CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-663

Administrative/Correspondence Reviews

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-663

NAME OF APPLICANT / NDA HOLDER
Ferring Pharmaceuticals Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Menopur ® (menotropins for injection, USP)

ACTIVE INGREDIENT(S)	STRENGTH(S)
human menopausal gonadotropin (FSH, LH)	75 IU each of FSH and LH

DOSAGE FORM
single dose vial, lyphilized menotropins

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
Ferring knows of no patent that claims this drug		

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

the patent referenced above, provide the following information on the drug substance, drug product and/or method of e that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

no patent

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

5. No Relevant Patents

or this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), rug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☒ Yes

Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
James H. Conover, Ph.D.	6/9/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name James H. Conover, Ph.D, Executive Director Regulatory Affairs	
Address 400 Rella Blvd. (Suite 300)	City/State Suffern NY
ZIP Code 10901	Telephone Number (845)770-2668
FAX Number *(if available)* (845)770-2663	E-Mail Address *(if available)* jim.conover@ferring.com

EXCLUSIVITY SUMMARY FOR NDA # 21-663 SUPPL #_____

Trade Name Menopur® Generic Name Menotropins

Applicant Name Ferring Pharmaceuticals HFD # 580

Approval Date If Known October 29, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b) (1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-047 Repronex®

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete

remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1 MFK/IVF/0399E

Investigation #2 2003-02

Investigation #3 _____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____	_____
_____	_____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____	_____
_____	_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_MFK/IVF/0399E_____	_____
_2003-02_____	_____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or

its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #IND 53,954 YES /_X__/ ! NO /___/ Explain: _____

Investigation #2

IND #IND 53,954 YES /_X__/ ! NO /___/ Explain: _____

Investigation #3

IND #IND _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased

(not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

Signature
Title:

Date

Signature of Office/
Division Director

Date

Form OGD-011347 Revised 05/10/2004

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

/s/

Daniel A. Shames
10/29/04 04:57:26 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-663 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: December 29, 2003 **Action Date:** October 29, 2004

HFD 580 **Trade and generic names/dosage form:** Menopur® (menotropins, USP)

Applicant: Ferring Pharmaceuticals **Therapeutic Class:**

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: In Vitro Fertilization

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply:** ____**Partial Waiver** ____**Deferred** ____**Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☒ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-663**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: __

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-663**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Jennifer L. Mercier
10/29/04 04:10:05 PM

16.0 DEBARMENT CERTIFICATION

Section 306(K)(1) of the FD&C Act; 21 U.S.C. 335a(k)(1)

The undersigned certifies that Ferring Pharmaceuticals Inc. did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)], in connection with NDA 21-663.

Signature

Name of Responsible Person: James H. Conover, Ph.D.
Executive Director, Regulatory Affairs

11-16-04

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-663	Efficacy Supplement Type SE-	Supplement Number	
Drug: Menopur®		Applicant:Ferring Pharmaceutical	
RPM: Martin Kaufman		HFD-580	Phone # 301-827-4234

Application Type: (X) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications: • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC)	(X) Standard ( ) Priority 3
❖ User Fee Goal Dates	October 29, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4651
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP) • Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP • Exception for review (Center Director's memo) • OC clearance for approval	( ) Yes (X) No
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	( ) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	(X) NO
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (**X**) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	(X)
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	9/29/04, 7/28/04, 10/15/04, 4/9/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	3/3/03
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	N/A
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	10/29/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See MO review
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	X
❖ Biopharmaceutical review(s) *(indicate date for each review)*	10/28/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	X
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	8/6/04, 10/26/04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See Chemistry Review
• Review & FONSI *(indicate date of review)*	See Chemistry Review
• Review & Environmental Impact Statement *(indicate date of each review)*	See Chemistry Review
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	10/12/04
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	9/13/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Martin Kaufman
11/16/04 03:32:30 PM

NDA 21-663

Menopur (menotropins for injection, USP)

Ferring Pharmaceuticals

Risk Management Plan

10/29/04

N/A

NDA 21-663

Menopur (menotropins for injection, USP)

Ferring Pharmaceuticals

Post-Marketing Commitments

N/A

10/29/04

NDA 21-663

Menopur (menotropins for injection, USP)

Ferring Pharmaceuticals

Controlled Substance Staff

10/29/04

N/A

NDA 21-663

Menopur® (menotropins for injection, USP)

Ferring Pharmaceutical

Project Manager
Martin Kaufman
HFD-580
301-827-4234

Application Integrity Policy

N/A

NDA 21-663

Menopur (menotropins for injection, USP)

Ferring Pharmaceuticals

Advisory Committee

10/29/04

N/A

NDA 21-663

Menopur (menotropins for injection, USP)

Ferring Pharmaceuticals

FR Notice

10/29/04

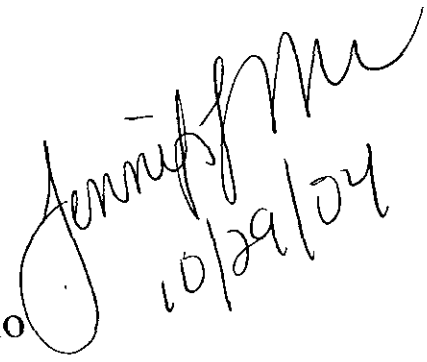
N/A

NDA 21-663

Menopur (menotropins for injection, USP)

Ferring Pharmaceuticals

Division Director Memo



N/A

NDA 21-663

Menopur (menotropins for injection, USP)

Ferring Pharmaceuticals

CAC/ECAC Report

10/29/04

N/A

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 29, 2004

TO: NDA [redacted]

FROM: J. Mercier

SUBJECT: **Cross-reference to NDA 21-663**
NDA [redacted] Menopur® (menotropins for injection, USP)

The purpose of this memorandum is to cross reference the reviews of Menopur® (menotropins for injection, USP) found in the files for NDA 21-663 to serve as documentation for NDA [redacted] The original application has been administratively split to accommodate the need to take separate actions on different aspects of the application.

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/s/

Jennifer L. Mercier
11/2/04 02:17:35 PM
CSO

MEMORANDUM OF TELECON

DATE: October 13, 2004

APPLICATION NUMBER: NDA 21-663, Menopur® (menotropins, USP)

BETWEEN:

Name: James Conover, Ph.D., Executive Director, Regulatory Affairs
[ ] Consultant
Phone: 845-770--2668
Representing: Ferring Pharmaceuticals

AND

Name: Dhruba Chatterjee, Ph.D., Clinical Pharmacologist, Division of Pharmaceutical Evaluation II, HFD-870
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580

SUBJECT: Bioequivalence Study 2003-02

Background: The Sponsor has submitted an NDA for Menopur® (menotropins for injection, USP), a more purified form of its product Repronex®, with the proposed indications of multiple follicular development in patients participating in Assisted Reproductive Technologies (ART). [ ]
The Sponsor submitted study MFK/IVF/0399E in which the European formulation of Menopur® was used. Bioequivalence Study 2003-02 was submitted to bridge the European and U.S. formulations of the drug. An Office of Clinical Pharmacology and Biopharmaceuticals (OCPB) Briefing for this NDA was held on October 12, 2004. This teleconference was requested to obtain clarification on several issues which were raised at the briefing.

Discussion:

- The sponsor reconfirmed that all PK calculations (e.g. AUC computations) were made using the period 1 baseline. They were asked to recalculate the period 2 PK parameters using the period 2, rather than the period 1, baseline.
- The sponsor was asked to provide a synopsis of the results of the statistical analysis of the confounding factors (treatment sequence, subject sequence, period, and formulation).
- The sponsor was asked to provide answers to the following questions:
  1. When only the period 1 data were used to assess bioequivalence, what statistical adjustments, if any, were made for that 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?

- An electronic submission of the period 2 baseline corrected data would be preferred.
- The sponsor mentioned that they would consider re-running the bioequivalence analysis using the new data set obtained after PK parameters are adjusted for baseline in period 2.

Action Items:

- The Sponsor should submit the requested data to the NDA, as well as a desk copy to the Project Manager.
- Meeting minutes to sponsor within thirty days.

/S/

Dhruba Chatterjee, Ph.D.
Clinical Pharmacologist

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

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/s/

Martin Kaufman
10/15/04 01:46:40 PM
CSO

Dhruba Chatterjee
10/18/04 11:28:19 AM
BIOPHARMACEUTICS
I concur.

Office of Drug Safety

Memo

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Tia Harper-Velazquez, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Alina Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support
HFD-420

CC: Martin Kaufman
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

Date: October 12, 2004

Re: ODS Consult 04-0018-1: Menopur (Menotropins for Injection, USP), 75 International Units FSH, 75 International Units LH; NDA 21-663

This memorandum is in response to a September 29, 2004, request from your Division for a re-review of the proprietary name, Menopur. In our last review, dated February 10, 2004, (ODS Consult # 04-0118), DMETS did not have any objections to the use of the proprietary name Menopur. DMETS previously reviewed the container labels, carton and insert labeling for Menopur. Please refer to ODS Consult # 04-0018, dated February 10, 2004, for recommendations and comments.

Since the initial review, the DMETS Expert Panel identified one additional proprietary name, Minipress, as having look-alike and sound-alike similarities to Menopur.

Minipress contains the active ingredient, prazosin, and is indicated for the treatment of hypertension. Minipress is available as an oral capsule in strengths of 1 mg, 2 mg, and 5 mg. The recommended starting dose is 1 mg administered two or three times daily. Both names contain three syllables, with the first syllable being similar in look and sound ("Min" vs. "Men"). The sounds of the letters "p" and "r" are also present in the last syllables of each name. Despite this, the endings of the names are different and distinguishable from each other when pronounced ("press" vs. "pur"). Minipress and Menopur also differ in route of administration (oral vs. subcutaneous), dosage form (injection vs. capsules), product strength (1 mg, 2 mg, and 5 mg vs. 75 International Units), and dosing regimen (two or three times daily vs. once daily). DMETS believes there is minimal potential for name confusion between Minipress and Menopur due to the lack of convincing look-alike and sound-alike similarities between the names, in addition to numerous product differences, such as route of administration, dosage form, strength, and dosing regimen. Therefore, we have no objections to the use of the proprietary name, Menopur.

Minipress	**Menopur**
Minipress	Menopur

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the DMETS' Project Manager, Sammie Beam at 301-827-2102.

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/s/

Tia Harper-Velazquez
10/15/04 03:04:02 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
10/15/04 05:15:06 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/15/04 05:37:16 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 04-0018
January 20, 2004	September 29, 2004 **PDUFA DATE:** October 29, 2004	

TO: Daniel Shames, MD
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Martin Kaufman
Project Manager
HFD-580

PRODUCT NAME:	**NDA SPONSOR:** Ferring Pharmaceuticals
Menopur® (Menotropins for Injection, USP) 75 International Units FSH, 75 International Units LH **NDA #: 21-663**	

AFETY EVALUATOR: Linda M. Wisniewski, RN

RECOMMENDATIONS:

1. DMETS has no objection to the use of the proprietary name, Menopur®. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Menopur® acceptable from a promotional perspective.

/S/

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
)ffice of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 10, 2004

NDA# 21-663

NAME OF DRUG: Menopur® (Menotropins for Injection, USP) 75 International Units FSH/ 75 International Units LH

NDA HOLDER: Ferring Pharmaceuticals

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580), for assessment of the proprietary name "Menopur®", regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Menopur® (menotropins for injection, USP) is a purified preparation of gonadotropins extracted from the urine of postmenopausal women. It is indicated for Multifollicular Development and Pregnancy in Assisted Reproductive Technology (ART). [redacted]

Each vial of Menopur® contains 75 International Units of follicle-stimulating hormone (FSH) activity and
75 International Units of luteinizing hormone (LH) activity in a sterile, lyophilized form intended for reconstitution with sterile 0.9% Sodium Chloride Injection, USP. Menopur® is administered by subcutaneous (SC) [redacted] injection and dosed on a daily basis. The recommended initial dose of Menopur® for Assisted Reproductive Technology for patients who have received a GnRH antagonist or GnRH agonist for pituitary suppression is 225 International Units, with individualized dosing after that, not to exceed 450 International Units and not to be dosed beyond 20 days. [redacted]

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Menopur to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Menopur. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC has no concerns regarding the proposed proprietary name from a promotional perspective.

2. The Expert Panel identified five proprietary names that were thought to have the potential for confusion with Menopur. These products are listed in Table 1 on page 4 along with the dosage forms available and usual dosage.

3. Through independent research, the proprietary name [ ] was identified as having potential to look and sound similar to Menopur. These products are listed in Table 1 on page 4 along with the dosage forms available and usual dosage.

---

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Menopur	Menotropins for Injection, USP Injection 75 International Units FSH / 75 International Units LH Vials.	Assisted Reproductive Technology: 225 International Units daily, with subsequent individualized dosing. Not to exceed 450 International Units. Ovulation Induction: initial dose of 75 International Units daily with subsequent individualized dosing.	N/A
Mevacor	Lovastatin Tablets 10 mg, 20 mg, and 40 mg For oral use.	Initially 20 mg or 40 mg daily. Range is 20 mg to 80 mg in single or divided doses.	SA/LA
Monopril	Fosinopril Sodium Tablets 10 mg, 20 mg, and 40 mg For oral use.	Initial dose of 10 mg daily. Range is 20 mg to 40 mg in single or divided doses up to 80 mg daily.	SA/LA
Venofer	Iron Sucrose Injection 20 mg/mL of elemental iron For injection into dialysis line only.	100 mg (5 mL) of elemental iron I.V. directly into the dialysis line (1 mL per minute) or by infusion (over 15 minutes) one to three times weekly to a total of 1,000 mg in 10 doses.	SA
Midamor	Amiloride Hydrochloride Tablets 5 mg For oral use.	5 mg daily. May increase to 10 mg daily, but not to exceed 20 mg daily.	SA
Menogen	Ingredients: Esterified estrogens, and methyltestosterone 1.25 mg/2.5 mg	1 tablet daily	L/A
[			]
	[ ]		

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
***Name pending approval. Not FOI releasable.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Menopur were discussed by the Expert Panel (EPD). No additional names of concern were identified in POCA that were not discussed in EPD.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Menopur with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses).

This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Menopur (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Menopur 75 IU 75 IU SQ daily x 2 days starting 2/5/04	Menopur 75 International Units Sig: Inject 75 International Units SQ daily X2 days starting 2/5/2004 #2
Inpatient RX: Menopur 75 IU SQ today	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Menopur, the primary concerns related to look-alike and sound-alike confusion with: Mevacor, Monopril, Venofer, Midomor, Menogen and [redacted].

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Menopur.

1. Venofer may look and sound like Menopur. Venofer is indicated for iron-deficiency anemia in patients undergoing long-term hemodialysis who are receiving supplemental erythropoietin therapy. The two names have some orthographic similarities. The first letter of each name 'v vs. m' may look similar, and the next three letters 'eno' are the

*** **NOTE: This review contains proprietary and confidential information that should not be released to the public.**

same. These latter letters also contribute to the phonetic similarity. Additionally, the ending letters 'er' and 'ur' are phonetically similar. Although both products are injectable drugs, there are different product characteristics that will help to distinguish the two: strength (75 International Units vs. 10 mg/mL), route of administration ([ ] subcutaneous vs. via hemodialysis catheter), dosing frequency (daily vs. one to three times weekly), prescribed dose (75 International Units to 225 International Units vs. 100 mg), context of use (Assisted Reproductive Technology vs. iron-deficiency anemia), and location of use (home or clinic vs. hemodialysis unit). The different product characteristics, context and location of use will help to distinguish these two products.

menapur
menapur

2. Monopril may sound and look similar to Menopur. Monopril is used to treat hypertension. Both names contain three syllables. The first four letters "meno versus mono" may sound similar when pronounced. However, the last letters "pur versus pril" are pronounced differently. Additionally, the letters 'Menop' and 'Monop' look similar when scripted which contributes to the orthographic similarity. Although both products are dosed once daily, there are product characteristics that will help to differentiate the two: storage location (injectables vs. oral solids), marketed strength (75 International Units vs. 10 mg, 20 mg and 40 mg), dosage form (powder for injection vs. tablet), route of administration (subcutaneous [ ] vs. oral), prescribed dosage (75 International Units to
225 International Units with individualized dosing vs. 10 mg to 40 mg) and context of use (Assisted Reproductive Technology vs. hypertension). The product characteristics and context of use will distinguish between these two products and minimize potential for confusion.

Monopril
Menapur

3. Mevacor may look and sound similar to Menopur. Mevacor is used to treat hypercholesterolemia. Mevacor and Menopur begin and end with letters that look similar when scripted ("Meno vs. Meva", and "ur vs. or"). However, the downstroke of the 'p' in Menopur may help to distinguish the two names when written (see below). The beginning (Me) and ending (or vs. ur) letters may sound similar when pronounced. Additionally, each name contains three syllables which contribute to the rhyming similarities. Although both products are dosed once daily, there are product characteristics that will help to differentiate the two: storage location (injectables vs. oral solids), marketed strength (75 International Units vs. 10 mg, 20 mg, and 40 mg), dosage form (powder for injection vs. tablets), route of administration ([ ] subcutaneous vs. oral), and prescribed dosage (75 International Units to 225 International Units with individualized dosing vs. 20 mg to 80 mg). The product characteristics will help distinguish these two products and decrease potential for confusion.

Mevacor
Menapur

4. Midamor may sound similar to Menopur. Midamor is indicated for hypertension. Both names contain three syllables, and have similar sounding letters 'mida vs. meno', and 'mor vs. pur'. Although each drug is dosed once daily, there are product characteristics that will help distinguish the two. These include dosage form (powder for injection vs. tablets), marketed strength (75 International Units vs. 5 mg), route of administration [ ] subcutaneous vs. oral), prescribed dosage (75 International Units to 225 International Units with individualized dosing vs. 5 mg to 20 mg), and context of use (Assisted Reproductive Technology [ ] vs. hypertension). The product characteristics will help minimize the potential for confusion with these two products.

5. [

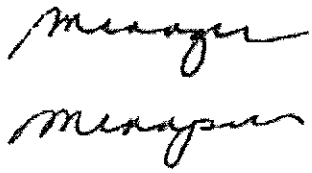
[ ]

[ ]

6. Menogen may look similar to Menopur. Menogen is a combination product consisting of esterified estrogens and methyltestosterone and is indicated in the treatment of moderate to severe vasomotor symptoms associated with menopause in those patients not improved by estrogens alone. Both names have the same number of letters (7), and begin with the same four letters (Meno). The names also have a downstroke in the same position, which contributes to the orthographic similarity. There are differentiating product characteristics. These unclude: dose (1.25 mg/2.5 mg vs. 75 International Units to 225 International Units), dosage form (tablet vs. injectable), strength (1.25 mg/2.5 mg and 0.625 mg/1.25 mg vs. 75 International Units), route of administration (oral vs. [ ] subcutaneous), indication of use (symptoms of menopause vs. Assisted Reproductive Technology), storage location (oral solids vs. injectables), and prescribing

*** **Name pending approval. Not FOI releasable**

practitioners (internists or family practice practitioners vs. fertility specialists). Although Menogen is no longer marketed, references to Menogen still appear in drug information resources (Red Book). If a practitioner receives a prescription for Menogen they can use various drug information resources to determine that it was marketed as a bioequivalent product to Solvay's Estratest. Thus they could fill the prescription with Estratest which is currently available. Additionally Menopur requires that a strength be noted prior to dispensing. If an order for Menopur is written without a strength and misinterpreted as Menogen, the quantity to be dispensed may help in differentiate the order. Menopur is marketed in a carton that contains 5 vials of Menotropins and 5 vials of diluent whereas Menogen is a tablet. Thus, a Menopur will likely be prescribed in quantities of 1 box or 5 vials. Due to the high cost and use of the product (IVF) it is unlikely that a patient will receive more than one Menopur carton at a time. Additionally, since Menopur is costly, it will likely be a special order item and prior contact will likely be made between the prescriber and the pharmacy. Although, there are orthographic similarities, the product characteristics, and conditions of use, may help to distinguish the two products and help minimize confusion.



III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Menopur, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. We note that the labels and labeling were submitted in black and white. Thus, DMETS did not have the opportunity to evaluate and comment on the use of colors, color fonts and/or graphics, etc.

2. DMETS does not recommend the use of the abbreviation "IU" as it can and has been misinterpreted as IV (intravenous). We recommend that the term "IU" be spelled out (i.e. International Units).

3. Revise the strength so that it reads "Follicle Stimulating Hormone 75 International Units/Luteinizing Hormone 75 International Units".

4. Relocate the strength so that it appears below the established name and above the sponsor's name.

B. CONTAINER LABEL (MENOPUR)

1. See General Comments.

2. Ensure the established name is at least one-half the size of the proprietary name. See 21CFR201.10(g)(2).

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

IV. RECOMMENDATIONS:

A. DMETS has no objections to the proprietary name Menopur. This is considered a tentative decision and the firm should be notified that this name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

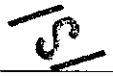
B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the proprietary name Menopur acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Linda M. Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:



Denise P. Toyer, PharmD.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A:

NDA 21-663 Menopur
ODS Consult 04-0018

Voice	Inpatient	Outpatient
Medipure	Menopron	Manoprin
Memapure	Menopur	Menapro
Memepir	Menopur	Menopen
Menapure	Menopur	Menopim
Menapure	Menopur	Menopin
Menapure	Menopur	Menopin
Menapure	Menopur	Menopin
Menavir	Menopur	Menopin
Menipur	Menopur	Menopin
Menipure	Menopur	Menopin
Menocure	Menopur	Menopin
Menocure	Menopur	Menoprim
Menopur	Menopur	Menoprim
Menopur	Menopur	Menoprin
Menopure	Menopur	Menoprin
Menopure	Menopur	Menoprin
Minapure	Menopur	Menoprin
Minapure	Menopur	Menoprin
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		Menoprn
		Menopur
		Menopur

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/s/

Linda Wisniewski
4/9/04 02:59:51 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/9/04 03:19:14 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/9/04 03:25:14 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
4/12/04 10:42:55 AM
DRUG SAFETY OFFICE REVIEWER

9-29-04

7 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

MEMORANDUM OF TELECON

DATE: September 13, 2004

APPLICATION NUMBER: NDA 21-663, Menopur® (menotropins, USP)

BETWEEN:

Name: James Conover, Ph.D., Executive Director, Regulatory Affairs
[redacted] Consultant
Dennis Marshall, M.D., Executive Director of Medical Affairs
Phone: 845-770--2668
Representing: Ferring Pharmaceuticals

AND

Name: Dhruba Chatterjee, Ph.D., Clinical Pharmacologist, Division of Pharmaceutical Evaluation II, HFD-870
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580

SUBJECT: Bioequivalence Study 2003-02

Background: The Sponsor has submitted an NDA for Menopur® (menotropins for injection, USP), a more purified form of its product Repronex®, with the proposed indications of multiple follicular development in patients participating in Assisted Reproductive Technologies (ART) [redacted]
The Sponsor submitted study MFK/IVF/0399E in which the European formulation of Menopur® was used. Bioequivalence Study 2003-02 was submitted to bridge the European and U.S. formulations of the drug. On September 8, 2004, the Division requested an additional data table in order to complete the review of this study. This teleconference is requested to obtain clarification of the data presented in that table.

Discussion:

- Clarification was requested on the location of baseline corrected data. The Sponsor confirmed that baseline corrected data had not been submitted. The Division requested that the Sponsor submit an additional data table with baseline corrected values for C_{max} and AUC for all subjects in the study.
- An electronic submission of the data file would be preferred.

Action Items:

- The Sponsor will submit the requested data to the NDA, as well as a desk copy to the Project Manager, within 2-3 days.
- Meeting minutes to sponsor within thirty days.

/S/

Dhruba Chatterjee, Ph.D.
Clinical Pharmacologist

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/s/

Martin Kaufman
9/20/04 04:47:42 PM
CSO

Dhruba Chatterjee
9/21/04 11:07:24 AM
BIOPHARMACEUTICS
I concur.

MEMORANDUM OF TELECON

DATE: September 8, 2004

APPLICATION NUMBER: NDA 21-663, Menopur® (menotropins, USP)

BETWEEN:

Name: James Conover, Ph.D., Executive Director, Regulatory Affairs
Vladimir Yankov, M.D., Executive Director, Medical Affairs
Phone: 845-770--2668
Representing: Ferring Pharmaceuticals

AND

Name: Dhruba Chatterjee, Ph.D., Clinical Pharmacologist, Division of Pharmaceutical Evaluation II, HFD-870
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580

SUBJECT: Bioequivalence Study 2003-02

Background: The Sponsor has submitted an NDA for Menopur® (menotropins for injection, USP), a more purified form of its product Repronex®, with the proposed indications of multiple follicular development in patients participating in Assisted Reproductive Technologies (ART) [redacted]
The Sponsor submitted study MFK/IVF/0399E in which the European formulation of Menopur® was used. Bioequivalence Study 2003-02 was submitted to bridge the European and U.S. formulations of the drug. An additional data table was needed to complete the review of this study. This teleconference was held to request the additional data.

Discussion:

- The Division requested that the Sponsor submit a data table that consolidates the individual PK parameters (C_{max}, T_{max}, and AUC) for all subjects in the study. This table should summarize data from all sites for all sequences and periods.
- An electronic submission of the data file would be preferred.

Action Items:

- The Sponsor will submit the requested data to the NDA, as well as a desk copy to the Project Manager, within 2-3 days.
- Meeting minutes to sponsor within thirty days.

/s/

Dhruba Chatterjee, Ph.D.
Clinical Pharmacologist

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/s/

Martin Kaufman
9/9/04 11:54:19 AM
CSO

Dhruba Chatterjee
9/9/04 03:35:23 PM
BIOPHARMACEUTICS
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

9-1-04

NDA 21-663

INFORMATION REQUEST LETTER

Ferring Pharmaceuticals, Inc.
Attention: James H. Conover, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

Please refer to your December 19, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Menopur® (menotropins for injection USP).

We also refer to your submission dated August 5, 2004.

We are reviewing the Biopharmaceutical section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

In the side-by-side table labeled "Ingredients per ml for Manufacture", we have noted that the European formulation has — higher active ingredient (menotropin) as compared to the US formulation. Explain this difference.

If you have any questions, call Martin Kaufman, D.P.M., M.B.A., Regulatory Project Manager, at 301-827-4234.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
9/1/04 02:53:19 PM

MEMORANDUM OF TELECON

DATE: July 29, 2004

APPLICATION NUMBER: NDA 21-663, Menopur® (menotropins, USP)

BETWEEN:

Name: James Conover, Ph.D., Executive Director, Regulatory Affairs
Phone: 845-770--2668
Representing: Ferring Pharmaceuticals

AND

Name: Martin Haber, Ph.D., Chemist, DNDC II, @ Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580

SUBJECT: Drug Substance Stability

Background: The Sponsor has submitted an NDA for Menopur® (menotropins for injection, USP), which is a more purified form of its product Repronex®, for the indications of multiple follicular development in patients participating in Assisted Reproductive Technologies (ART) [ ] Issues concerning the drug substance stability were identified during the Chemistry, Manufacturing, and Controls (CMC) review of this NDA. The Division requested this teleconference to convey these issues to the Sponsor, and to request the Sponsor's input in their resolution.

Discussion:

- The Sponsor has proposed a retest period of [ ] for drug substance stability in the NDA. The Division considers this to be too long a period of time. If a lot passes the first retest, it would go another [ ] without additional testing.
- The Division proposed either a retest period of [ ] expiry date on the drug substance.
- The Sponsor's chemists will need to discuss this issue and submit a proposed amendment to the Project Manager.

Action Items:

- The Sponsor will submit a proposed CMC amendment to the Project Manager.
- Meeting minutes to sponsor within thirty days.

/S/

Martin Haber, Ph.D.
Chemist

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/s/

Martin Kaufman
8/4/04 05:01:54 PM
CSO

Martin Haber
8/5/04 09:50:17 AM
CHEMIST

8/24/04

21 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

8-19-04

NDA 21-663

INFORMATION REQUEST LETTER

Ferring Pharmaceuticals, Inc.
Attention: James H. Conover, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

Please refer to your December 29, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Menopur® (menotropins for injection, USP).

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Study MFK/IVF/0399E
   a. Confirm the correct criteria for down-regulation. Different criteria are given for down-regulation. Volume 30 – Protocol Amendment #1 (p. 211) states Estradiol level < 200 pmol/L and/or LH level < 5 mIU/mL. The same protocol amendment (p. 219) states ultrasound and/or documentation of pituitary down-regulation (estradiol < 50 pmol/L and LH < 2 mIU/mL. The Clinical Study Report section (p. 66) states down-regulation was established by an estradiol level of < 200 pmol/L.
   b. Confirm that the number of subjects (n) in the ITT group of Table 34 of the Biometric Report (p. 365) is correct. It differs from the number of subjects that had embryos transferred in Table 21 of the Biometric Report (p. 359).
   c. Provide a list of the number of subjects in each of the two treatment groups that received blastocyst transfer.
   d. Provide a list of any subjects that were converted from in vitro fertilization to intrauterine insemination.
   e. Confirm whether "experimental procedures", such as blastomere biopsy or assisted hatching, were permitted.
   f. Provide pregnancy outcome data (livebirths, multiple births, any known congenital anomalies) for this study.
   g. Confirm if there is any information on the number of couples in each treatment group that had "severe" male factor.

2. Study 2000-02
   One of the inclusion criteria for this study was a male partner with semen analysis showing "normalcy". In the Statistical Report Table 2B (p. 306), 9 subjects were reported to have male factor. Confirm whether these subjects meet the criteria listed in Appendix B (p. 115) containing the Revised WHO Normal Values of Semen Variables. If not, provide the semen analyses data for these subjects if available.

3. Provide case report forms for the following subjects:
   a. Study MFK/IVF/0399E – PID #222009
   b. Study 2000-02 – PID # 01-008/SCR 01S013
   c. Study 2001-01 – PID# 03-003/SCR 03S007
   d. Study 2000-01 – PID #08-007/SCR 08S-009

If you have any questions, call Martin Kaufman, D.P.M., M.B.A., Regulatory Project Manager, at 301-827-4234.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
8/19/04 05:06:58 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7-30-04

NDA 21-663

INFORMATION REQUEST LETTER

Ferring Pharmaceuticals, Inc.
Attention: James H. Conover, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

Please refer to your December 19, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Menopur® (menotropins for injection, USP).

We also refer to your submission dated May 10, 2004.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide LH bioassay data for [redacted]

2. Provide data regarding the amount of hCG present in the drug substance.

3. Regarding labeling, delete the first two sentences of the second paragraph in the DESCRIPTION section of the package insert.

4. The table of proposed specifications for the drug substance has a typographic error; the acceptance limit for the LH bioassay should be LH IU, not FSH IU.

If you have any questions, call Martin Kaufman, D.P.M., M.B.A., Regulatory Project Manager, at 301-827-4234.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
@ Division of Reproductive and Urologic
Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
7/30/04 03:08:19 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 28, 2004

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Martin Kaufman, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of "Directions for using Menopur" (menotropins for Injection, USP), NDA 21-663

Background and Summary

The sponsor submitted (December 29, 2003) a package insert (PI) with instructions for use entitled, "Directions for using Menopur" appended to the PI for NDA 21-663. No patient information in the form of a patient package insert was submitted for review.

We have the following comments and recommendations:

1. The "Directions for using Menopur" are deficient in that they are lacking important specific steps to guide a patient in safely and effectively administering the medication. Instructions for using injectable products should be comprehensive and specific in content information and include diagrams and/or pictures to illustrate important steps. A patient should be able to refer to instructions for step by step directions. The "Directions for using Menopur" omit important specific steps of the injection process such as the size and type of needle and syringe to use, the process for drawing the diluent into the syringe, and the SC injection process, to name a few. We suggest the sponsor rewrite comprehensive instructions for use, referring to the April 19, 2001, CDRH *Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers* and use other well written

injectable product instructions for use as guides.

2. Important safety/risk information should be conveyed to the patient via Patient Information (a PPI) since the patient will be self-administering this medication. A PPI, following the Medication Guide question and answer type format and content (see 21CFR 208) and written at a 6^{th} to 8^{th} grade reading comprehension level is the optimal vehicle for communication. Package Inserts are written at a high literacy level for prescribers.

Please call us if you have any questions.

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/s/

Jeanine Best
7/28/04 10:15:50 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
7/28/04 04:11:49 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

MEMORANDUM OF TELECON

DATE: June 14, 2004

APPLICATION NUMBER: NDA 21-663, Menopur® (menotropins for injection, USP)

BETWEEN:

Name: Ken Kashkin, MD, Vice President, Medical and Regulatory Affairs
Jim Conover, Ph.D., Executive Director, Regulatory Affairs
Michael Bernhard, Ph.D., Senior Vice President for Regulatory Affairs
Michael Zudiker, Ph.D., Executive Director, Chemistry, Manufacturing, and Controls
Phone: 845-770-2631
Representing: Ferring Pharmaceutical

AND

Name: Eric Duffy, Ph.D., Director, Division of New Drug Chemistry II (DNDC II), HFD-820
Blair Fraser, Ph.D., Deputy Director, DNDC II, HFD-820
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, DNDC II, @ Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580
Martin Haber, Ph.D., Chemist, DNDC II, @ Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, DRUDP, HFD-580

SUBJECT: Issues concerning established name.

Background: The Sponsor has submitted an NDA for Menopur® (menotropins for injection, USP), which is a more purified form of its product Repronex®, for the indications of multiple follicular development in patients participating in Assisted Reproductive Technologies (ART) [ ]. Issues concerning the use of the established name menotropins were identified during the Chemistry, Manufacturing, and Controls (CMC) review of this product. The Division requested this teleconference to convey these issues to the Sponsor, and to request the Sponsor's input in their resolution.

Discussion:

- The Division explained that follicle-stimulating hormone (FSH) has [ ] used to produce the drug product. If this were to happen, then the purified drug product would actually [ ] This

raises the question of whether the established name menotropins would still be appropriate for a purified version such as Menopur® or whether a new name may be needed.

- The Division's preliminary review seems to indicate that Menopur® meets the USP and USAN definitions for menotropins, and that the similarities between Menopur® and other menotropins appear to be preponderant. The Division asked if the Sponsor had any names that they felt would better describe the drug product, and the rationale for using that name rather than menotropins.
- The Sponsor expressed its goal of having a name that is clear to the practicing physician, and expressed its willingness to do whatever is necessary in order to achieve that goal. The current established name was picked because they felt it was supported by the CMC section of the NDA. If there is another name, supported by the CMC section and the drug specifications, they would be willing to consider it.
- The Division will continue to discuss this issue internally and will keep the Sponsor updated.
- The Sponsor was asked to submit any information which they feel might be helpful.

Action Items:

- Meeting minutes to sponsor within 30 days.
- The Sponsor will submit requested information.

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader

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/s/

Martin Kaufman
7/9/04 09:18:20 AM
CSO

Moo-Jhong Rhee
7/9/04 01:46:51 PM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-663

3-12-04

Ferring Pharmaceuticals
Attention: James H. Conover, Ph.D.,
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

Please refer to your December 19, 2003 new drug application (NDA), received December 29, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Menopur® (menotropins for injection, USP).

We also refer to your submissions dated January 27, February 12, 13, 18, 20, and 26 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 27, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Clinical:

1. All three clinical studies will be assessed using the ITT population.

2. Clinical pregnancy rates will be closely scrutinized in the review.

3. A preliminary review of Study 2000-02 shows that purified Menopur®, when administered subcutaneously, does not appear to meet the primary efficacy endpoint for mean oocytes retrieved.

4. The protocol for MFK/IVF/0399E was not reviewed by the Division. Additional review issues may be noted upon detailed review of the protocol, the three protocol amendments, and the study data.

5. If the United States formulation (as used in Studies 2000-01 and 2000-02) is not bioequivalent to the European formulation, then Study MFK/IVF/0399E will not be an acceptable study to support approval. This is a major review issue.

6. The Division's position is that non-inferiority will be decided based on a two-sided 95% confidence interval.

7. Patient cancellation rates in the three clinical studies will be a review issue.

8. The use of ICSI in Study MFK/IVF/0399E protocol will be a review issue.

9. The use of insulin sensitizing agents in Study 2000-01 will be a review issue.

10. Any significant differences in the treatment groups in the three studies, in terms of ovarian hyperstimulation syndrome or serious adverse events, will be review issues.

Clinical Pharmacology:

In the proposed labeling, the product will be indicated for [redacted] subcutaneous [redacted] administration. This will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. An additional electronic dataset entitled, "Ovarian Hyperstimulation Syndrome (OHSS)" for each study (2000-01, 2000-02, and MFK/IVF/0399E). This dataset should include all patients who had the diagnosis of ovarian hyperstimulation in the study. The dataset should have the following variables: the patient identifier, treatment group, date of hCG administration (or if none given), serum estradiol at time of hCG (in pg/ mL), date of ovarian hyperstimulation first noted, severity of ovarian hyperstimulation (for IVF studies, include column with the number of oocytes retrieved), and whether the patient became pregnant. Submit one dataset for each study.

2. All tables with hormonal values from Study MFK/IVF/0399E with estradiol levels in pg/ mL and progesterone in ng/ mL.

3. For Studies 2000-02 and MFK/IVF/0399E, a dataset with patient identifier, type of gonadotropin agonist used (and dose) and the down-regulated estradiol level (in pg/ mL).

4. Confirmation as to whether Protocol Amendment # 1 dated December 1, 2000, for Study 2000-02 was previously submitted for review.

5. A rationale for the choice of "- 10%" as the non-inferiority threshold for Study MFK/ IVF/ 0399E (EU non- inferiority study).

6. A rationale for the choice of "30% of the expected mean number of oocytes" as the non-inferiority margin for study 2000-02 (US IVF Study).

7. [

]

8. [

]

9. The test method and proposed acceptance limits for percent protein in the drug product.

10. As an additional test for purity, [ ] testing should be added to the drug substance specifications. [ ] testing may also be necessary for drug product testing. Alternatively, provide test data demonstrating that [ ] is not stability indicating, using stressed or aged samples of drug product.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Martin Kaufman, D.P.M., M.B.A., Regulatory Project Manager, at (301) 827-4234.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
3/12/04 04:26:12 PM

MEMORANDUM OF TELECON

DATE: February 10, 2004

APPLICATION NUMBER: NDA 21-663, Menopur (Menotropins for injection, USP)

BETWEEN:

Name:	Ken Kashkin, MD, V.P., Medical and Regulatory Affairs Jim Conover, Ph.D., Executive Director, Regulatory Affairs Vladimir Yankov, M.D., Executive Director, Medical Affairs [ ] Statistical Consultant
Phone:	845-770-2631
Representing:	Ferring Pharmaceutical

AND

Name:	Shelley Slaughter, M.D., Ph.D., Medical Team Leader, Meeting Chair Audrey Gassman, M.D., Medical Officer Lisa Kammerman, Ph.D., Statistical Reviewer Martin Kaufman, D.P.M., M.B.A., Regulatory Project Manager Jennifer Mercier, Regulatory Project Manager Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Significant deficiencies in the statistical section of the NDA

Background: The Sponsor has submitted an NDA for Menopur® (Menotropins for injection, USP), which is a more purified form of its product Repronex®, for the indication of *in vitro* fertilization [ ] The clinical development program for Menopur® included three pivotal, phase III trials: MFK/IVF/0399E (EU non-inferiority study), 2000-02 (US IVF study), and 2000-01[ ] During the initial review of this NDA, significant deficiencies in the statistical section were discovered that are filing issues. This teleconference was scheduled to convey these deficiencies to the Sponsor.

Discussion:

The Division identified the following deficiencies in the NDA:

- The submission does not describe in adequate detail the randomization scheme and procedures.
- The submission provides only a general description of how the randomization was carried out for each of the three studies.
- For study MFK/IVF/0299E the only description is "randomization will be achieved by allocation of the next available patient number from the sequence as each patient enters the trial."
- For study 2000-02, the protocol states "patients will be assigned to a treatment sequence according to the randomization schedule provided to each investigational site."

- [ ]

- The submission does not contain a data listing for the patient randomization in study MFK/IVF/0399E. For studies 2000-02 and 2000-01, the data listings for patient randomization are not included in Item 10.
- Pertinent data listings (e.g., "individual patient outcomes") are not included in Item 10 of the submission. Data listings important to the statistical review need to be included in Item 10 instead of their current location in Item 11.

The Division requested that the Sponsor:

- Submit a detailed description explaining how randomization was carried out for each of the three studies.
- Submit the randomization schedules of all three studies including a listing of patient randomizations.
- Check the rand.xpt SAS transport file for each clinical study (2000-01, 2000-02 and MFK/IVF/0399E). A randomization code should be attached to each patient randomized regardless of whether they received treatment.
- Submit the data listings, in paper, as a whole volume for all three studies. In addition, an archival copy needs to be submitted.

The Sponsor confirmed that the original randomization lists were available for both the U.S. and European studies. The Sponsor indicated that the transport files have sections that contain the randomization schedules, however, these would be rechecked. The Sponsor agreed to submit all requested information by February 20, 2004.

The Division stated that these are the initial deficiencies noted, and the response to these would be necessary for filing. The Division also stated that this list is not a complete list of deficiencies for the submission. Other deficiencies that were noted in the initial review will be conveyed to the Sponsor in the 74-day letter.

Action Items:

- Meeting minutes to sponsor within 30 days.
- The sponsor will submit the requested information to the significant deficiencies in the statistical section by February 20, 2004.

/s/

Shelley Slaughter, M.D., Ph.D.
Medical Team Leader

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/s/

Martin Kaufman
3/2/04 08:49:52 AM
CSO

Shelley Slaughter
3/2/04 09:18:18 AM
MEDICAL OFFICER
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

1-6-04

NDA 21-663

Ferring Pharmaceuticals
Attention: James H. Conover, Ph.D.,
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Menopur® (Menotropins for Injection, USP)

Review Priority Classification: Standard (S)

Date of Application: December 19, 2003

Date of Receipt: December 29, 2003

Our Reference Number: NDA 21-663

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 27, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 29, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are, however, waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, (HFD-580)
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Martin Kaufman, Regulatory Project Manager, at (301) 827-4234.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
1/6/04 05:40:20 PM
Chief, Project Management Staff

MEETING MINUTES

Date: March 3, 2003 **Time:** 1:00 – 2:30 PM **Location:** Conf. Rm. C

IND: 53,954 **Drug:** Repronex® (menotropins for injection, USP)

Sponsor: Ferring Pharmaceuticals, Inc.

Indication: Multiple follicular development (controlled ovarian stimulation)

Meeting Chair: Shelley R. Slaughter, M.D., Ph.D.

External Participant Lead: Kenneth Kashkin, M.D.

Meeting Recorder: Archana Reddy, MPH

Ferring Participants:
Kenneth B. Kashkin, MD, Vice President, Regulatory and Medical Affairs
Dennis C. Marshall, RN, PhD, Executive Director, Medical Affairs
Michael Zudiker, PhD, Executive Director, Operations
Michael I. Bernhard, PhD, Senior Director, Regulatory Affairs
Claudio Wolfenson, PhD, Production Manager, Instituto Massone
Martin Hendenfalk, Manager, Regulatory Affairs
Regulatory Consultant
Statistical Consultant

FDA Participants:
Daniel Shames, M.D., Division Director, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D., Medical Team Leader, DRUDP (HFD-580)
Gerald Willett, M.D., Medical Officer, DRUDP (HFD-580)
Audrey Gassman, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, MPH, Regulatory Project Manager, DRUDP (HFD-580)
David Lin, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry (DNDC II) @ DRUDP (HFD-580)
Martin Haber, Ph.D., Chemistry Reviewer, DNDC II @ DMEDP (HFD-510)
Duu-Gong Wu, Ph.D., Deputy Director, DNDC II
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, DRUDP (HFD-580)
Moo Jee Ng, M.S., Biostatistician, Division of Biometrics II (DB II) @ DRUDP (HFD-580)
James McVey, Ph.D., Microbiologist, Office of Microbiology (HFD-805)
Roy Blay, Ph.D., Director, Regulatory, OMP/Division of Scientific Investigations, HFD-42

Background:

Ferring submitted a Pre-NDA meeting request for a more purified form of Repronex® (menotropins for injection, USP) with a letter date of January 10, 2003 received on January 13, 2003. NDA 21-047 for Repronex® was approved on August 27, 1999 for the same indication. Ferring plans to continue to market NDA 21-047 for Repronex® and provide patients with a new menotropin, HP-menotropins for injection. Ferring represents that HP menotropins for injection is a human menopausal gonadotropin with fewer injection site reactions than currently available menotropins.

Meeting Objectives: Pre-NDA meeting for Repronex®.

Discussion:
Clinical
Question: Does the Division agree that the US — IVF studies and the non-US IVF study provide an adequate basis for evaluation of the efficacy and safety of HP menotropins for injection (by — SC routes of injection) for — IVF indications?
DRUDP Response:

- Yes, this is sufficient to submit for filing.

Clinical Comments

- The Division noted three efficacy issues:
  1. (2000-01) -
  2. U.S. In Vitro Fertilization trial (2000-02) - An analysis including statistical adjustments for baseline co-variants for trial 2000-02 will be considered a secondary analysis. The Division agreed on October 11, 2001 that the stated delta of 3.9 oocytes will be accepted as a clinically meaningful difference in the test of non-inferiority. The analysis presented in the briefing document shows that the lower bound of the 95% confidence interval (-4.4) does not exclude a difference of -3.9 oocytes. Therefore, non-inferiority of HP-Repronex SC to Repronex SC has not been established in this trial.
  3. The European/Israeli trial In Vitro Fertilization trial (MFK/IVF/0399E) - The Division will need information on the formulation of recombinant FSH (Gonal f®) to determine if this is the same as the one approved in the United States. The Division is supportive of a trial that looks at pregnancy as a primary endpoint. If efficacy is demonstrated, data from this trial may be sufficient for this indication with HP-Repronex SC if the Gonal-f® utilized in this trial is the same as the U.S. registered drug product.

- The Division had the following safety comments for the sponsor:
  1. Superiority claims of any drug requires two prospectively designed clinical trials; therefore, no safety superiority claims for Repronex® HP will be considered.
  2. The following four adverse events criteria need to be provided to the Division:
     - Ovarian hyperstimulation
     - Cycle cancellation.
     - Nausea
     - Abdominal pain
  3. The sponsor was asked to provide a classification of three adverse event criteria for ovarian hyperstimulation, nausea and abdominal pain into categories of mild, moderate and severe and submit the adverse event data to the Division.
  4. The sponsor was asked to provide the individual safety reports for the following subjects:
     - Subject 13 (hemi-plegic migraine) in trial MFK/I/1098- pharmacokinetic data.
     - Subjects in trials 2000-01 and 2000-02 who experienced serious adverse events: ovarian hyperstimulation syndrome, ectopic pregnancy, pelvic abscess, dehydration, and ruptured ovary with hemothorax.
  5. The sponsor was asked to provide the local tolerance reports for all subjects:
     - The parameters of the scoring system used for local tolerance in all trials.
     - The score for each patient that had an injection site reaction.
  6. The sponsor was asked to provide a specific electronic data set for the clinical review at the time of the NDA submission. The data set will combine dosing, ultrasonography, and pertinent lab analysis - so that each subject's stimulation cycle can be evaluated.

Statistical Comments:

- All tables should provide 2-sided 95 % confidence intervals.
- Appropriate methods should be used to adjust for multiple treatment group comparisons.
- Clarify the stratification categories of age and body mass index.
- Provide study protocol and all amendments.
- Provide clinical trials efficacy data in electronic format per the industrial guidance document.

Chemistry:

Question 1. Does the Division agree that HP menotropins drug substance has been adequately characterized as a menotropin?

DRUDP Response:

Regarding characterization, provide [redacted] data.

Question 2. Does the Division agree that the proposed tests and methods are adequate for the release of this HP menotropins drug substance?

DRUDP Response:

Regarding the drug substance specifications, [redacted]

Question 3. Does the Division agree that the proposed tests and methods are adequate for the stability assessment of the HP menotropins drug substance?
DRUDP Response:
Regarding the drug substance specifications, [redacted]

Question 4. Does the Division agree that the proposed tests and methods are adequate for the release of this HP menotropin for injection drug product?
DRUDP Response:
Regarding the drug product specifications, [redacted]

Question 5. Does the Division agree that the proposed tests and methods are adequate for the stability assessment of the HP menotropins for injection drug product?
DRUDP Response:
Yes.

CMC Comments:

- Ferring should consider submitting an alternate tradename for review as the initials [redacted] will not be acceptable; the sponsor must clearly distinguish between the two formulations
- Sponsor agreed to perform [redacted] validation
- Ferring was advised that the USP monograph for menotropins may be revised to eliminate the percentage limit on hCG content. (Clarification added post-meeting)

Additional comment added post-meeting:

- Ferring should provide a purity estimate of the percent of impurities in the drug substance

Microbiology Comments:

- Ferring agreed to submit a complete [redacted] package for review.
- Drug product [redacted] validation and calculations for endotoxin limits were specifically mentioned.

Clinical Pharmacology/Biopharmaceutics

1. Sponsor needs to clarify in detail the following formulation issues:
   a) Identify the to-be-marketed formulation.
   b) Clarify how the to-be-marketed formulation is different from the clinical trial formulation(s).
   c) Clarify that the active control formulations in US and EU trials are similar to the products approved in US.

The sponsor stated that the HP-Repronex formulation used in the US trials is the intended-for-market product. The formulation used in the EU/Israel trial is Menopur (approved in EU but different from the US product with respect to [redacted] excipient). Also, sponsor stated that the active controls are similar to those approved in US. Ferring should document all this in their NDA submission.

2. Since EU/Israel clinical data may be important for clinical safety/efficacy assessment of the NDA, the sponsor needs to bridge the formulation used in this trial to the to-be-marketed product via a bioequivalence study; DRUDP recommends a single dose study for this evaluation and the sponsor is encouraged to refer to the guidance on Bioavailability and Bioequivalence Studies; Ferring should submit a protocol for review
3) If the sponsor intends to pursue — SC — routes of administration in the label for a given indication, clinical trials showing efficacy need to be conducted with these routes; in absence of acceptable clinical studies for — SC — routes, (e.g., if clinical data is available for sc only) bioequivalence information could be used to get the other site of administration approved.
4) Provide individual and mean data for all pharmacokinetic (PK) studies at the time of NDA submission.

Division of Scientific Investigations

- Further information of the names and investigators will be requested at the time of NDA submission.

Decision Reached:

- Ferring should provide a complete NDA package with all requested information as discussed at the Pre-NDA meeting for the highly purified form of Repronex.

Action Item:

1. The PM will fax the minutes of the meeting to the sponsor.

/S/

Signature: Meeting Chair
See appended electronic signature page

Note to Sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Cc:
Arch IND 53,954
HFD-580/Division Files
HFD-580/Reddy/Slaughter/Willett/Gassman/Ng/Lin/Shames/Parekh
HFD-510/Haber/Wu
HFD-805/McVey

Created by: Archana Reddy/3/10/03
Concurrence: ag/3.11.03, jm/3.12.03, mh/3.11.03, mjn/3.19.03, ap/3.20.03, ss/3.26.03
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MEETING MINUTES

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/s/

Shelley Slaughter
3/27/03 02:09:08 PM
I concur.