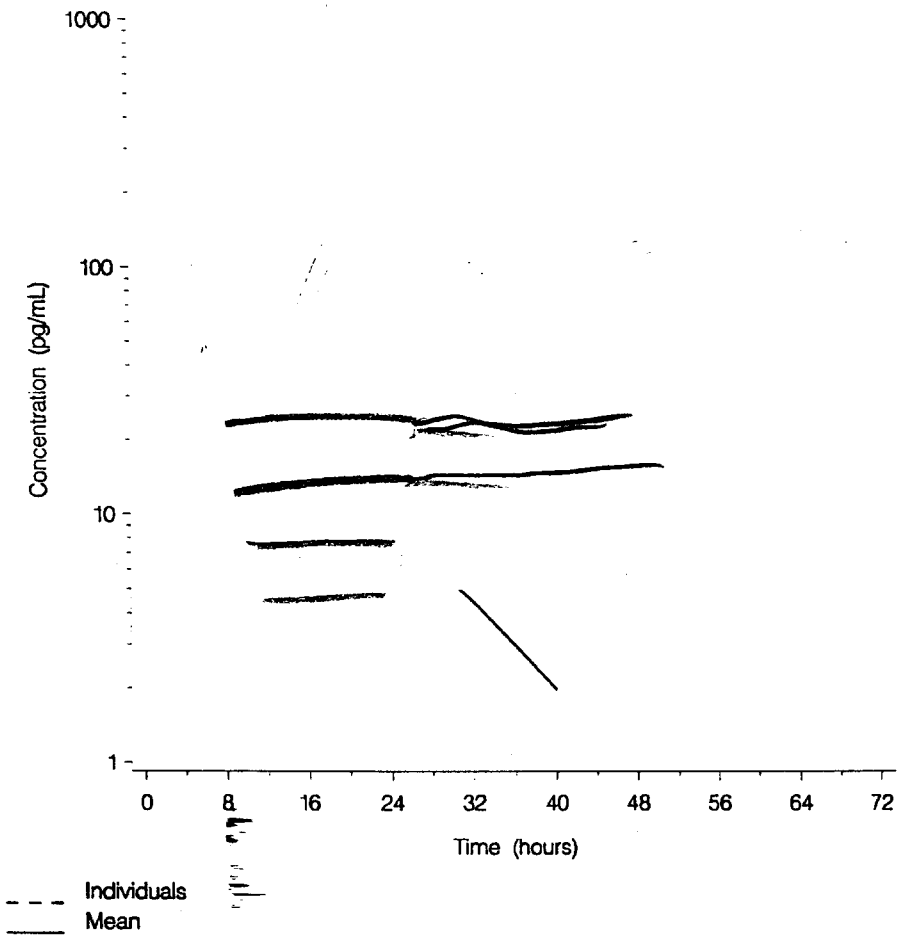

FIG. 52 UNCONJUGATED DELTA8,9-DEHYDROESTRONE PLASMA CONCENTRATIONS: TWO PREMARIN 0.30 MG TABLETS

Figure 52
Unconjugated Delta8,9-Dehydroestrone Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg Tablets
Protocol 0713D2-120-US

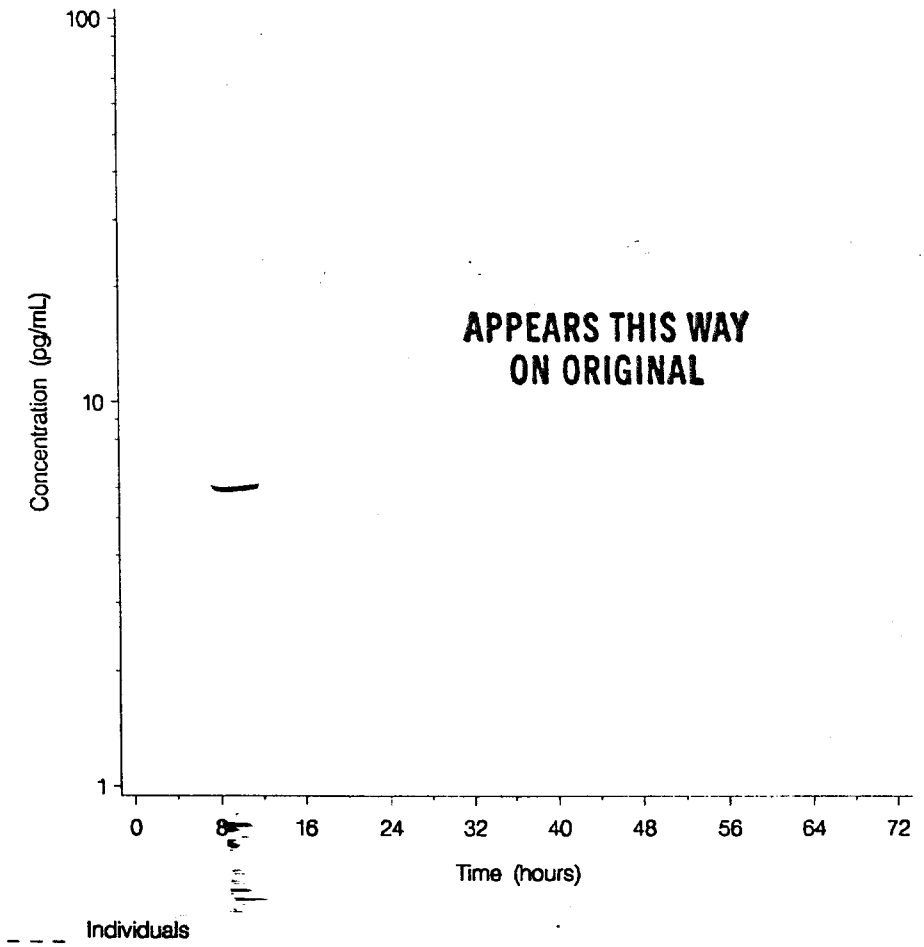

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FIG. 57 UNCONJUGATED 17BETA-DELTA8,9-DEHYDROESTRADIOL PLASMA CONCENTRATIONS: TWO PREMARIN 0.30 MG TABLETS

Figure 57
Unconjugated 17Beta – Delta8,9 – Dehydroestradiol Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg Tablets
Protocol 0713D2-120-US

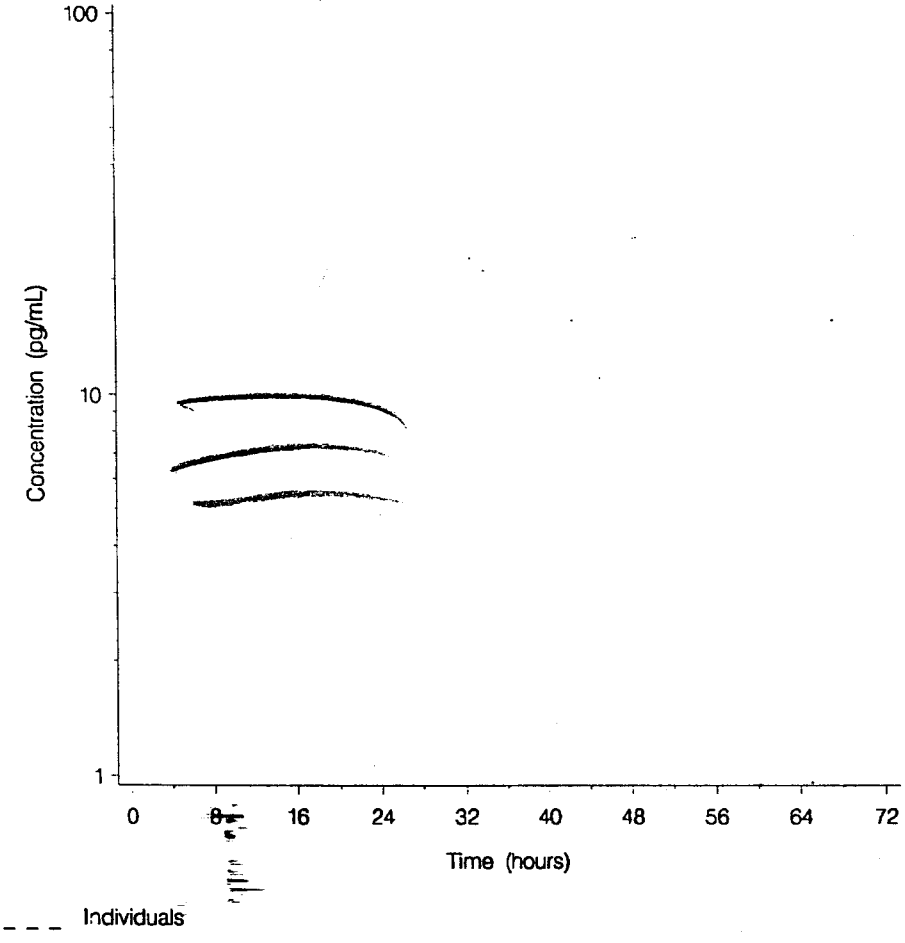


FIG. 63 TOTAL ESTRONE PLASMA CONCENTRATIONS: TWO PREMARIN 0.30 MG TABLETS

Figure 63
Total Estrone Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg Tablets
Protocol 0713D2–120–US

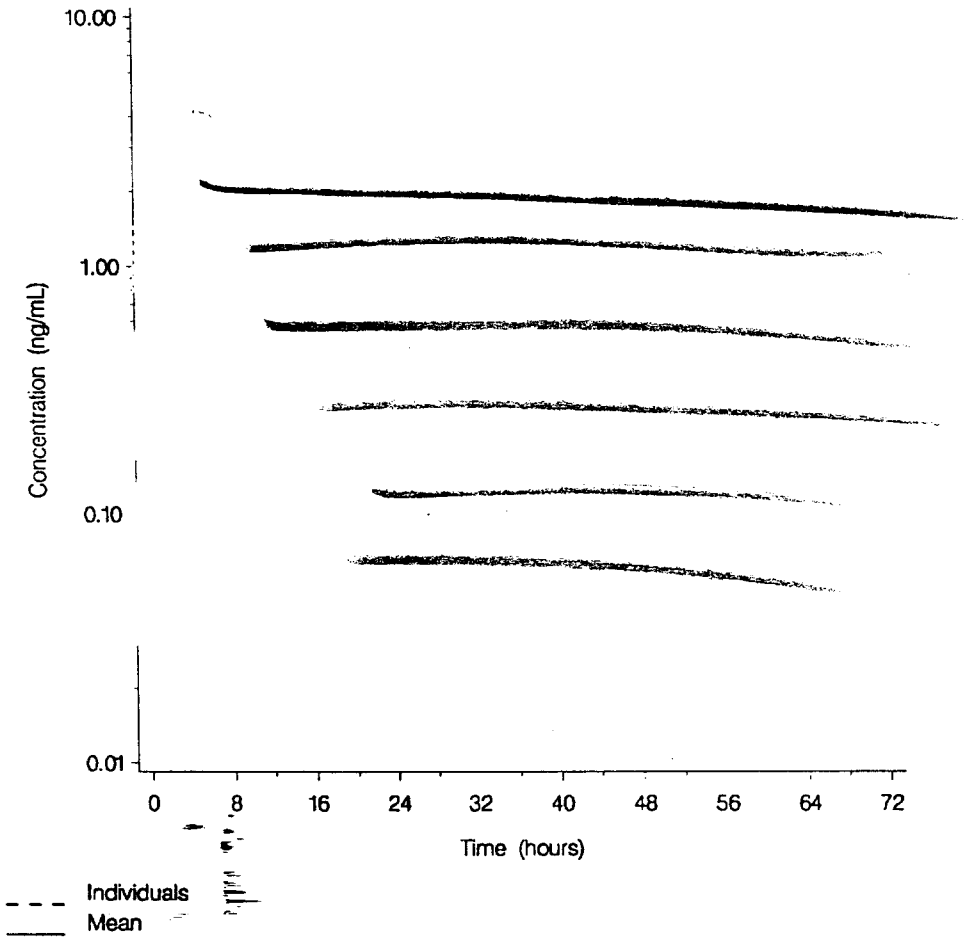


FIG. 71 TOTAL ESTRONE PLASMA CONCENTRATIONS ADJUSTED FOR BASELINE: TWO PREMARIN 0.30 MG TABLETS

Figure 71
Total Estrone Plasma Concentrations Adjusted for Baseline
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg Tablets
Protocol 0713D2–120–US

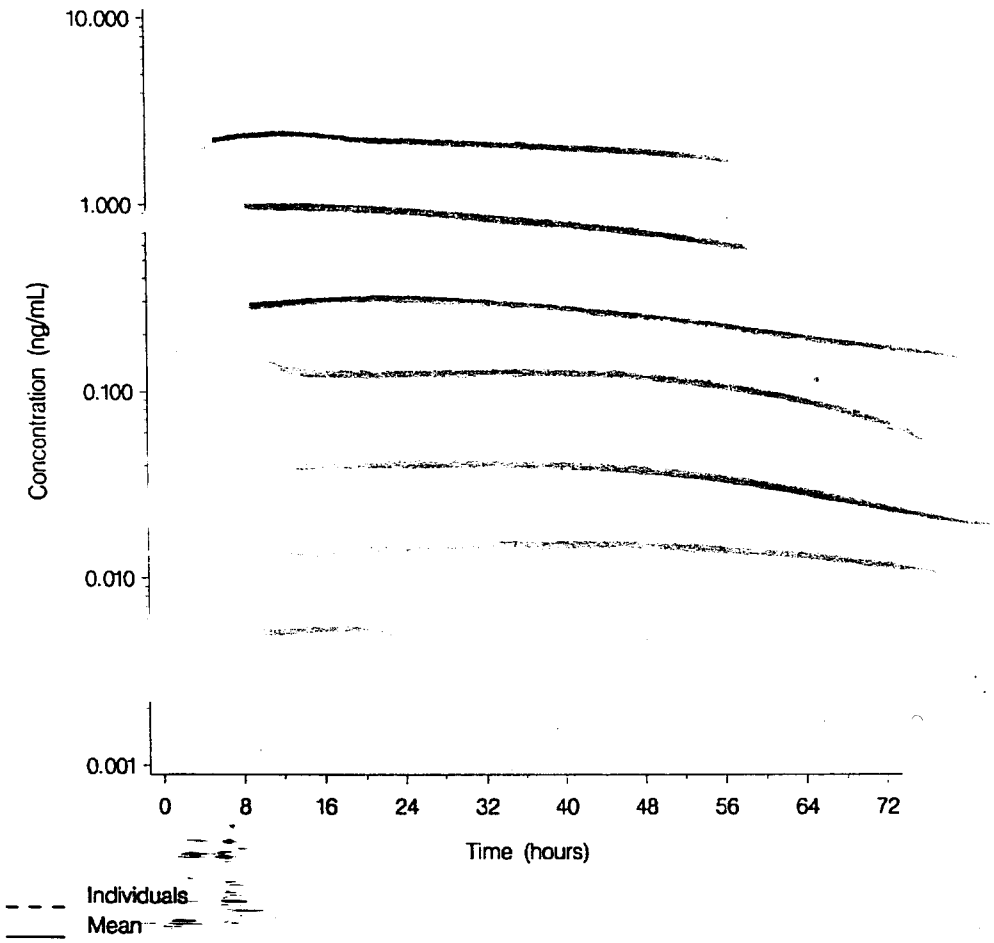


FIG. 79 TOTAL EQUILIN PLASMA CONCENTRATIONS: TWO PREMARIN 0.30 MG TABLETS

Figure 79
Total Equilin Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg Tablets
Protocol 0713D2-120-US

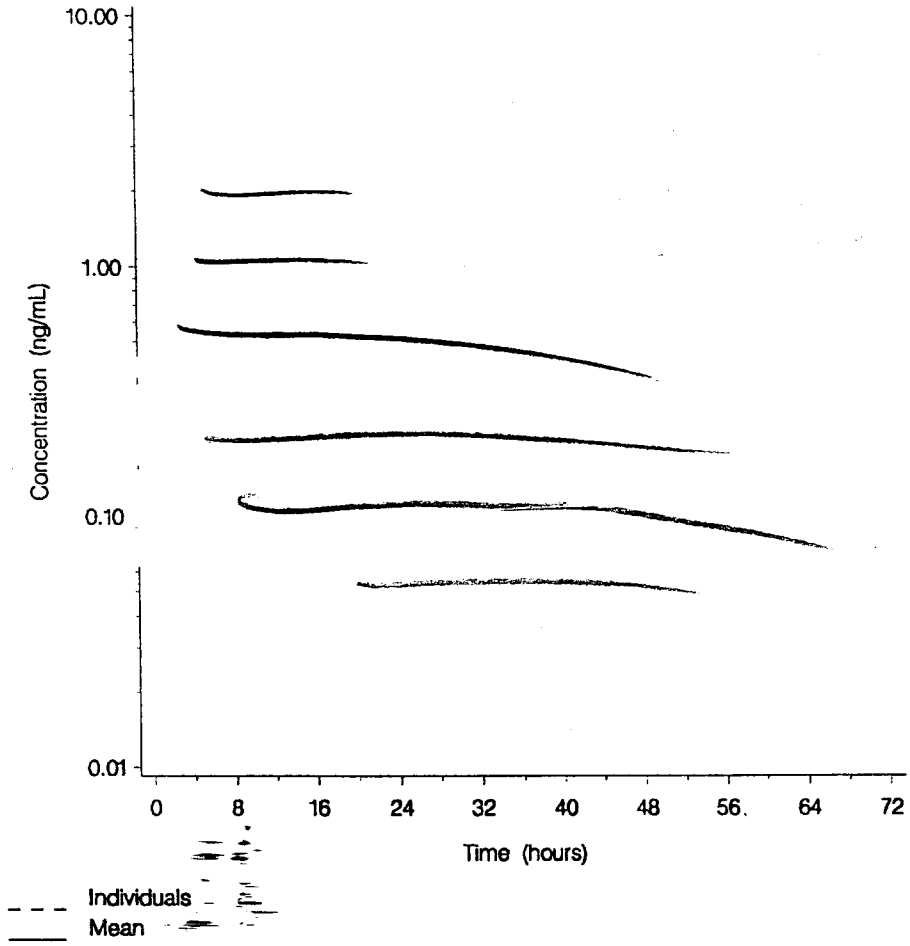


FIG. 87 TOTAL 17BETA-ESTRADIOL PLASMA CONCENTRATIONS: TWO PREMARIN 0.30 MG TABLETS

Figure 87
Total 17Beta–Estradiol Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg Tablets
Protocol 0713D2–120–US

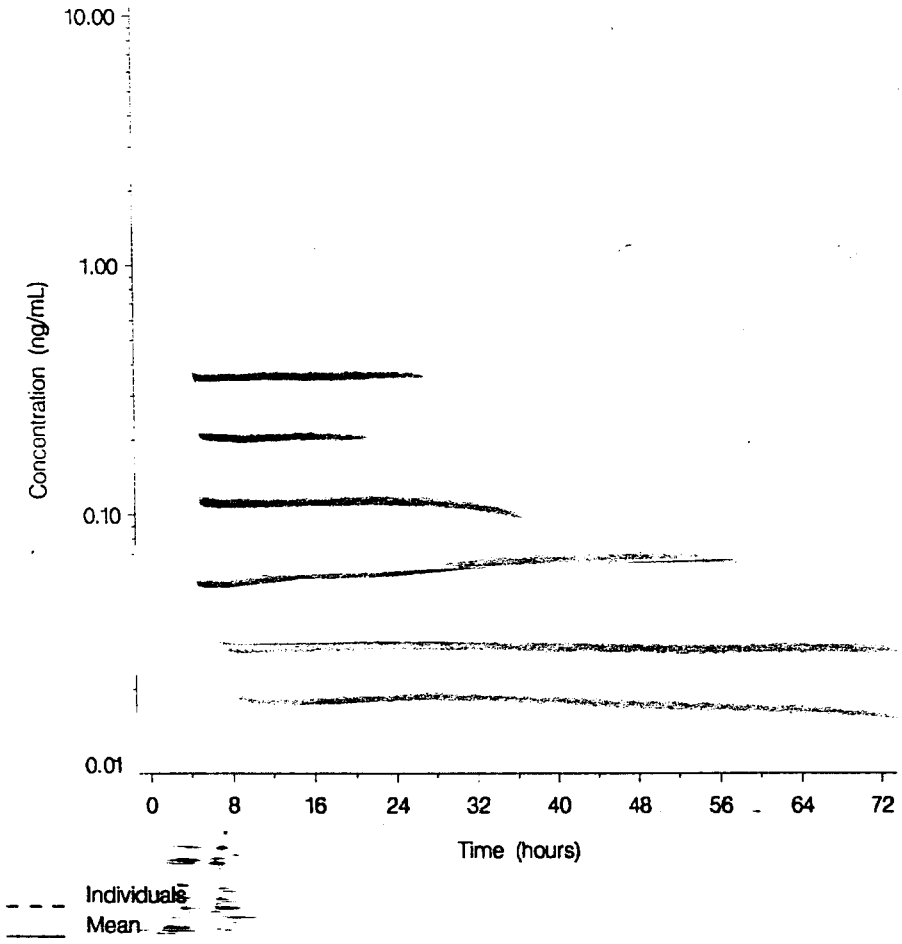


FIG. 95 TOTAL 17BETA-ESTRADIOL PLASMA CONCENTRATIONS ADJUSTED FOR BASELINE: TWO PREMARIN 0.30 MG TABLETS

Figure 95
Total 17Beta-Estradiol Plasma Concentrations Adjusted for Baseline
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg Tablets
Protocol 0713D2-120-US

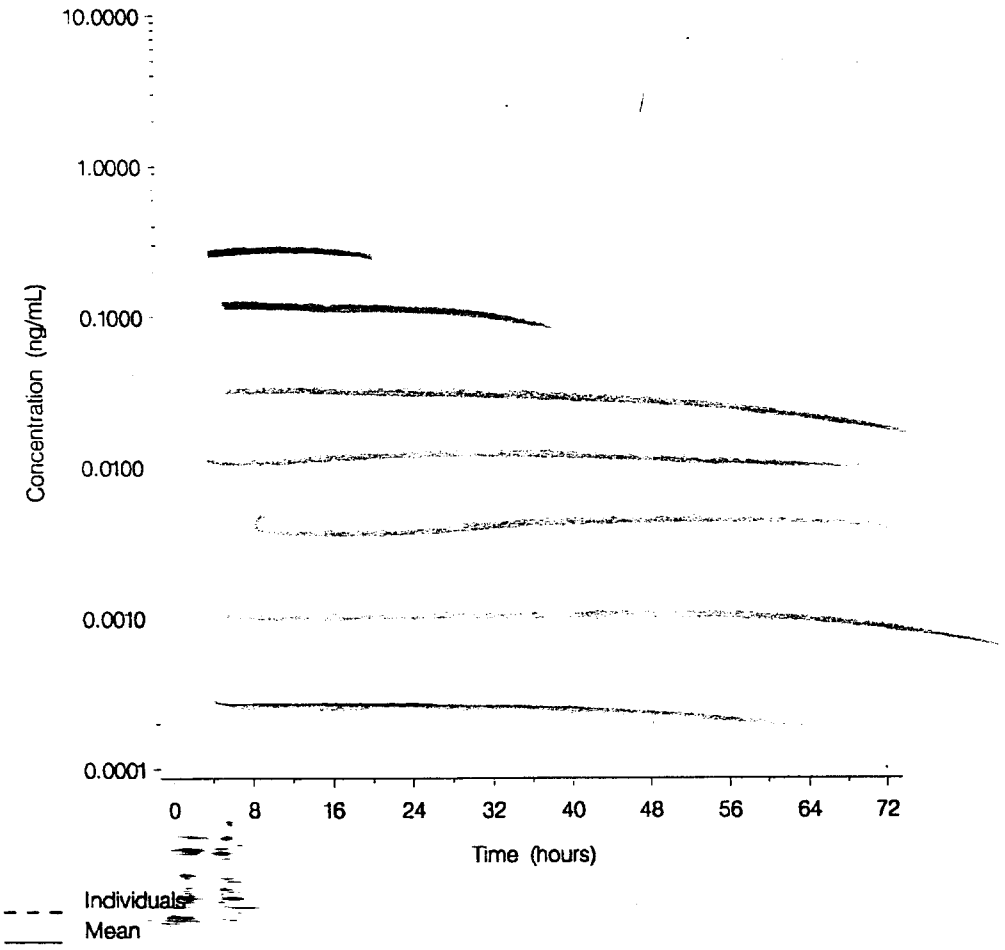


FIG. 103 TOTAL 17BETA-DIHYDROEQUILIN PLASMA CONCENTRATIONS: TWO PREMARIN 0.30 MG TABLETS

Figure 103
Total 17Beta – Dihydroequilin Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg Tablets
Protocol 0713D2–120–US

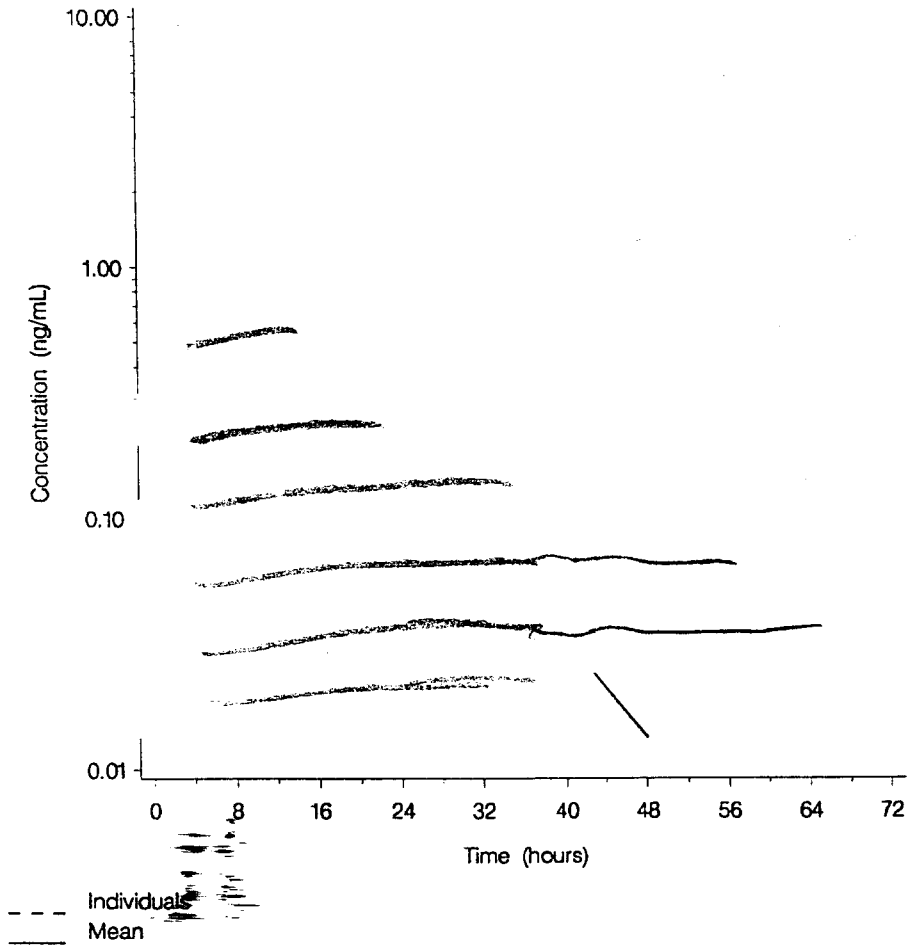


FIG. 111 TOTAL DELTA8,9-DEHYDROESTRONE PLASMA CONCENTRATIONS: TWO PREMARIN 0.30 MG TABLETS

Figure 111
Total Delta8,9 – Dehydroestrone Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg Tablets
Protocol 0713D2 – 120 – US

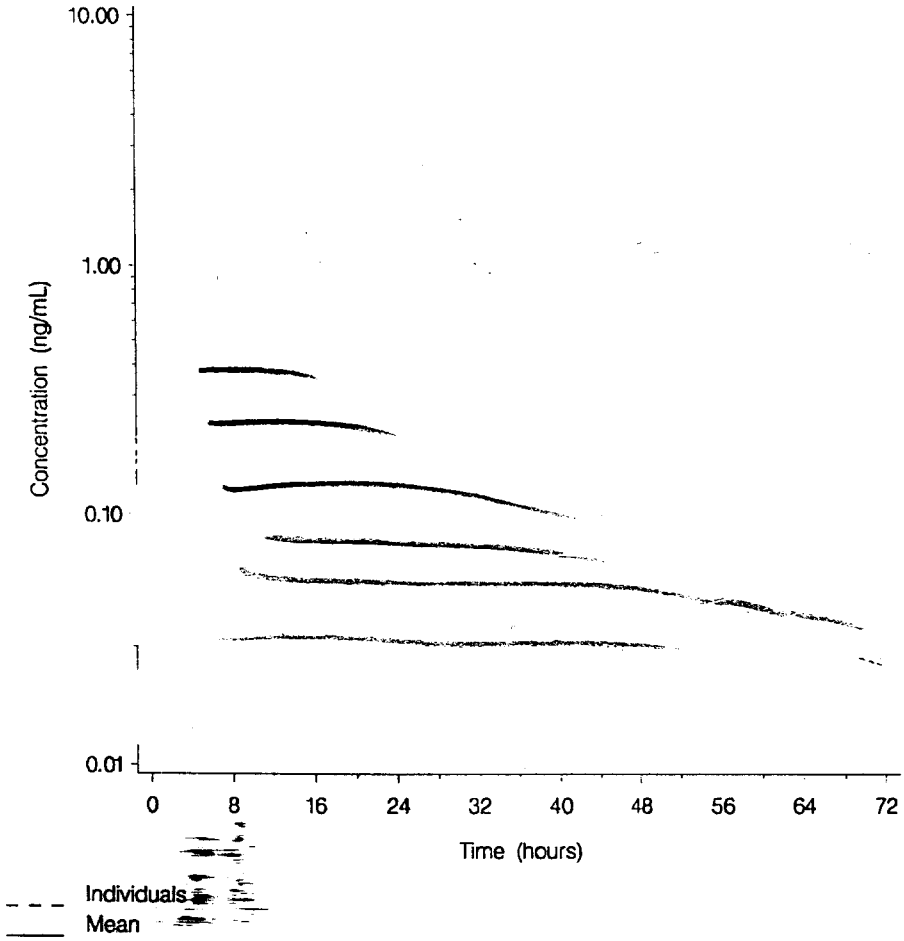


FIG. 119 TOTAL 17BETA-DELTA8,9-DEHYDROESTRADIOL PLASMA CONCENTRATIONS: TWO PREMARIN 0.30 MG TABLETS

Figure 119
Total 17Beta – Delta8,9 – Dehydroestradiol Plasma Concentrations
in Healthy Postmenopausal Women Receiving
Two Premarin 0.30 mg Tablets
Protocol 0713D2 – 120 – US

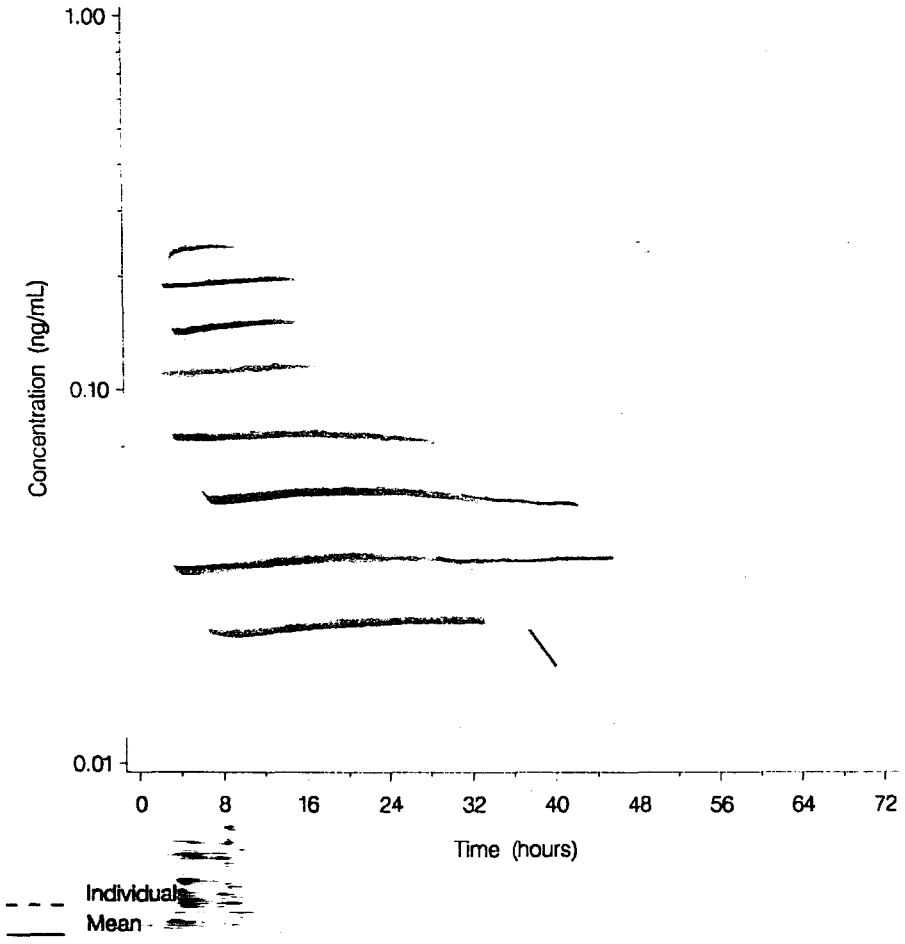


TABLE 1.3.1F. UNCONJUGATED ESTROGEN PHARMACOKINETIC PARAMETERS (MEAN ± SD) FOLLOWING 2 X 0.3 MG CE ADMINISTRATION

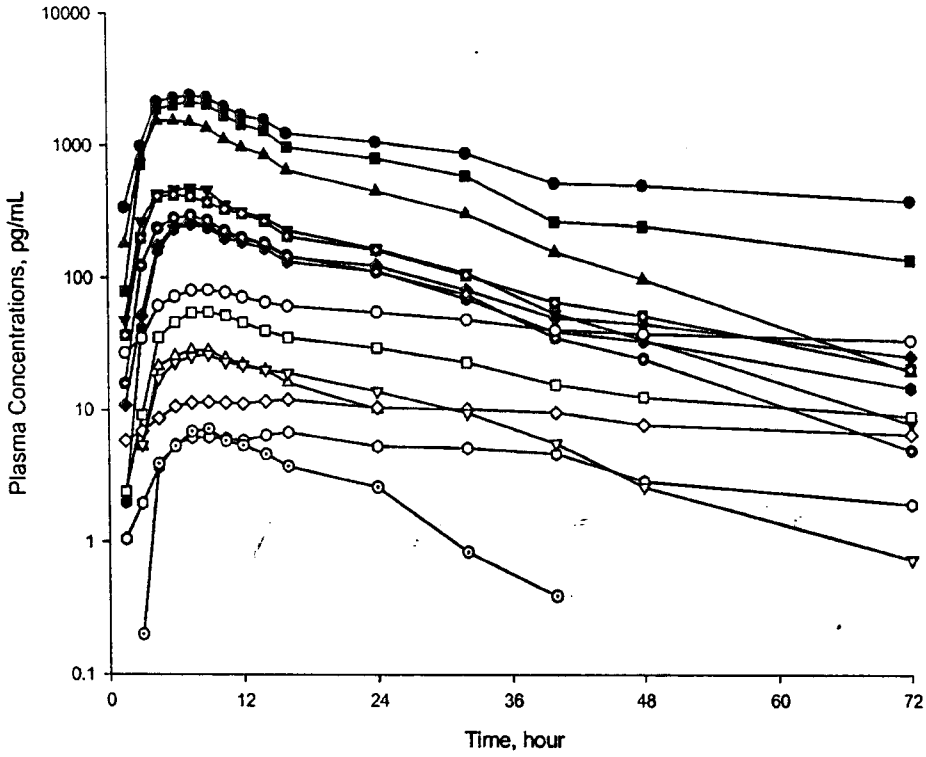
Component	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	81.5 ± 26.8	7.8 2.1	54.7 ± 23.0	5390 ± 2677
Estrone Adjusted for Baseline	58.1 ± 24.6	7.8 ± 2.1	21.1 ± 9.4	1467 ± 604
Equilin	30.7 ± 14.3	7.2 ± 2.0	18.3 ± 20.1	652 ± 444
17β-Estradiol	11.9 ± 3.9	10.2 ± 3.6	48.7 ± 18.3	857 ± 463
17β-Estradiol adjusted for baseline	8.6 ± 3.8	10.2 ± 3.6	20.8 ± 6.1	301 ± 111
17β-Dihydroequilin	24.3 ± 8.6	8.0 ± 2.8	13.5 ± 5.1	514 ± 171
$\Delta^{8,9}$-Dehydroestrone	NA[a]	NA	NA	NA
17β-$\Delta^{8,9}$-Dehydroestradiol	7.5 ± 1.8	7.4 ± 2.2	NA	59 ± 28

a: NA = Not available due to low plasma concentrations.

TABLE 1.3.1G. TOTAL ESTROGEN PHARMACOKINETIC PARAMETERS (MEAN ± SD) FOLLOWING 2 X 0.3 MG CE ADMINISTRATION

Component	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Estrone	2.53 ± 0.80	6.5 ± 1.9	25.4 ± 5.5	61.0 ± 26.1
Estrone adjusted for baseline	2.35 ± 0.75	6.5 ± 1.9	16.2 ± 5.5	40.8 ± 14.5
Equilin	1.59 ± 0.64	5.9 ± 1.6	11.8 ± 2.5	22.4 ± 9.5
17β-Estradiol	0.26 ± 0.13	8.5 ± 4.1	20.0 ± 8.1	4.8 ± 1.6
17β-Estradiol adjusted for baseline	0.25 ± 0.13	8.5 ± 4.1	15.9 ± 6.4	4.0 ± 1.4
17β-Dihydroequilin	0.39 ± 0.13	5.7 ± 1.5	11.5 ± 4.2	6.1 ± 2.3
$\Delta^{8,9}$-Dehydroestrone	0.46 ± 0.13	5.9 ± 1.1	16.2 ± 3.1	8.2 ± 2.5
17β-$\Delta^{8,9}$-Dehydroestradiol	0.19 ± 0.06	7.0 ± 2.1	13.2 ± 3.6	3.5 ± 1.0

Figure 1.3.1A. MEAN ESTROGEN PLASMA CONCENTRATIONS IN POSTMENOPAUSAL WOMEN RECEIVING 2 X 0.45 mg CONJUGATED ESTROGENS



- Total Estrone
- Total Estrone Adjusted for Baseline
- Total Equilin
- Total 17Beta-Estradiol
- Total 17Beta-Estradiol Adjusted for Baseline
- Total 17Beta-Dihydroequilin
- Total Delta8,9-Dehydroestrone
- Total 17Beta-Delta8,9-Dehydroestradiol
- Estrone
- Estrone_Adjusted for Baseline
- Equilin
- 17Beta-Estradiol
- 17Beta-Estradiol Adjusted for Baseline
- 17Beta-Dihydroequilin
- 17Beta-Delta 8,9-Dehydroestradiol

TABLE 1.3.1D. UNCONJUGATED ESTROGEN PHARMACOKINETIC PARAMETERS (MEAN ± SD) FOLLOWING 2 X 0.45 MG CE ADMINISTRATION

Component	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	91.7 ± 29.0	8.7 ± 2.4	56.4 ± 38.3	6344 ± 3549
Estrone Adjusted for Baseline	65.4 ± 25.9	8.7 ± 2.4	20.3 ± 7.8	1940 ± 779
Equilin	34.8 ± 16.5	7.6 ± 2.5	21.9 ± 24.7	849 ± 513
17β-Estradiol	14.3 ± 5.8	17.3 ± 9.7	47.0 ± 20.4	1152 ± 761
17β-Estradiol adjusted for baseline	9.2 ± 3.7	17.5 ± 9.8	24.6 ± 13.1	401 ± 211
17β-Dihydroequilin	30.5 ± 11.8	8.9 ± 4.1	16.2 ± 4.3	775 ± 264
$\Delta^{8,9}$-Dehydroestrone	6.3 ± 2.1	8.0 ± 2.8	NA[a]	NA
17β-$\Delta^{8,9}$-Dehydroestradiol	9.7 ± 3.3	8.9 ± 1.7	NA	122 ± 90

a: NA = Not available due to low plasma concentrations.

TABLE 1.3.1E. TOTAL ESTROGEN PHARMACOKINETIC PARAMETERS (MEAN ± SD) FOLLOWING 2 X 0.45 MG CE ADMINISTRATION

Component	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Estrone	2.82 ± 1.29	7.1 ± 1.9	27.6 ± 9.6	77.1 ± 25.6
Estrone adjusted for baseline	2.56 ± 1.22	7.1 ± 1.9	14.7 ± 6.2	48.0 ± 17.9
Equilin	1.86 ± 0.96	5.9 ± 1.9	11.8 ± 3.8	29.2 ± 15.9
17β-Estradiol	0.37 ± 0.21	10.4 ± 6.6	22.9 ± 12.7	7.3 ± 2.0
17β-Estradiol adjusted for baseline	0.35 ± 0.21	10.4 ± 6.6	18.4 ± 11.1	6.0 ± 2.4
17β-Dihydroequilin	0.58 ± 0.28	6.6 ± 2.2	12.4 ± 4.6	9.8 ± 4.5
$\Delta^{8,9}$-Dehydroestrone	0.48 ± 0.18	6.3 ± 1.8	18.3 ± 5.4	10.0 ± 3.5
17β-$\Delta^{8,9}$-Dehydroestradiol	0.34 ± 0.21	7.1 ± 2.0	13.1 ± 3.8	6.4 ± 3.5

Attachment 3

TABLE 1.3 1C. DOSE PROPORTIONALITY ANALYSIS FOR ESTROGEN COMPONENTS AND MPA FOR ALL DOSE GROUPS IN 119 AND 120 STUDIES

Component	Pharmacokinetic Parameter	95% Confidence Limit for Exponent of Power Model
Unconjugated estrone adjusted for baseline	C	0.729-1.135
	AUC_t	0.926-1.375
	AUC	0.885-1.350
Unconjugated equilin	C_{max}	0.588-1.004
	AUC_t	1.058-1.572
	AUC	0.571-1.046
Unconjugated 17β- estradiol adjusted for baseline	C_{max}	0.604-0.974
	AUC_t	0.833-1.239
	AUC	0.716-1.161
Unconjugated 17β- dihydroequilin	C_{max}	0.727-1.077
	AUC_t	0.927-1.301
	AUC	0.797-1.126
17β-$\Delta^{8,9}$-dehydroestradiol	C_{max}	0.616-0.946
	AUC_t	1.251-1.981
	AUC	NA[a]
Total estrone adjusted for baseline	C_{max}	0.621-1.021
	AUC_t	0.766-1.151
	AUC	0.756-1.160
Total equilin	C_{max}	0.655-1.077
	AUC_t	0.709-1.139
	AUC	0.682-1.097
Total 17β-estradiol adjusted for baseline	C_{max}	0.654-1.173
	AUC_t	0.817-1.228
	AUC	0.764-1.165
Total 17β- dihydroequilin	C_{max}	0.762-1.168
	AUC_t	0.884-1.304
	AUC	0.822-1.221
Total $\Delta^{8,9}$-dehydroestrone	C_{max}	0.526-0.876
	AUC_t	0.651-1.007
	AUC	0.613-0.948
Total 17β-$\Delta^{8,9}$-dehydroestradiol	C_{max}	0.875-1.340
	AUC_t	0.983-1.469
	AUC	0.827-1.244
MPA	C_{max}	0.722-1.195
	AUC_t	0.847-1.272
	AUC	0.697-1.100

a: NA = not available due to low plasma concentrations.

Attachment 4

APPEARS THIS WAY
ON ORIGINAL

MPA [redacted] and [redacted] is in multiples of [redacted] tablets. During development, the production of clinical trial batches of core tablets may have been produced from less than [redacted] batches.

Table 1.4A lists the formulations for the CE and CE/MPA tablets used in the referenced clinical studies.

TABLE 1.4A. FORMULATIONS USED IN CLINICAL STUDIES

	Study		
Component (mg)	119-US	120-US	309-US
CE 0.3		0930329B	0930329B
CE 0.45	0930287B		0930287B
CE 0.625			0929535B
CE 0.3/MPA 1.5		0930328B	0930328B
CE 0.45/MPA1.5	0930288B	0930288B	0930288B
CE 0.45/MPA 2.5	0930289B		0930289B
CE 0.625/MPA 2.5	0930230B	0930230B	0930230B

Table 1.4B presents specific batch information for the tablets used in the pharmacokinetic and clinical efficacy studies.

[redacted]

TABLE 1.4B. TABLETS USED IN CLINICAL STUDIES

Component (mg)	Formulation Number	Batch Number	Study	Date of Manufacture
CE 0.3	0930329B	3THP	120-US, 309-US	3/94
		1997B0092	309-US	7/97
CE 0.45	0930287B	3TEL	119-US,	11/93
		1997B00091	309-US	7/97
CE 0.625	0929535B	3TFQ	309-US	5/93
		9610332	309-US	6/96
CE 0.3/MPA 1.5	0930328B	3THN	120-US,	3/94
		1997B0093	309-US	7/97
CE 0.45/MPA	0930288B	3TEM	119-US, 309-US	11/93
		1997B0089	309-US	7/97
CE 0.45/MPA	0930289B	3TEN	119-US,	11/93
		1997B0090	309-US	7/97
CE 0.625/MPA	0930230B	2TQA	119-US,	7/93
		2TPW	309-US	6/93
		2TPT	309-US	5/93
		9610328	309-US	6/96

Formulation details for the batches used in the current clinical protocols, including 0.3 mg, 0.45 mg, and 0.625 mg CE cores and subsequent [redacted] leading to the 0.3 mg/1.5 mg, 0.45 mg/1.5 mg, 0.45 mg/2.5 mg, and 0.625 mg/2.5 mg CE/MPA are presented in Table 1.4C.

TABLE 1.4C. COMPOSITION OF CLINICAL TRIAL FORMULATIONS USED IN PIVOTAL CLINICAL STUDIES

[redacted]	Amount per Tablet (mg)						
	0.3 mg	0.45 mg	0.625 mg	0.3mg/ 1.5 mg	0.45 mg/ 1.5 mg	0.45 mg/ 2.5 mg	0.625 mg/ 2.5 mg
	----------Formulation----------						
Ingredients	0930329B	0930287B	0929535B	0930328B	0930288B	0930289B	0930230B
Core Tablet							
Conjugated Estrogens (CE) [redacted]	[redacted]						
[redacted]							
Lactose [redacted]							
Methylcellulose, 15 cps							
Magnesium Stearate							
[redacted]							
Methylene Chloride [d]							
[redacted]							
Polyethylene Glycol [redacted]							
Glyceryl Monooleate							
[redacted]							
Pharmaceutical Glaze [e]							
Calcium Sulfate [redacted]							

TABLE 1.4C. COMPOSITION OF CLINICAL TRIAL FORMULATIONS USED IN PIVOTAL CLINICAL STUDIES

[redacted]	Amount per Tablet (mg)						
	0.3 mg	0.45 mg	0.625 mg	0.3mg/ 1.5 mg	0.45 mg/ 1.5 mg	0.45 mg/ 2.5 mg	0.625 mg/ 2.5 mg
	Formulation						
Ingredients	0930329B	0930287B	0929535B	0930328B	0930288B	0930289B	0930230B
[redacted]							
Sucrose							
Titanium Dioxide							
[redacted]							
Povidone							
Sucrose							

TABLE 1.4C. COMPOSITION OF CLINICAL TRIAL FORMULATIONS USED IN PIVOTAL CLINICAL STUDIES

	Amount per Tablet (mg)						
	0.3 mg	0.45 mg	0.625 mg	0.3mg/ 1.5 mg	0.45 mg/ 1.5 mg	0.45 mg/ 2.5 mg	0.625 mg/ 2.5 mg
	Formulation						
Ingredients	0930329B	0930287B	0929535B	0930328B	0930288B	0930289B	0930230B
Sucrose							
Titanium Dioxide							
Carnauba Wax							

NDA #21-417

02 April 2002

Premarin Tablets, 0.3 mg and 0.45 mg
Osteoporosis Indication

CE DISSOLUTION DATA FOR 0.3 mg CLINICAL TABLET BATCHES USED IN STUDIES 120-US AND 309-US
TABLET FORMULATION 0930329B

Batch 3THP Date of Manufacture: March 1994
Method 3256-178 (USP 24 [redacted] N=12

Time (hours)	% Dissolved	Range	Average	Std. Dev.
1	[redacted]	[redacted]	7	2.1
2	[redacted]	[redacted]	33	3.2
4	[redacted]	[redacted]	73	3.1
6	[redacted]	[redacted]	95	2.4
10	[redacted]	[redacted]	105	1.9

Batch 1997B0092 Date of Manufacture: July 1997
Method 3256-178 (USP 24 [redacted] N=12

Time (hours)	% Dissolved	Range	Average	Std. Dev.
2	[redacted]	[redacted]	33	4.5
5	[redacted]	[redacted]	80	4.3
8	[redacted]	[redacted]	96	5.9

Premarin Tablets, 0.3 mg and 0.45 mg
Osteoporosis Indication

CE DISSOLUTION DATA FOR 0.3 mg MARKET PRODUCT TABLET BATCHES

Batch R014240 Date of Manufacture: March 2001
Method L20744-005 (USP 24 [redacted] N=24

Time (hours)	% Dissolved	Range	Average	Std. Dev.
2	[redacted]	[redacted]	35	3.4
5	[redacted]	[redacted]	83	3.8
8	[redacted]	[redacted]	99	3.0

Batch R014165 Date of Manufacture: January 2001
Method L20744-005 (USP 24 [redacted] N= [redacted]

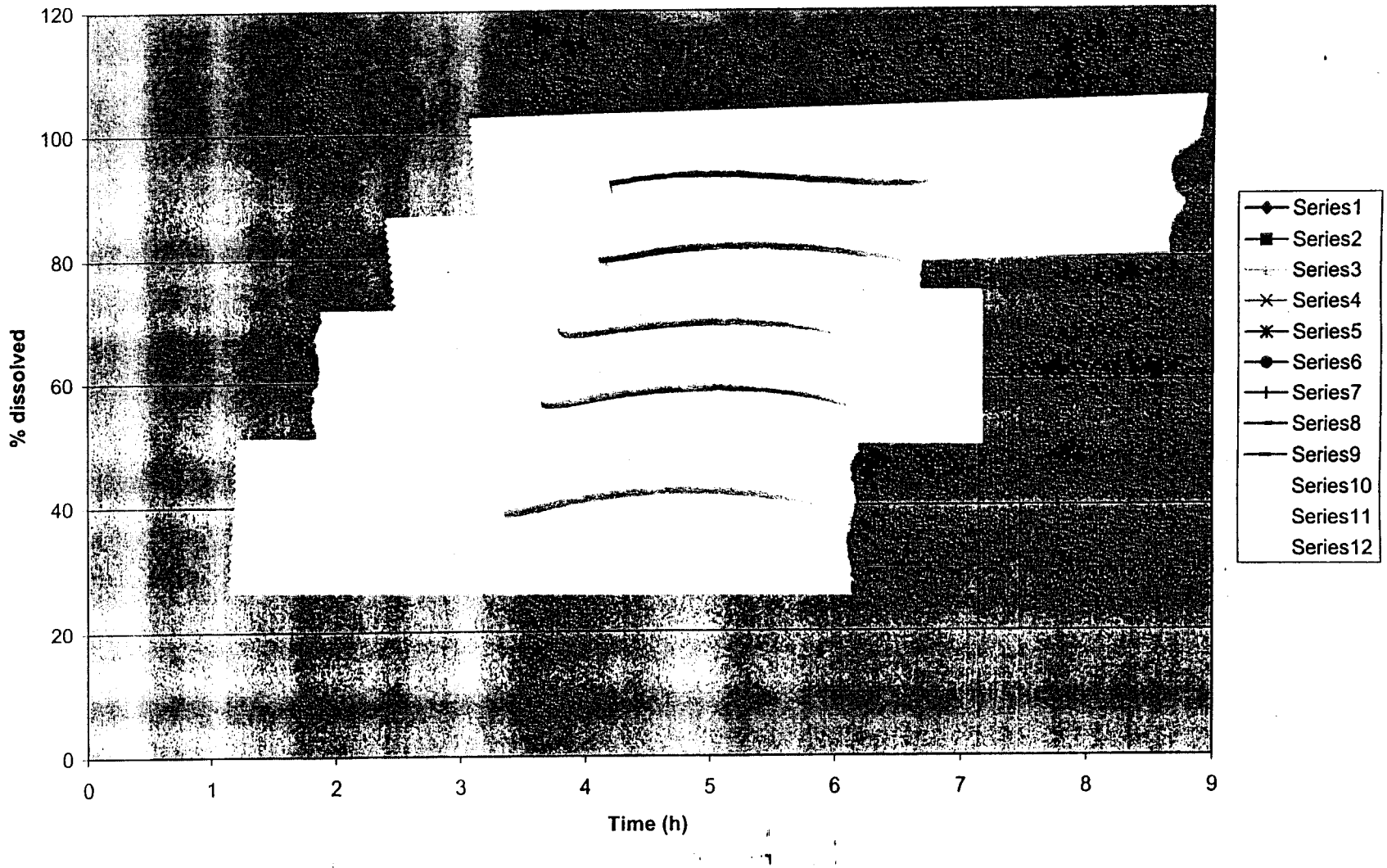
Time (hours)	% Dissolved	Range	Average	Std. Dev.
2	[redacted]	[redacted]	34	3.3
5	[redacted]	[redacted]	82	3.1
8	[redacted]	[redacted]	98	2.2

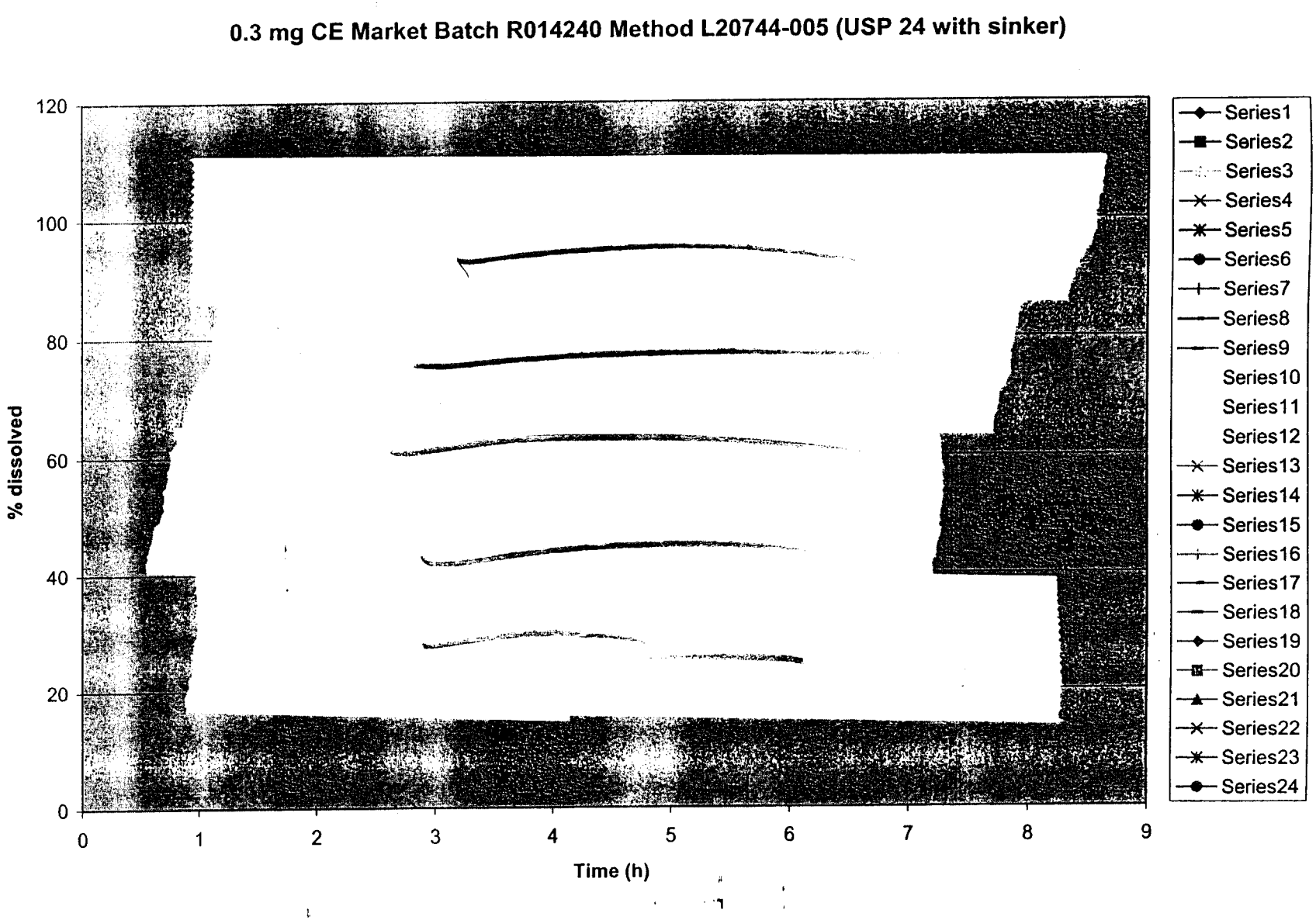
Premarin Tablets, 0.3 mg and 0.45 mg
Osteoporosis Indication

CE DISSOLUTION DATA FOR 0.3 mg MARKET PRODUCT TABLET BATCHES

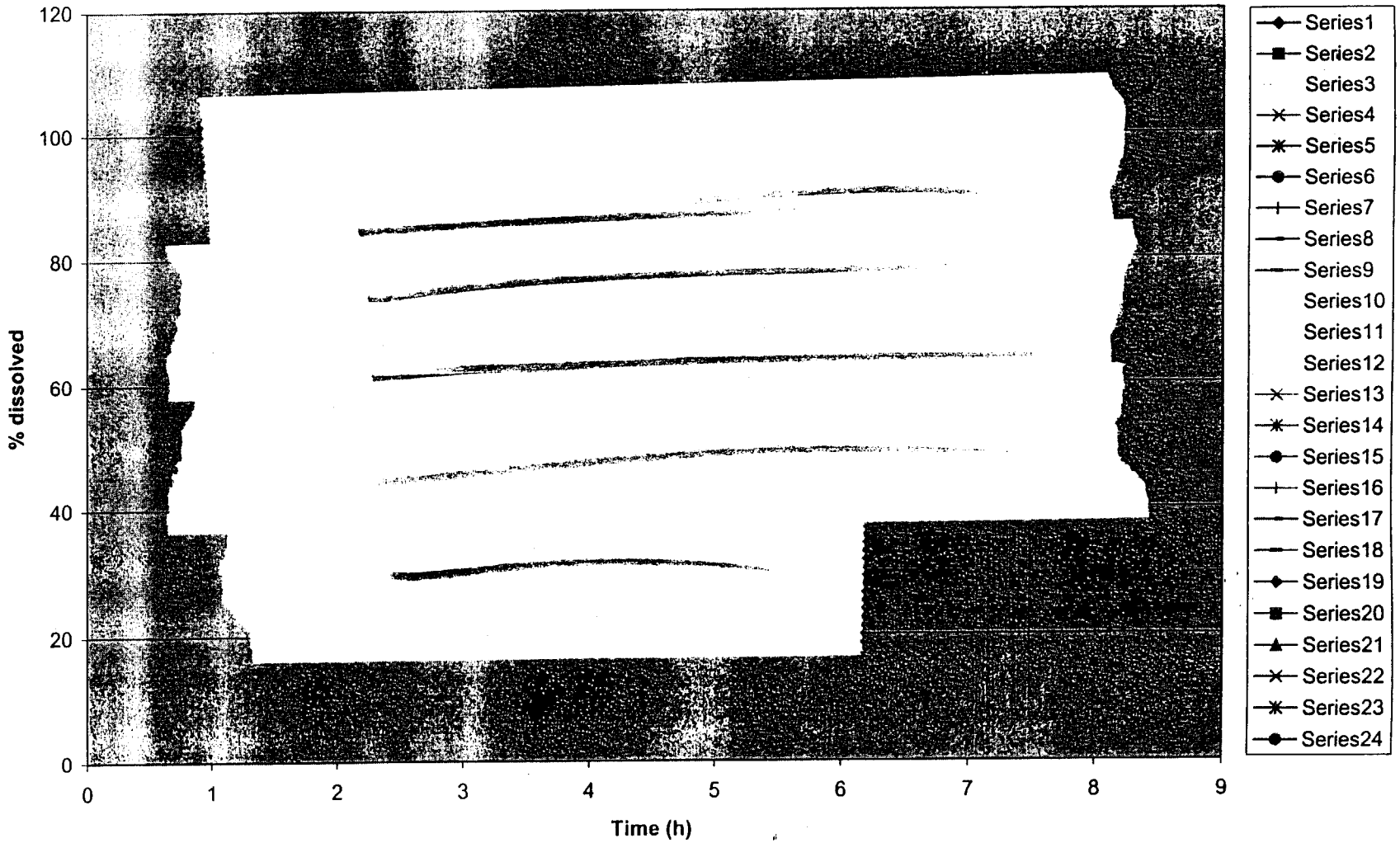
Batch R014147 Date of Manufacture: April 2001
Method L20744-005 (USP 24 [redacted] *N=24*

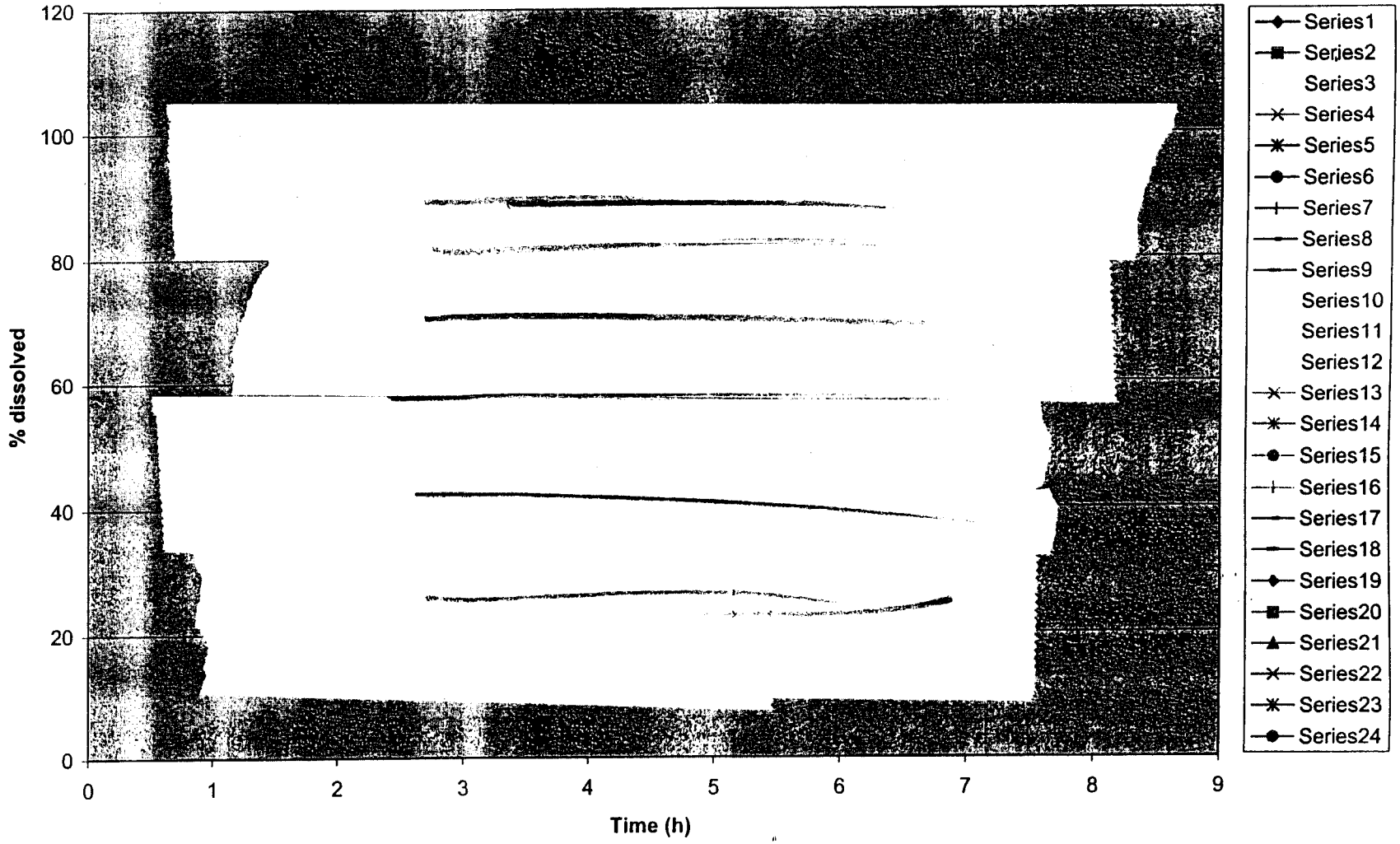
Time (hours)	% Dissolved	Range	Average	Std. Dev.
2	[redacted]	[redacted]	26	3.8
5	[redacted]	[redacted]	76	3.8
8	[redacted]	[redacted]	96	2.1


0.3 mg CE Clinical Batch 1997B0092 Method 3256-178 (USP 24 without sinker)
% dissolved
120
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
Time (h)
Series1
Series2
Series3
Series4
Series5
Series6
Series7
Series8
Series9
Series10
Series11
Series12


0.3 mg CE Market Batch R014240 Method L20744-005 (USP 24 with sinker)
% dissolved
120
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
Time (h)
Series1
Series2
Series3
Series4
Series5
Series6
Series7
Series8
Series9
Series10
Series11
Series12
Series13
Series14
Series15
Series16
Series17
Series18
Series19
Series20
Series21
Series22
Series23
Series24

0.3 mg CE Market Batch R014165 Method L20744-005 (USP 24 with sinker)




0.3 mg CE Market Batch R014147 Method L20744-005 (USP 24 with sinker)
% dissolved
120
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
Time (h)
Series1
Series2
Series3
Series4
Series5
Series6
Series7
Series8
Series9
Series10
Series11
Series12
Series13
Series14
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Series16
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Series23
Series24

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S.W. Johnny Lau
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Hae-Young Ahn
10/17/02 03:54:16 PM
BIOPHARMACEUTICS