CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-663

Clinical Pharmacology and Biopharmaceutics Review

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-663	*Brand Name*	Menopur
OCPB Division (I, II, III)	DPE II (HFD 870)	*Generic Name*	Menotropins
Medical Division	DRUDP (HFD 580)	*Drug Class*	Female Gonadotropins
OCPB Reviewer	Dhruba J. Chatterjee, Ph.D.	*Indication(s)*	Assisted Reproductive Technologies (ART)
OCPB Team Leader	Ameeta Parekh, Ph.D.	*Dosage Form*	Injectable solution
Date of Submission	12/29/2003	*Dosing Regimen*	Once daily (for few days during ART procedure)
Estimated Due Date of OCPB Review	9/15/2004	*Route of Administration*	Subcutaneous injection
PDUFA Due Date	10/29/2004	*Sponsor*	Ferring Pharmaceuticals Inc.
Division Due Date	9/29/2004	*Priority Classification*	3S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	4		
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

body wt.				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		• Sponsor mentions (CMC section Vol 1.3, Pg 164) that intended commercial formulation is same as that in Phase 3 • Sponsor claims in label that product is fine either from SC — — - this is a review issue • An animal study to determine bioactivity submitted in this section will be deferred to Pharm/Tox for review
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

OCPB Briefing held on 10/12/2004 was attended by J. Hunt, A. Parekh, S. Slaughter, A. Gassman, M. Kauffman, S. Apparaju and DJ Chatterjee

Clinical Pharmacology & Biopharmaceutics Review

NDA:	21-663
Product Trade Name:	Menopur® (menotropins for injection)
Active Ingredient/s:	Human Follicle-stimulating Hormone (FSH) and Luteinizing Hormone (LH)
Indication:	[redacted] pregnancy in Assisted
Reproductive:	Technologies (ART)
Submission Date:	Dec 29, 2003
Sponsor:	Ferring Pharmaceuticals
Type of Submission:	Original NDA (3S)
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.

Table of Contents

Synopsis

Sponsor has submitted 3 Phase 3 clinical studies (2 ART studies [ ] and additional CPB studies in support of efficacy and safety of this product. The product contains 75 IU each of FSH and LH to be administered via either the subcutaneous (SC) or the intramuscular (IM) routes. Among the 3 studies relevant to OCPB, one is a pivotal bioequivalence study linking the US (proposed commercial) formulation to the one used in the European study. These two formulations are different.

Background

Menopur® is a [ ] purified preparation of the human gonadotropins extracted from the urine of postmenopausal women. It contains equal amounts of follicle stimulating hormone (FSH) and luteinizing hormone (LH). Menopur® (purified urinary human FSH [u-hFSH]) is a new purified formulation of a currently approved human menotropin product, Repronex®, which is approved for induction of ovulation and multiple follicular development in ART when administered by the intramuscular route.

Recommendation

This application is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. Changes in labeling language is detailed in the 'Labeling Comments' section and have been communicated to the sponsor.

Phase IV Commitments

None

Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

- The sponsor has submitted 2 pharmacokinetic (PK) studies to support the PK profile of Menopur following subcutaneous and intramuscular administrations. The studies provide evidence of an acceptable PK profile for Menopur. Results from the studies show that exposure to FSH from the IM route of administration may be 15% lower as compared to that from the SC route.

- The US Phase III clinical trial with the US formulation (subcutaneous) did not provide evidence of efficacy for the ART indication. The sponsor is relying on the results of a Phase III safety/efficacy study conducted in the EU using the subcutaneous route in support of this NDA (for approval of the subcutaneous route of administration for the ART indication). The formulation of EU Menopur is different (20 fold higher in amount of polysorbate 20) as compared to that proposed for commercial use in the US. To 'link' this difference, the sponsor provided results from a pivotal bioequivalence study in addition to the two PK studies mentioned above.

- The results of the pivotal BE study show that the two formulations are bioequivalent with respect to FSH exposure.

- This product is a combination of proteins with its efficacy possibly linked to a tertiary structure. In the absence of evidence that the tertiary structure of the proteins is unaltered with this formulation change (or pharmacodynamic equivalence), mere evidence of similarity based on a BE study between two formulations *may not* reflect clinical equivalence.

Background

Questions addressed in this section:

What are the highlights of chemistry and formulation of the drug and drug product?
What is the mechanism of action, proposed indication and main goal of therapy?
What are other drugs available in this class, and what is its foreign marketing history?

The subject of this submission, Menopur®, contains 75 IU of FSH and 75 IU of LH activity (per vial). Menopur® is supplied in sterile vials as a lyophilized powder. The patient will dissolve the contents of one to four vials of Menopur® in one milliliter of sterile saline and administer subcutaneously or intramuscularly.

Proposed indications for Menopur® administered subcutaneously or intramuscularly are (a) the development of multiple follicles and pregnancy in the ovulatory patient participating in an ART program [ ] [ ] FSH (along with LH) stimulates follicular development and prepares the reproductive tract for implantation and pregnancy.

There are two approved gonadotropin products available on the market in the United States for treatment of infertility that contain urinary-derived human follicle stimulating (FSH) and luteinizing hormone (LH) in equal amounts. These FSH/LH preparations are used for multiple follicular development in patients undergoing Assisted Reproductive Technology (ART) therapy and patients undergoing ovulation induction. In addition, several recombinant and urinary-derived human follicle stimulating hormone (FSH) products are also available for the same indications of ovulation induction and multiple follicular development in a patient undergoing ART therapy. The new formulation of Menopur® (menotropins for injection USP) contains the same active urinary-derived h-FSH (and h-LH) as the approved Repronex® formulation; however, the urine from postmenopausal women will be processed using a different purification method. The new Menopur® formulation will be available as a freeze-dried cake that is administered after reconstitution with a buffered solution (identical to Repronex®).

Ferring has marketed menotropins in Europe and the Middle East under the brand name of Menogon® since June 1993. Ferring's approved product Repronex® is only marketed in the United States. Menopur® has been marketed overseas since 1999 using a slightly different formulation from the one proposed for use in the United States (please see Table 1). The sponsor has used terms "purified or highly purified Repronex" or "purified menotropin" to describe Menopur® in this submission. **The reader is strongly recommended to refer also to the Medical Officer's review for a more detailed background of this class of drugs as well as the regulatory background for this NDA.**

In support of this current approval for the US market, the sponsor has submitted three completed study reports relevant to OCPB (in addition to three controlled Phase III clinical studies with safety/efficacy information).

Table 1. Composition of the US and the European Menopur formulations

Product Component	US Menopur	Europe Menopur
Menotropin	75 IU	82.5 IU
Lactose Monohydrate	21 mg	[ ]
Polysorbate 20	[ ]	[ ]
pH Adjustment		
[ ]		[ ]
[ ]		[ ]
Phosphoric acid [ ]	As needed	
Sodium phosphate dibasic heptahydrate [ ]	As needed	
[ ]	[ ]	

[Please refer to the section on review of the BE Study 2003-02 for a discussion on formulation issues].

Clinical Pharmacology

Are all the appropriate moieties monitored in relevant biological fluids for assessment of PK parameters?

Sponsor analyzed and monitored serum levels of only FSH for determination of PK parameters, although the active ingredients are FSH and LH. On discussion with the Medical Reviewer for this NDA, it was confirmed that the majority of pharmacodynamic effect for the sought indication resides with FSH and hence, this is acceptable. Note also that for NDA 21-047 for Repronex, only FSH was analyzed for PK parameters.

What studies related to clinical pharmacology and biopharmaceutics have been submitted in support of this NDA?

Sponsor has submitted 3 studies related to OCPB as follows:

- Study 2000-03: A study to compare the clinical pharmacokinetics of Purified Repronex SC, Purified Repronex IM, Repronex SC and Repronex IM
- Study MFK/I/1098: A study to compare the PK parameters following administration of menotropin via the IM or SC routes
- Study 2003-02: A clinical study to assess the bioequivalence of the proposed US commercial formulation of menotropin relative to the currently marketed European formulation of menotropin for injection

In addition, the sponsor has submitted analytical method and validation reports on the FSH assay.

Note: The subject of this NDA, Menopur, is also referred to as 'purified Repronex' in some of the studies mentioned above.

What are single and multiple dose pharmacokinetic parameters of FSH following SC and IM administration of purified Repronex as compared to Repronex?

Study 2000-03 was a randomized, open-label, cross-over, parallel group multi-center study comparing the PK parameters of FSH (and LH) following administration of either Repronex or purified Repronex (each formulation administered SC and IM) in 33 normal, pre-menopausal, down-regulated female subjects. Following screening and baseline determinations, subjects were randomized to (4 blocks) receive 225 IU FSH:LH either SC Repronex, IM Repronex, SC purified Repronex or IM purified Repronex (Phase I of study). In phase II of the study, the subjects were crossed over to another formulation (eg. subjects receiving purified Repronex in Phase I as SC received Repronex as SC in Phase II, and those who received purified Repronex as IM in Phase I, received Repronex as IM in Phase II). In Phase III of the study, all subjects were crossed over again to receive multiple doses of purified Repronex via a different route than in Phases I and II (dose – day 1 was 225 IU followed by 150 IU FSH:LH QD x 6). There was a 7-day gap between the 3 treatment Phases. In Phases I and II, 12 PK blood samples were collected between 0 – 120 hours post dose. In Phase III, serial blood sampling was performed on days 1 and 7 (8 samples between 0 – 24h) and trough samples on days 2 – 6.

Results

Table 2A.

Table A summarized PK parameters for a single dose of purified Repronex[@] and Repronex[$] by route of administration (SC and IM)

TABLE A
SUMMARY STATISTICS FOR FSH PHARMACOKINETIC PARAMETERS AFTER SINGLE DOSE (PHASE I AND II)

Treatment	Dose	Route	Parameter	Units	Mean	STD	%CV	Count	Min	Max
Repronex[$]	Single	SC	Cmax	mIU/mL	10 02	2 96	29 5	16		
			Tmax	Hr	23 0	21 0	91 0	16		
			AUC24	Hr-mIU/mL	201 9	64 81	32 1	16		
			AUC120	Hr-mIU/mL	798 83	265 94	33 3	16		
purified Repronex[@]	Single	SC	Cmax	mIU/mL	8 52	2 48	29 1	16		
			Tmax	Hr	18	5 75	31 9	16		
			AUC24	Hr-mIU/mL	169 65	57 99	34 2	16		
			AUC120	Hr-mIU/mL	726 18	243 00	33 5	16		
Repronex[$]	Single	IM	Cmax	mIU/mL	9 13	3 05	33 4	17		
			Tmax	Hr	24 35	25 77	105 8	17		
			AUC24	Hr-mIU/mL	182 69	66 88	36 6	17		
			AUC120	Hr-mIU/mL	739 81	248 34	33 6	17		
purified Repronex[@]	Single	IM	Cmax	mIU/mL	7 77	2 42	31 1	17		
			Tmax	Hr	27 53	25 37	92 2	17		
			AUC24	Hr-mIU/mL	144 72	44 8	31 0	17		
			AUC120	Hr-mIU/mL	656 13	233 66	35 6	17		

Table 2B.

TABLE B
MULTIPLE DOSE (PHASE III) SUMMARY STATISTICS FOR
FSH PHARMACOKINETIC PARAMETERS

Treatment	Route	Parameter	Units	Mean	STD	%CV	n	Min	Max
purified Repronex®	SC	Cmax1	mIU/mL	11 39	2 16	18 9	17		
		Tmax1	Hr	19	6	32 3	17		
		AUC24	Hr-mIU/mL	220 72	29 45	13 3	17		
		Cmin24	mIU/mL	10 45	2 29	21 9	17		
		Cmin48	mIU/mL	11 71	2 72	23 2	17		
		Cmin72	mIU/mL	12 23	2 86	23 4	17		
		Cmin96	mIU/mL	12 39	3 01	24 3	17		
		Cmin120	mIU/mL	12 58	3 33	26 4	17		
		Cmin144	mIU/mL	12 67	3 32	26 2	17		
		Cmin168	mIU/mL	12 30	2 96	24 1	17		
		Cmaxss	mIU/mL	14 96	3 63	24 3	17		
		Tmaxss	Hr	8	3	34 1	17		
		AUCss	Hr-mIU/mL	622 69	152 96	24 6	17		
purified Repronex®	IM	Cmax1	mIU/mL	9 54	2 14	22 5	16		
		Tmax1	Hr	23	3	15 0	16		
		AUC24	Hr-mIU/mL	188 15	41 69	22 2	16		
		Cmin24	mIU/mL	9 32	1 96	21 0	16		
		Cmin48	mIU/mL	10 15	1 95	19 2	16		
		Cmin72	mIU/mL	10 32	1 99	19 3	16		
		Cmin96	mIU/mL	11 01	1 92	17 4	15		
		Cmin120	mIU/mL	11 38	1 97	17 3	16		
		Cmin144	mIU/mL	11 47	1 69	14 7	16		
		Cmin168	mIU/mL	11 26	1 83	16 3	16		
		Cmaxss	mIU/mL	12 45	2 27	18 3	16		
		Tmaxss	Hr	9	7	73 2	16		
		AUCss	Hr-mIU/mL	546 15	91 21	16 7	16		

Reviewer's comments:

- From Table A, there was a 10 – 15 % (approximately) lower exposure (C_{max} and AUC_{120}) to FSH from the purified formulation as compared to regular Repronex. LH levels were < LOQ.
- There was also about a 10% lower exposure to FSH from IM administration as compared to the same formulation given SC.
- Sponsor presented another table (not shown here) with calculated PK parameters, and the $t_{1/2}$ observed following the single doses were about 25 hrs. This $t_{1/2}$ was observed to be appreciably lower (11 – 13 hrs) as compared to that following single doses (probably a sampling artifact).
- From Table B, there was accumulation of FSH at steady state – about 1.3 fold based on C_{max} and 3 fold based on AUC.
- At steady state, there was approximately a 15% lower mean C_{max} and AUC of FSH with IM administration as compared to that from SC (this may not be significant statistically due to

power of the study). Hence, there is evidence of both a lower rate and extent of drug absorption from the IM administration as compared to SC.

Study MFK/I/1098 was an open label randomized 3-way crossover multiple dose study to compare the PK of FSH (and LH) after IM and SC administration of highly purified (HP) menotropin versus IM administration of Menagon (an approved menotropin in UK).

This study involved 22 healthy female volunteers down-regulated for endogenous FSH production for 5 weeks pre-study. Each volunteer was randomized for one treatment each in Study periods 1, 2 and 3. Each formulation was given in the same dosage regimen: FSH (150 IU) and LH (150 IU) daily for 7 days with at least a 3 week washout period between treatments. Blood samples were taken at baseline, day -6 and 0 of each study period, pre-dose on days 1 – 7 and up to 72 hours following drug administration on day 7 of each study period. PK assessments were made for FSH, LH and estradiol.

Results

The following tables summarize the PK results from this study on day 7 (at SS) (Note: Volunteer 5 was treated as an outlier as she had an unusually high baseline of 7.9 mIU/ml in period 2):

Table 3A

Mean of FSH C_{max} (adjusted) by treatment

Treatment	C_{max} (mIU/ml)		Log_e C_{max} (mIU/ml)	
	Mean ± SD	Min→Max	Mean ± SD	Min→Max
Menogon® i.m. n=18	93 ± 32		22 ± 04	
HPM s.c. n=18	89 ± 35		21 ± 04	
HPM i.m. n=18	79 ± 37		18 ± 11	
HPM i.m. n=17 (without volunteer 5)	84 ± 32		20 ± 05	

SD = standard deviation

Table 3B

Summary of statistical analysis of FSH $\log_e$ C_{max} (adjusted) (n=17, without subject 5)

Treatment comparison	Mean (treatment difference in $\log_e$)	p-value (overall treatment effect)	90% confidence interval	$e^{90\%\ CI}$
A/B	0 06	0 24	-0 028 → 0 155	0 97 → 1 17
A/C	0 15	0 07	0 015 → 0 294	1 02 → 1 34
B/C	0 09	0 31	-0 060 → 0 242	0 94 → 1 27

A = Menogon® i m
B = HPM s c
C = HPM i m

Table 3C

Mean FSH AUC (adjusted) by treatment

Treatment	AUC (h mIU/ml)		$\log_e$ AUC (h mIU/ml)	
	Mean ± SD	Min→Max	Mean ± SD	Min→Max
Menogon® i.m. n=18	186 ± 66		5 2 ± 0 4	
HPM s c n=18	180 ± 77		5 1 ± 0 5	
HPM i.m. n=18	157 ± 76		4 6 ± 1 6	
HPM i m. n=17 (without volunteer 5)	166 ± 67		5 0 ± 0 5	

SD = standard deviation

Table 3D

Summary of statistical analysis of FSH $\log_e$ $AUC_{0\text{-}24}$ (adjusted) (n=17)

Treatment comparison	Mean (treatment difference in $\log_e$)	p-value (overall treatment effect)	90% confidence interval	$e^{90\%\ CI}$
A/B	0 07	0 28	-0 040 → 0 184	0 96 → 1 20
A/C	0 18	0 07	0 020 → 0 336	1 02 → 1 40
B/C	0 11	0 30	-0 066 → 0 279	0 94 → 1 32

A = Menogon® i.m
B = HPM s c
C = HPM i m

Reviewer's comments:

- Steady state C_{max} from the HP menotropin formulation (SC) was generally comparable to that obtained from Study 2000-03 (AUC_{24} comparison could not be made due to the different time cut off for AUC between the two studies at steady state).
- Although the three formulations were generally comparable in the PK parameters, Menagon and HP menotropin were not BE (based on the IM data).

- The SC vs. IM administrations of HP menotropin produced comparable PK profiles, but, were *not* strictly bioequivalent.
- T_{max} values were generally comparable between the three treatments (6.4 – 7.3 hr).
- Clear PK parameter conclusions could not be made for LH, since many of the samples had LH levels below LOQ.
- C_{max}, T_{max} and AUC_{24} parameters were generally comparable for estradiol following administration of the three treatments.

Hence, the two PK studies confirm that the IM administration results in lower exposure to FSH as compared to the SC route. Also, FSH exposure from HP Menotrpin is lower than that obtained from either Repronex or Menagon.

Study 2003-02 was conducted to assess bioequivalence between the US and European formulations of Menopur.

The sponsor has provided results from a Phase III clinical trial conducted in the EU. The regulatory action on the subcutaneous administration of Menopur for the ART indication is dependent on the outcome of this BE study, since evidence of efficacy and safety of Menopur for ART was not provided from the SC route in the US Phase III clinical trial (but evidence of safety/efficacy was provided in the Phase III trial conducted in EU). The formulation used in this EU study is different than that is proposed to be marketed in the US. Hence, this BE study is a key study bridging the two formulations. The difference in the two formulations is presented in Table 1 in the "Background" section of this review.

Note: As seen in Table 1, in addition to the difference in the amount of polysorbate 20, the amount of active ingredient is — higher in the EU product as compared to the proposed US formulation. On inquiring, the sponsor mentioned that that is because of the difference in overfill allowed by the two different manufacturing processes. Additionally, the US and EU batches used for the BE study was assayed (bioassay) at the same time and the FSH and LH units/vial was almost identical (please see attached Facsimile from sponsor in Appendix II).

This was a multi-center, randomized, open-label, single-dose, two-treatment period, crossover study in healthy female subjects. To induce pituitary down-regulation, subjects received Lupron Depot (3.75 mg IM) 28 days and then 7 days prior to the first treatment period. Additionally, another Lupron Depot dose was administered 7 days before second treatment period. Blood samples for serum FSH were pulled at 0 (before) and 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 72, 96, 120 hours post dose. The study was conducted in 57 subjects. However, 52 subjects had completed data from the 2 treatments and only those were used for the final BE analysis. The BE was based only on FSH, as sponsor determined necessary sensitive method of assay for LH is currently unavailable to use for BE determination. Both the treatments were administered subcutaneously and there was a 21 day washout period between them.

The PK parameters were obtained using WinNonlin 4.0.1. The baseline FSH was determined from the mean of 5 pre-dose assessments of FSH prior to Period 1 or Period 2, however, for

baseline-correction of the data, FSH baseline values from Period 1 was used to correct all plasma concentration values of FSH from both periods. [Note: The sponsor determined (possibly later after the study was completed) that there was a statistically significant higher baseline during Period 2 than the baseline for Period 1.] BE was assessed according to the statistical analysis recommended by the Agency's guidance on BE.

Results

The sponsor presented the results in numerous ways, eg.:

- BE analysis with data uncorrected for baseline
- BE analysis with data corrected for baseline
- BE analysis with data uncorrected for baseline only for Period 1 population (since the sponsor determined that there was a significant Period effect and effect of Period 1 'carried over' to Period 2.

In order to re-run the BE analysis, the sponsor was requested for data sets and asked for clarification on baseline correction methods via teleconferences (on Sep 8 & 13, 2004). The relevant data sets were submitted. The BE analysis was repeated with sponsor submitted data sets using WinNonlin 4.0. Results from the re-analysis are also presented herein.

Table 4A. Mean (± SD) values and BE comparison for unadjusted serum FSH levels

	EU Menopur (Ref)	US Menopur (Test)	Test/Ref	90% CI
C_{max} (mIU/mL)	15.4 ± 3.4	13.8 ± 3.0	89.7%	83.7 – 96.1%
AUC_{0-120} mIU*hr/mL)	1138 ± 210	1040 ± 215	91.4%	85.9 – 97.2%
T_{max} (hr)	18.8 ± 6.7	19.6 ± 6.3	104.2%	92.7 – 115.6%

Table 4B. Mean (± SD) values and BE comparison for baseline-adjusted serum FSH levels (Sponsor's analysis using SAS)

	EU Menopur (Ref)	US Menopur (Test)	Test/Ref	90% CI
C_{max} (mIU/mL)	12.3 ± 3.2	10.7 ± 2.6	87.1%	80.5 – 94.3%
AUC_{0-120} mIU*hr/mL)	761 ± 204	668 ± 176	87.8%	79.9 – 96.5%
T_{max} (hr)	18.8 ± 6.7	19.6 ± 6.3	104.2%	92.7 – 115.6%

Reviewer's Comments

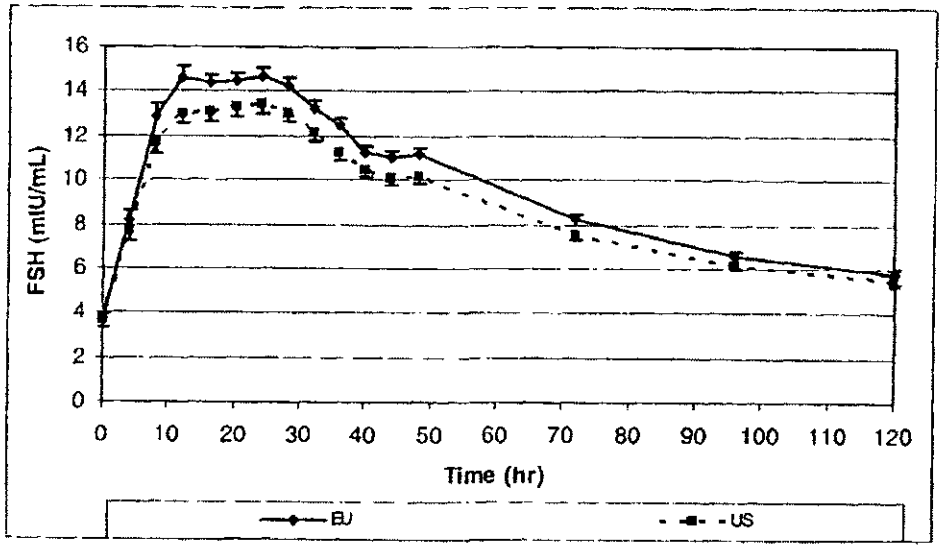
- Based on the sponsor's analysis of baseline adjusted data using SAS, both mean C_{max} and AUC_{0-120} are 12 -13% lower with the US formulation as compared to EU Menopur.

- While the 90% CI for C_{max} falls within the Agency's BE criteria of 80 – 125%, the lower bound of the 90% CI for the AUC_{0-120} barely misses the 80% mark. Hence, according to the sponsor's analysis of the data, the US formulation is not strictly BE to the EU formulation.
- The data set was re-analyzed by this reviewer using the "Bioequivalence Wizard" of WinNonlin 4.0 and the following results were obtained:

Table 4C. Mean (± SD) values and BE comparison for baseline-adjusted serum FSH levels (Reviewer's re-analysis using sponsor-submitted data on WinNonlin)

	EU Menopur (Ref)	US Menopur (Test)	Test/Ref	90% CI
C_{max} (mIU/mL)	12.7 ± 3.2	11.0 ± 2.6	87.1%	83.4 – 91.1%
AUC_{0-120} mIU*hr/mL)	789 ± 204	695 ± 176	87.8%	84.2 – 91.5%
T_{max} (hr)	18.8 ± 6.7	19.6 ± 6.3	105.7%	96.2 – 116.2%

Figure 1. Mean (±SEM) Serum FSH Concentration Following SC Injection of EU and US Formulations of Menopur



- Based on data presented on Table 4C above, the 90% CI for all the key PK parameters fall within the Agency's established BE criteria.
- At the request of OCPB, a DSI inspection was conducted (see Appendix I).

As mentioned earlier, the baseline for Period 1 was used to correct for baseline for Period 2 although Period 2 baseline values were obtained. On inquiry, the sponsor mentioned that this plan was decided *a priory* based in input from their clinical and statistical teams. Since this unique baseline correction method was not fully explained (other than an 'anticipated' effect of treatment in Period 1 in the baseline on Period 2), additional points (as below) were given due consideration:

- Normal levels of FSH in a pre-ovulatory adult female may range from 12 – 30 mIU/mL. In this study, most of the plasma levels of FSH ranged between 10 – 20 mIU/mL, with mean baselines around 3 – 4 mIU/mL. Note that, although the two mean baseline levels for the 2 treatments were almost identical, there was a statistically significant higher baseline value for Period 2 of the treatment. This may be due to an effect of treatment in Period 1 (see Table 5).

Table 5: Baseline serum FSH levels (mIU/mL)

	Period 1	**Period 2**	**Periods 1&2**
EU Base	3.39 ± 1.76	3.95 ± 1.86	3.67 ± 1.81
US Base	2.72 ± 1.73	4.59 ± 2.16	3.65 ± 2.15

Sequence 1: US in Period 1, EU in Period 2

Sequence 2: EU in Period 1, US in Period 2

- Sponsor re-analyzed for BE data from all patients for Period 1 only, and that analysis shows that the 90% CI values for both C_{max} and AUC were within the Agency recommended limits of 80 – 125%.
- Via TCON on 10/13/2004 (post-OCPB Briefing), sponsor was asked to provide the following additional information/clarification and recalculated data:

  - The sponsor confirmed that all PK parameters were obtained using the Period 1 baseline correction. They were asked to recalculate the Period 2 AUC using the Period 2, rather than the Period 1 baseline values, re-analyze BE and re-submit electronically the new data sheet and results.
  - The sponsor was asked to provide a synopsis of the results of the statistical analysis of the confounding factors (drug sequence, subject sequence, period, and formulation).
  - The sponsor was also asked to provide answers to the following questions:
    1. When only the Period 1 data was used to assess bioequivalence, what statistical adjustments, if any, were made for that analysis?
       [Sponsor responded that they had *not* treated the data as a parallel treatment arm of two sets of volunteers receiving two different treatments when used the Period I only analysis]
    2. Were the batch sizes of the European and U.S. formulations used for the bioequivalence study representative of sizes used in the clinical and/or commercial batches?
    3. What was the range of stability, in terms of IU, for the European and U.S. formulations?

Please see Appendix III for response from the sponsor on the above.

The sponsor sent in re-analyzed PK parameters (C_{max}, T_{max}, and AUC_{120}) after correcting for the baseline values from the appropriate Periods of treatment (eg. serum concentrations of FSH from

Period I was corrected with Period I baseline FSH values and that from Period II was corrected using Period II baseline FSH values). This new dataset using C_{max} and AUC_{120} values were re-analyzed for BE using WinNonlin 4.0 BE Wizard, and 90% CI for both C_{max} and AUC_{120} fell with the Agency prescribed 80 – 125%. Hence, the study results may be accepted as evidence of bioequivalence between the EU and the US formulation.

Analytical Methodology

For the assay of FSH, the sponsor has utilized the [redacted] assay method [redacted] Assay). This method is a [redacted] immunoenzymometric assay whereby the FSH in the test sample is [redacted] in the test cup. The [redacted] The amount [redacted] is directly proportional to the FSH concentration in the test sample. Thus, a linear standard curve is created with an intercept and a slope. This enzyme immunoassay was validated according to the manufacturer's suggestions. As per the validation of the assay, the assay was acceptably linear. All inter-assay precision and accuracy values ranged between ± 15%, with mostly values less than ± 5%. The lower limit of quantification (LLOQ) was [redacted] mIU/mL with C.V. of 20%.

Reviewer's Comments

- Several of the baseline values for FSH (used to correct individual serum concentrations of FSH) in the BE study were below the LLOQ (in the range of [redacted] mIU/mL). Hence, baseline correction in those subjects might not be a very dependable, and results from baseline uncorrected values should be as useful as that following baseline correction (for a majority of those subjects with a reported < 3.0 mIU/mL baseline FSH).
- Overall, the analytical method and validation for serum FSH determination was acceptable.

Based on the DSI inspection conducted on BE Study 2003-02, a reason for concern was identified in Item 13, and the sponsor was presented (by DSI) with a Form 483 listing the deficiencies (see Appendix 1). In brief, while conducting a [redacted] Experiment", DSI noted that the measured concentration of FSH in human serum spiked with Ferring supplied FSH was determined to be [redacted] of the spiked concentrations. When the sponsor was asked to clarify the issue via a teleconference, they responded with a facsimile (dated October 21, 2004) in which they rationalized that the assay standards used with the [redacted] (for FSH assay used throughout this NDA) had a different source than that was used for Ferring manufactured FSH, and a mean "normalization factor" of 0.537 would have to be used in order to compare the two sources. Use of this 'normalization factor' may explain a significant portion of the discrepancy observed as delineated in Item 13 of the DSI report. The sponsor clarified that the normalization factor was not used in the BE study and that the same lot of API FSH was used in both, US and EU formulations of Menopur. The sponsor further backed this up with a written response on October 25, 2004 (via facsimile).

Immunoassays and or bioassays used for assaying macromolecules such as FSH is appreciably complex (involving many issues due to source of protein and WHO standards) and different than small molecules. While bioassays measure biological activity, immunoassays are a measure of the quantity of epitopes present and the two may not be equivalent. The Chemistry Team Leader (Moo Jhong Rhee) was consulted on this issue who further suggested the input of Drs. Yvonne Yang, Martin Haber and Blair Fraser (Chemists in HFD-510 and CMC Deputy Director, respectively). DSI issues as well as the response and explanation by the sponsor were reviewed by these experts. Relevance of these issues to the findings from the bioequivalence study was emphasized. This CMC team went over the responses sent by the sponsor and confirmed that the sponsors rationale of using the 'normalization factor' was appropriate for the [redacted] experiment' and that it is supported by data and science. It was noted that this is not unusual and may be due to different populations of immunoreactive proteins as measured using the specific immunoassay. Based on this consultation and expert evaluation of the sponsor's response, results of the BE study are acceptable.

Labeling Comments

CLINICAL PHARMACOLOGY

Menopur®, administered for 7 to 20 days, produces ovarian follicular growth and maturation in women who do not have primary ovarian failure. In order to produce final follicular maturation and ovulation in the absence of an endogenous LH surge, hCG must be administered following Menopur® treatment, at a time when patient monitoring indicates sufficient follicular development has occurred.

PHARMACOKINETICS

[redacted]

Table 21: Mean (± SD) FSH Pharmacokinetic Parameters Following Menopur® Administration (Study 2000-03)

PK Parameters	Single Dose (225 IU)		Multiple Dose (225 IU x 1 day then 150 IU x 6 days)	
	SC	IM	SC	IM
C_{max}[1] (mIU/mL)	8.5 (2.5)	7.8 (2.4)	15.0 (3.6)	12.5 (2.3)
T_{max} (hr)	17.9 (5.8)	— 27.5 (25.4)	8.0 (3.0)	9.0 (7.0)
AUC[1] (hr-mIU/mL)	726.2 (243.0)	656.1 (233.7)	622.7 (153.0)	546.2 (91.2)

[1] Single dose C_{max}, AUC_{120} and multiple dose $C_{max,ss}$, AUC_{ss}

[redacted]

Absorption

The SC route of administration trends toward greater bioavailability than the IM route for single and multiple doses of Menopur® [redacted]

Distribution

Human tissue or organ distribution of FSH and LH has not been studied for Menopur®.

Metabolism

Metabolism of FSH and LH has not been studied for Menopur® in humans.

Elimination

The elimination half-lives for FSH in the multiple-dose phase were — similar (11 - 13 hours) for Menopur® SC and Menopur® IM.

Pediatric Populations

[redacted]

Geriatric Populations

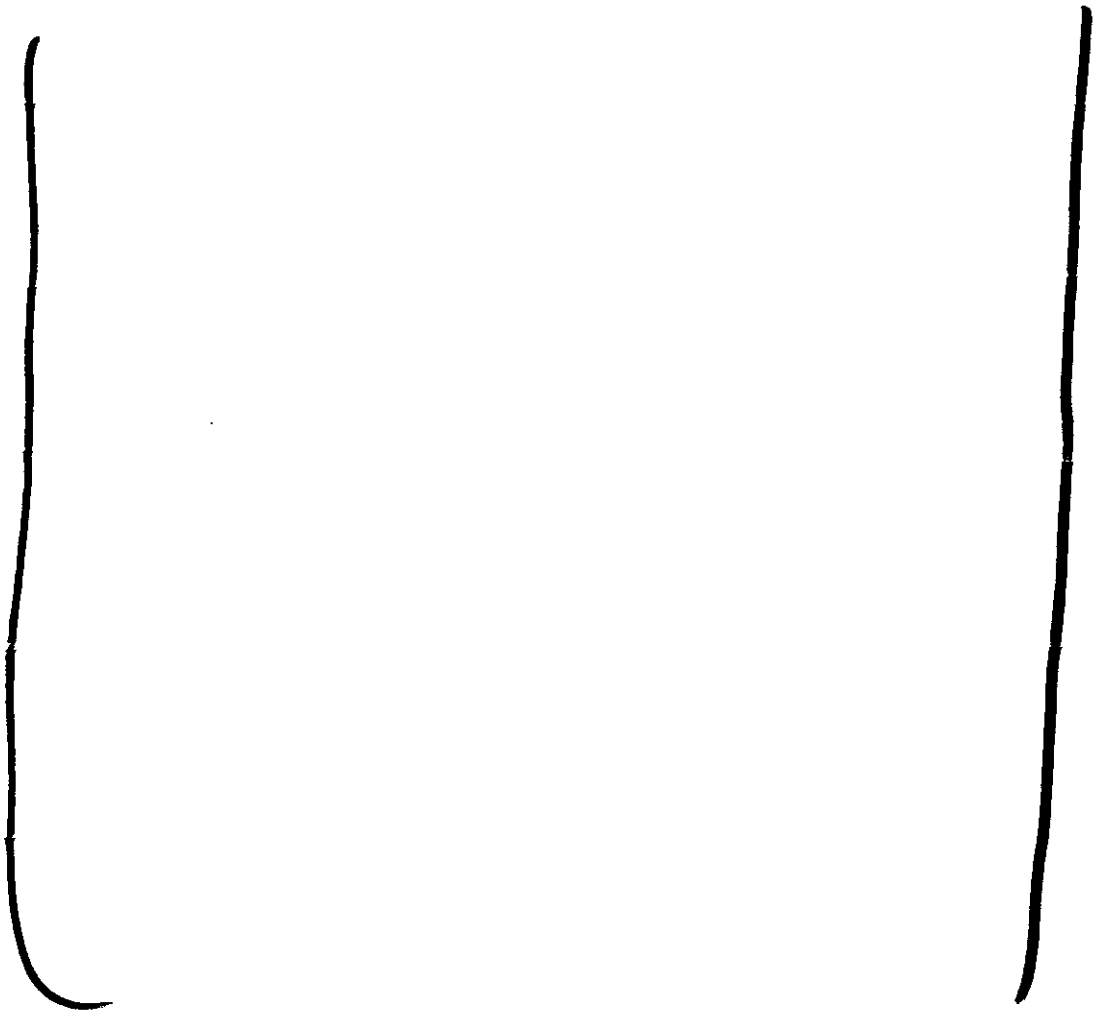
[redacted]

Special Populations

The safety and efficacy of Menopur® in renal and hepatic insufficiency have not been studied.

Drug Interactions

No drug/drug interaction studies have been conducted for Menopur® in humans.



19 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dhruba Chatterjee
10/28/04 03:30:43 PM
BIOPHARMACEUTICS
CPB Review of Original NDA.
Final version.

Ameeta Parekh
10/28/04 03:35:49 PM
BIOPHARMACEUTICS
Concur